SCIENTIFIC HIGHLIGHTS REPORT

EANM25 WORLD LEADING MEETING

38th Annual Congress of the European Association of Nuclear Medicine

BARCELONA

OCTOBER 4-8, 2025

eanm25.eanm.org

TABLE OF CONTENTS

FOREWORD

The EANM'25 Congress in Barcelona set a new record with 9,431 participants, marking a milestone as we celebrated four decades of innovation and collaborative efforts in the field of nuclear medicine.

The congress offered an opportunity to reflect on our journey since 1985, honouring the achievements we have made over the past forty years and providing a chance to look ahead to the bright future for our specialty. The congress brought together a diverse community of specialists, providing a platform for international collaboration and professional development.

This report explores the latest developments in research and clinical practice that are transforming nuclear medicine and features expert-led presentations from eight key sessions from the congress programme.

Faistauer Photography

1 CME 1: INFLAMMATION & INFECTION COMMITTEE - THE ROLE OF FAPI PET/CT IN INFLAMMATION DISEASES

SUNDAY, 5 OCT, 08:00 - 09:30

CHAIRS: PROF. OLIVIER GHEYSENS AND PROF. CRISTINA WAKFIE-CORIEH

THE TRUTH IS IN THE TISSUE

Speaker: Prof. Mark Coles, University of Oxford, Kennedy Institute of Rheumatology, Oxford, UK

Prof. Mark Coles opened the CME session by reframing fibroblasts as central orchestrators of inflammation rather than passive structural cells. Once regarded merely as tissue "scaffolds," fibroblasts are now recognised as key regulators of immune responses, vascular function, tissue repair, fibrosis, and even cancer biology. Prof. Coles described them as the "hidden majority" of immunology: abundant yet underappreciated and existing largely beneath the visible tip of the immune iceberg. Present in virtually all tissues except the brain, fibroblasts must be understood in their spatial context since "the truth," he noted, "is in the tissue."

Describing fibroblasts as "multi-talented cells," Prof. Coles highlighted their remarkable diversity and plasticity. They maintain extracellular matrix integrity, secrete cytokines and growth factors, and shape both immune and vascular microenvironments. Their functions vary by tissue, combining "public" inflammatory pathways with "private" site-specific adaptations. This spatial and functional heterogeneity underscores the need to study fibroblasts within their native tissue rather than relying solely on blood-based analyses.

Fibroblast activation protein (FAP) has emerged as a highly specific marker of activated fibroblasts across immune-mediated and malignant conditions.[1] However, Prof. Coles cautioned that while FAP is invaluable for imaging and targeting, it is not mechanistically essential and clinical inhibition trials have not yet shown therapeutic benefit. Still, its distinctive expression pattern makes it an ideal candidate for visualising and quantifying inflammatory fibroblast activity in vivo.

Prof. Coles showcased insights from large-scale single-cell and spatial transcriptomic studies, which form a comprehensive "fibroblast atlas" that now encompasses tens of millions of cells across tissues and disease states. These maps reveal the dynamic plasticity of fibroblasts as tissues transition from health to disease. In rheumatoid arthritis, for instance, fibroblasts display distinct subsets that shape myeloid, lymphoid, and stromal-rich pathotypes, orchestrating immune landscapes like unseen conductors. Two particularly influential populations have emerged: vascular-interacting fibroblasts that activate endothelial cells, and immune-interacting fibroblasts that drive tertiary lymphoid structures and inflammatory cascades.

He concluded by outlining an inflammation to fibrosis continuum, from homeostatic fibroblasts to FAP-positive inflammatory states, and ultimately to irreversible fibrotic myofibroblasts. Mapping this trajectory through molecular imaging offers powerful insights into chronic disease mechanisms. Fibroblasts, Prof. Coles emphasised, are not passive bystanders; they are active architects of disease and promising targets for therapeutic modulation.

1 Korsunsky, I., Wei, K., Pohin, M., et al. (2022). Cross-tissue, single-cell stromal atlas identifies shared pathological fibroblast phenotypes in four chronic inflammatory diseases. Med (New York, N.Y.), 3(7), 481–518.e14.

FAPI PET AS A WINDOW INTO CARDIAC FIBROBLAST ACTIVATION

Speaker: Dr. Neil Craig, University of Edinburgh, BHF Centre of Cardiovascular Science, Edinburgh, UK

Dr. Neil Craig explored the emerging role of FAPI PET/CT in imaging cardiac fibrosis, highlighting fibroblast activation as a shared mechanism across ischemic, hypertrophic, and toxic myocardial injury. He described fibrosis as a "double-edged sword," necessary for structural stability after acute injury but harmful when chronic, as it drives stiffness, arrhythmias, and heart failure.

Current imaging approaches, such as cardiac MRI with late gadolinium enhancement or T1 mapping, can reveal extracellular expansion but not the underlying biology. They are also limited in thin-walled structures such as the atria or right ventricle and provide little insight into whether disease is active or burnt out. In contrast, FAPI PET visualises activated fibroblasts directly, offering a dynamic measure of disease activity rather than static scarring.

Across cardiac conditions, Dr. Craig summarised early evidence showing consistent FAPI uptake in regions of active fibroblast activity. In acute myocardial infarction, uptake peaks within weeks and declines during recovery, with higher initial burden predicting adverse remodelling and reduced ventricular function.[2] In atrial fibrillation, FAPI detects fibroblast activation that is absent on standard imaging,[3] while in aortic stenosis, signal intensity correlates with myocardial strain and biomarkers of dysfunction. Similar findings have been reported in hypertrophic cardiomyopathy, amyloidosis,[4] and anthracycline cardiotoxicity, where FAPI uptake reflects modifiable disease activity.[5]

Beyond imaging, Dr. Craig discussed the therapeutic relevance of FAP as a molecular target, from fibroblast-directed cell therapies to bispecific immune modulators. He emphasised FAPI PET's utility as a trial biomarker, enabling patient selection, confirmation of biological activity, and early monitoring of therapeutic response.

While acknowledging current limitations, such as small cohorts, heterogeneous acquisition protocols, and access challenges, he concluded that FAPI PET adds a fibroblast-specific dimension to cardiac imaging. It is trial-ready, particularly as a secondary endpoint in Phase 2 antifibrotic studies, with strong potential to guide precision therapy in fibrotic cardiomyopathies.

2 Barton, A. K., Craig, N. J., Loganath, K. et al. (2025). Myocardial fibroblast activation after acute myocardial infarction: A positron emission tomography and magnetic resonance study. JACC, 85(6).

3 Li, L., Gao, J., Chen, B. X., Liu, X. et al. (2023). Fibroblast activation protein imaging in atrial fibrillation: a proof-of-concept study. Journal of nuclear cardiology: official publication of the American Society of Nuclear Cardiology, 30(6), 2712–2720.

4 Wang X et al. Feasibility of ^{68}Ga-FAPI-04 PET/CT in detecting myocardial fibroblast activation in light-chain cardiac amyloidosis. JACC: Cardiovascular Imaging. 2022 Nov;15(11):1960–1970.

5 Wei, Z., Xu, H., Chen, B., Wang, J., Yang, X., Yang, M. F., & Zhao, S. (2024). Early detection of anthracycline-induced cardiotoxicity using [68 Ga]Ga-FAPI-04 imaging. European journal of nuclear medicine and molecular imaging, 51(8), 2204–2215.

FAPI PET/CT IN LUNG DISEASES

Speaker: Dr. Anne-Leen Deleu, Jules Bordet Institute (H.U.B.), Brussels, Belgium

Dr. Anne-Leen Deleu discussed how FAPI PET/CT can address critical gaps in assessing interstitial lung diseases (ILDs), a group of disorders characterised by chronic inflammation and/or fibrosis of the pulmonary interstitium. She presented idiopathic pulmonary fibrosis (IPF) as the prototypical progressive fibrosing ILD, with a median untreated life expectancy of only three to five years. Moreover, up to 15–40% of patients with non-IPF ILDs will also progress to an irreversible fibrotic phenotype known as progressive pulmonary fibrosis (PPF).[6] This shared biology highlights the need for tools that can detect fibrotic activity before irreversible damage occurs.

Dr. Deleu outlined the biological rationale of FAPI PET imaging in ILD: premature epithelial senescence and aberrant wound-healing responses drive fibroblast activation and fibroblast-to-myofibroblast transition, with FAP expression marking this activated state. Across early studies, pulmonary FAPI uptake aligns closely with fibrotic regions on CT, but its true strength lies beyond co-localisation. By visualising areas of active fibroblast biology, FAPI PET offers a forward-looking perspective, predicting future lung function decline before structural changes are evident.

In both idiopathic and connective-tissue-related ILDs, distinct "progressor" phenotypes have been identified, where high FAPI signal intensity marks patients at greater risk of deterioration despite stable CT findings. Several cohorts have shown that the magnitude of FAPI uptake independently predicts pulmonary function loss, highlighting its potential as a dynamic biomarker of disease activity rather than a static indicator of damage.

Pilot studies in post-COVID fibrosis and connective-tissue-associated ILD further demonstrate that FAPI can visualise active fibroblast biology even when FDG PET is negative, indicating greater sensitivity to fibrotic rather than purely inflammatory processes. Preliminary longitudinal data also show that changes in FAPI signal mirror treatment response, increasing in patients with functional decline and stabilising in those with disease control.

Dr. Deleu outlined four potential clinical applications for FAPI PET/CT in ILDs: early diagnosis, treatment-response monitoring, risk stratification, and decision support for antifibrotic therapy. Remaining challenges include tracer standardisation, quantification methods, and acquisition timing, as multiple radiotracers and analytical approaches are still in use. Nonetheless, correlations with CT extent and lung function measures have been consistently strong across studies.

Dr. Deleu concluded that, although current evidence remains preliminary and heterogeneous, emerging data indicate that FAPI PET/CT provides a novel, biology-based lens for evaluating ILD activity, complementing structural imaging with functional insight. She highlighted that its most promising clinical application may reside in patient risk stratification, thereby paving the way for more personalised antifibrotic treatment strategies in pulmonary disease. Future research should prioritise standardisation of FAPI radiopharmaceutical use, optimisation of image acquisition timing, and harmonisation of image interpretation and quantification.

6 Ryerson, C. J., Adegunsoye, A., Piciucchi, S., et al. (2025). Update of the International Multidisciplinary Classification of the Interstitial Pneumonias: An ERS/ATS Statement. The European respiratory journal, 2500158. Advance online publication.

MAPPING FIBROBLAST ACTIVITY IN AUTOIMMUNE DISEASE

Speaker: Dr. Maria Sandovici, University Medical Center Groningen, Dept. of Rheumatology & Clinical Immunology, The Netherlands

Dr. Maria Sandovici concluded the session by highlighting the potential of FAPI PET/CT to illuminate fibroblast-driven inflammation and remodelling in rheumatologic diseases, including rheumatoid arthritis (RA), systemic sclerosis (SSc), vasculitis, and IgG4-related disease (IgG4-RD). She emphasised that while FDG PET reflects inflammatory metabolism, FAPI imaging provides complementary insight into fibroblast activation, a central mediator of chronic tissue damage and fibrosis.[7]

In RA, dual-tracer studies show that FAPI and FDG identify a similar number of affected joints, but FAPI often demonstrates higher uptake values and correlates closely with subsequent structural progression. Longitudinal scans reveal reduced signal with effective therapy,[1] suggesting utility for disease activity monitoring. FAPI-PET may also be instrumental in the prediction of treatment response.[8]

In SSc and SSc-associated interstitial lung disease (ILD), FAPI uptake in skin and lung correlates with histological markers of fibroblast activation. FAPI uptake in lung predicts pulmonary function decline, supporting its role in risk stratification and treatment guidance.[9]

In vasculitis, FAPI PET visualises vascular wall inflammation and remodelling even when patients are in clinical remission and FDG and MRI show minimal inflammatory activity, revealing fibroblast activity persistence after immune resolution.[10] This capability may redefine how clinicians assess vascular healing and fibrosis. Similarly, in IgG4-RD, organ-specific FAPI uptake—particularly in the pancreas, bile duct/liver and lacrimal glands—complements FDG findings[11] by distinguishing fibrotic from inflammatory components and enabling more targeted management.

Dr. Sandovici underscored the need for harmonised imaging protocols and outcome-linked multicentre trials to establish quantitative thresholds for "active remodelling." Despite current heterogeneity, emerging evidence consistently demonstrates that FAPI PET expands the diagnostic and prognostic toolkit in rheumatology. By directly visualising fibroblast activity, it offers novel insights into the tissue remodelling processes that drive chronicity and irreversible damage across immune-mediated diseases.

7 Luo, Y., Pan, Q., Zhou, Z. et al. (2023). [^{68}Ga]Ga-FAPI PET/CT for rheumatoid arthritis: A prospective study. Radiology, 307(3), e222052.

8 Pan, Q., Yang, H., Zhou, Z. et al. (2024). [68 Ga]Ga-FAPI-04 PET/CT may be a predictor for early treatment response in rheumatoid arthritis. EJNMMI research, 14(1), 2.

9 Broens, B., van der Laken, C. J., Radonic, T. et al. (2025). GLUT and FAPα as molecular markers for interstitial lung disease in systemic sclerosis. Respiratory Research, 26, Article 283.

10 Röhrich, M., Rosales, J. J., Hoppner, J. et al. (2024). Fibroblast activation protein inhibitor-positron emission tomography in aortitis: fibroblast pathology in active inflammation and remission. Rheumatology (Oxford, England), 63(9), 2473–2483.

11 Luo, Y., Pan, Q., Yang, H. et al. (2021). Fibroblast Activation Protein-Targeted PET/CT with 68Ga-FAPI for Imaging IgG4-Related Disease: Comparison to 18F-FDG PET/CT. Journal of nuclear medicine: official publication, Society of Nuclear Medicine, 62(2), 266–271.

2 PLENARY 2 - WORLD'S BEST THERANOSTICS COMES TO EANM'25

SUNDAY, 5 OCT, 11:30 – 13:00

CHAIRS: PROF. VALENTINA GARIBOTTO, MD AND DR. RER. MEDIC. PEDRO FRAGOSO COSTA

TARGETED ALPHA THERAPY: A DISTINCT MODALITY IN PRECISION ONCOLOGY

Speaker: Prof. Mike Sathekge, Steve Biko Academic Hospital & University of Pretoria, South Africa

The plenary opened with **Prof. Mike Sathekge** receiving the Marie Curie Lecture award for his work on Radiotheranostics. He then went on to demonstrate his extensive expertise with a presentation on the power of targeted alpha therapy (TAT), which he described as a distinct therapeutic modality rather than a "stronger" form of radiation. Drawing on decades of clinical and preclinical experience, he showed how TAT uniquely integrates radiobiology, theranostic imaging, and potent cell-killing capacity to address unmet needs in oncology.

Prof. Sathekge outlined the physics of alpha therapy, explaining that alpha particles have high linear energy transfer and short tissue range, producing dense DNA double-strand breaks in a few cell layers while sparing healthy tissue. TAT is also characterised by a tripartite antitumour mechanism: local (direct tumour cell kill), regional (bystander effect), and systemic (abscopal effect). These mechanisms underpin its powerful therapeutic potential, especially when guided by insights from molecular imaging. This makes TAT especially effective against radioresistant, hypoxic, and micrometastatic disease.

Beyond its direct cytotoxic effects, when combined with immunotherapy or agents targeting the tumour microenvironment, TAT can reshape the tumour milieu, modulating immune activity, converting immunologically "cold" lesions into "hot," and enhancing synergy with immunotherapies. With appropriate protocols and an improved understanding of radiobiology and dosimetry, alongside the use of biomarkers, it is increasingly possible to predict therapy outcomes, particularly in relation to bone marrow reserve and treatment tolerability.

Prof. Sathekge reviewed the decay properties, imaging surrogates, and logistical considerations of key alpha-emitting radioisotopes ^{225}Ac, ^{212}Pb, ^{211}At, ^{223}Ra, noting differences in half-life, imaging compatibility, and chemical behaviour that influence clinical application and safety. Clinical efficacy has been demonstrated across prostate cancer, neuroendocrine tumours, and thyroid cancer, where alpha-labelled vectors have achieved high response rates and meaningful survival benefits with manageable toxicity.[12,13,14,15] Remaining challenges include daughter recoil, redistribution, and limited isotope supply, underscoring the need for industrial-scale production and improved waste management.

Prof. Sathekge concluded with a roadmap positioning TAT as a renaissance in oncology, embodying a reimagining of cancer care focused on scaling isotope production, optimising vector design, standardising dosimetry, and expanding prospective trials on sequencing and combination strategies. He emphasised that success relies on a transdisciplinary approach that strategically realigns pan-cancer targets and multitargeted strategies, supported by strong regulatory frameworks, reliable supply chains, and global capacity-building efforts.

12 Morgenstern, A., Apostolidis, C., Kratochwil, C. et al. (2018). An Overview of Targeted Alpha Therapy with 225Actinium and 213Bismuth. Current radiopharmaceuticals, 11(3), 200–208.

13 Bidkar, A. P., Zerefa, L., Yadav, S. et al. (2024). Actinium-225 targeted alpha particle therapy for prostate cancer. Theranostics, 14(7), 2969–2992.

14 Zuo, D., Wang, H., Yu, B. et al. (2024). Astatine-211 and actinium-225: two promising nuclides in targeted alpha therapy. Acta biochimica et biophysica Sinica, 57(3), 327–343.

15 Sathekge MM, Lawal IO, Bal C, Bruchertseifer F, et al. Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study. Lancet Oncol. 2024 Feb;25(2):175-183.

REDEFINING PSMA-TARGETED THERANOSTICS AND BEYOND THROUGH COMBINATION STRATEGIES

Speaker: Prof. Grace Kong, Peter MacCallum Cancer Centre & University of Melbourne, Australia

Prof. Grace Kong delivered a comprehensive overview of Prostate-specific membrane antigen (PSMA) -targeted theranostics in prostate cancer, illustrating how radioligand therapy (RLT) has redefined the management of advanced disease. While PSMA-targeted therapy demonstrates high efficacy, she emphasised that monotherapy alone cannot address all tumour phenotypes due to lesion heterogeneity, discordant biology, and the presence of sanctuary sites. Maximising benefit requires integrating radionuclide selection, molecular imaging, patient-specific dosimetry, predictive/prognostic biomarkers, rational sequencing, or combination strategies.

Prof. Kong highlighted the growing role of alpha-emitting agents for resistant or micrometastatic disease and the promise of sequential and dual-isotope approaches to tailor treatment according to disease burden and biology. Molecular imaging remains central to this paradigm, with combined PSMA and FDG PET used alongside blood biomarkers and genomic profiling to refine patient selection and enable early response prediction. Actionable dosimetry, she noted, is essential for guiding administered activity, cycle planning, and retreatment decisions.

Combination strategies formed the core of her presentation, drawing on several landmark Australian Phase 1 and 2 studies. One trial evaluating androgen-receptor pathway inhibition with or without PSMA-targeted therapy in high-risk prostate cancer demonstrated clinically meaningful improvements in progression-free survival, overall survival (OS), and quality of life (QoL).[16] Another, assessing combination therapy with taxane-based chemotherapy in high-volume, hormone-sensitive disease, showed longer progression-free survival (PFS) and higher rates of undetectable Prostate-specific antigen (PSA) without additional toxicity.[17]

Immunotherapy combinations have also shown encouraging results. Early-phase studies combining PSMA-targeted therapy with checkpoint inhibitors produced strong PSA and radiographic responses,[18] although immune-related adverse events (AE) such as myocarditis require careful monitoring.[19] DNA-repair pathway inhibition has been explored as a radiosensitising approach, yielding promising clinical responses. Sequential alpha- and beta- emitter approaches have also shown feasibility and tolerability in bone-predominant disease.[20]

Extending beyond prostate cancer, Prof. Kong described ongoing research in combination trials with 177Lu-DOTATATE therapy for neuroendocrine neoplasms. For radioactive iodine refractory thyroid cancer, targeted tyrosine kinase inhibitor-based redifferentiation can potentially restore radioiodine uptake and enable subsequent theranostic therapy in specific molecular subtypes.

Prof. Kong concluded that combination-based theranostics deepen response, extend survival, and expand access to personalised radionuclide therapy while maintaining tolerability. She stressed that future progress depends on predictive biomarkers and collaborative trial designs that balance efficacy with safety and ensure equitable access to next-generation innovation.

16 Emmett, L., Subramaniam, S., Crumbaker, M. et al. (2025). Overall survival and quality of life with [177Lu]Lu-PSMA-617 plus enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer (ENZA-p): secondary outcomes from a multicentre, open-label, randomised, phase 2 trial. The Lancet. Oncology, 26(3), 291–299.

17 Azad, A. A., Bressel, M., Tan, H., et al. (2024). Sequential [177Lu]Lu-PSMA-617 and docetaxel versus docetaxel in patients with metastatic hormone-sensitive prostate cancer (UpFrontPSMA): a multicentre, open-label, randomised, phase 2 study. The Lancet. Oncology, 25(10), 1267–1276.

18 Inderjeeth, A. J., Iravani, A., Subramaniam, S., Conduit, C., & Sandhu, S. (2023). Novel radionuclide therapy combinations in prostate cancer. Therapeutic advances in medical oncology, 15, 17588359231187202. https://doi.org/10.1177/17588359231187202

19 Sandhu, S., Subramaniam, S., Thomas, H. et al. (2025). 177Lu-PSMA-617 with ipilimumab (ipi) and nivolumab (nivo) in metastatic castration-resistant prostate cancer (mCRPC): An investigator-initiated phase 2 trial (EVOLUTION; ANZUP2001) [Conference abstract]. Journal of Clinical Oncology, 43(16_suppl), 5016.

20 Kostos, L., Buteau, J. P., Yeung, T. et al. (2022). AlphaBet: combination of radium-223 and [^177Lu]Lu-PSMA-I&T in men with metastatic castration-resistant prostate cancer (clinical trial protocol). Frontiers in Medicine, 9.

INTEGRATING IMAGING AND GENOMIC FOR PRECISION THERANOSTICS

Speaker: Dr. Heather Jacene, Dana-Farber Cancer Institute, Boston, USA

Dr. Heather Jacene highlighted the expanding role of molecular imaging and genomic integration in precision oncology, emphasising how next-generation sequencing (NGS) and circulating tumour DNA (ctDNA) analysis enhance the predictive power of theranostics. She described theranostics as the convergence of phenotypic imaging, molecular targeting, and personalised treatment, enabling highly tailored interventions across diverse malignancies.

Dr. Jacene presented biomarker data linking ctDNA fraction to treatment outcomes, noting that in the Phase 2 TheraP Biomarker Study, higher ctDNA levels and mutations in TP53, PTEN, or RB1 were associated with poorer prognosis among patients treated with PSMA-targeted RLT.[21]

In contrast, combining imaging and molecular profiling helps refine patient selection and predict response. Beyond prostate cancer, Dr. Jacene discussed NGS applications in neuroendocrine tumours, focusing on the NETest and PRRT Predictive Quotient (PPQ), tools that exemplify how dynamic biomarkers can guide peptide receptor radionuclide therapy (PRRT) and monitor response longitudinally.[22]

She also summarised evidence on DNA damage repair (DDR) gene alterations across theranostic applications. Retrospective analyses indicate that DDR mutations predict worse outcomes for beta-emitter therapies but do not necessarily enhance response to PSMA or alpha emitters, reinforcing the need for tailored approaches and combination strategies such as PARP inhibitors.[23]

Dr. Jacene concluded that molecular imaging, when integrated with genomic and transcriptomic data, transforms theranostics from a purely diagnostic field into a precision medicine engine, optimising patient selection, improving prediction of response, and driving next-generation trial design that unites imaging, genomics, and targeted radionuclide therapy.

21 Kwan, E. M., Ng, S. W. S., Tolmeijer, S. H. et al. (2025). Lutetium-177-PSMA-617 or cabazitaxel in metastatic prostate cancer: circulating tumor DNA analysis of the randomized phase 2 TheraP trial. Nature medicine, 31(8), 2722–2736.

22 Bodei, L., Raj, N., Do, R. K. et al. (2023). Interim Analysis of a Prospective Validation of 2 Blood-Based Genomic Assessments (PPQ and NETest) to Determine the Clinical Efficacy of ^{177}Lu-DOTATATE in Neuroendocrine Tumors. Journal of nuclear medicine: official publication, Society of Nuclear Medicine, 64(4), 567–573.

23 Privé, B. M., Slootbeek, P. H. J., Laarhuis, B. I. et al. (2022). Impact of DNA damage repair defects on response to PSMA radioligand therapy in metastatic castration-resistant prostate cancer. Prostate cancer and prostatic diseases, 25(1), 71–78.

OPTIMISING RADIUM-223 THERAPY:

Speaker: Prof. Elba Etchebehere, University of Campinas (UNICAMP), Brazil; President of the Brazilian Society of Nuclear Medicine and Molecular Imaging (SBMN); President-Elect of the Latin American Societies of Nuclear Medicine, Biology and Molecular Imaging (ALASBIMN)

Prof. Elba Etchebehere traced the evolution of radium-223 therapy in Metastatic castration-resistant prostate cancer (mCRPC), charting its development from early clinical studies to optimised contemporary practice. Early trials demonstrated selective bone uptake, reduced alkaline phosphatase levels, and meaningful palliative benefit. A landmark multicentre, placebo-controlled Phase 2 study confirmed a survival advantage with four radium-223 doses administered every four weeks (median overall survival 16.3 vs 12.2 months).[24] Subsequent Phase 3 data showed that combining radium-223 with bone-protective agents extended median skeletal event-free survival to 19.6 months versus 10.2 months for placebo ($p < 0.001$).[25]

Drawing on data from over 12,000 administered cycles, Prof. Etchebehere emphasised that completion of five to six treatment cycles is associated with a two- to five-fold improvement in overall survival compared with patients receiving fewer than four cycles. She discussed the benefits of extending cycle intervals, noting that delaying treatment to 6–12 weeks instead of the standard 4-week schedule is associated with longer median overall survival (12.9 vs 9.8 months), likely reflecting reduced cumulative toxicity and augmented bystander effects.

She noted that lower intermittent activity and flexible scheduling improve tolerability and facilitate safe integration with combination regimens. The high linear energy transfer (LET = 27.4 MeV) of radium-223 underpins its potent antitumour effect, and when paired with bone-protective agents or hormonal therapies, toxicity remains manageable.

Prof. Etchebehere concluded that optimised cycle completion, adjusted dosing intervals, and early integration before chemotherapy are key to maximising radium-223's therapeutic index. She underscored its enduring value as a cornerstone of bone-targeted therapy, improving survival, preserving mobility, and reducing opioid dependence in appropriately selected patients.

Importantly, she emphasised that the main challenge for nuclear medicine physicians is mastering sequencing rather than fostering competition. She highlighted

the need to recognise that alpha- and beta-emitters, including radium-223 and PSMA-targeted agents, should be applied complementarily and thoughtfully to maximise their potential and improve patients' quality of life.

24 Nilsson, S., Franzén, L., Parker, C. et al. (2007). Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. The Lancet. Oncology, 8(7), 587–594.

25 Sartor, O., Coleman, R., Nilsson, S. et al. (2014). Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. The Lancet. Oncology, 15(7), 738–746.

BUILDING A FUTURE FOR SCALABLE THERANOSTICS

Speaker: Dr. Rakesh Kumar, All India Institute of Medical Sciences, New Delhi, India

Dr. Rakesh Kumar addressed the growing demand for theranostics and the infrastructural, logistical, and workforce challenges associated with scaling advanced nuclear medicine services. He highlighted the rising utilisation of beta- and alpha-emitting radiopharmaceuticals and the strain on global supply chains, hybrid imaging platforms, and skilled personnel.

He outlined key bottlenecks, which include isotope production limitations, shortage of trained nuclear medicine professionals, uneven access to imaging equipment, and fragmented regulatory pathways. To address these, Dr. Kumar advocated for hub-and-spoke GMP radiopharmacy models, strategic workforce training, scalable imaging infrastructure, and harmonised protocols for dosimetry and treatment.

Examples from India illustrate progress, such as the expansion of cyclotron facilities, integration of digital PET, establishment of high-throughput therapy suites, and early adoption of alpha therapies. He emphasised the importance of regional collaboration, multicentre trials, and sustainable investment to ensure equitable access.

Dr. Kumar concluded that modernised nuclear medicine infrastructure is essential to translate theranostics from niche innovation into routine patient care. Investments in people, technology, and supply chains will determine whether global populations can fully benefit from these advances.

PIONEERING A NEXT-GENERATION ALPHA-THERANOSTIC APPROACH TO THYROID CANCER

Speaker: Prof. Tadashi Watabe, University of Osaka, Japan

Prof. Tadashi Watabe presented early-phase clinical experience with astatine-211 (^{211}At) in radioiodine-refractory thyroid cancer. He highlighted ^{211}At's high linear energy transfer, short path length, and halogen chemistry, which permits thyroid-targeted therapy analogous to iodine-based approaches while minimising off-target toxicity.

Prof. Watabe detailed cyclotron production, GMP-compliant synthesis, and dosimetry approaches, including Single-photon emission computed tomography (SPECT) imaging to track biodistribution and absorbed doses. A Phase 1 investigator-initiated trial demonstrated safety and preliminary efficacy, including partial and complete responses on ^{131}I-SPECT, with manageable hematologic and gastrointestinal.[26] Observed organ-specific dose correlations emphasise the importance of dosimetry in dose-escalation studies.

Challenges include optimising repeated dosing, refining TSH-stimulation protocols, and scaling production to support multicentre trials. Prof. Watabe stressed the need for continued collaboration between production facilities, clinical teams, and researchers to establish ^{211}At as a next-generation alpha-theranostic option bridging traditional radioiodine therapy and modern targeted therapy.

26 Watabe, T., Mukai, K., Naka, S. et al. (2025). First-in-human study of [^211At]NaAt as targeted α-therapy in patients with radioiodine-refractory thyroid cancer (Alpha-T1 trial). Journal of Nuclear Medicine, 66(9).

3 SPECIAL TRACK 3: ONCOLOGY & THERANOSTICS COMMITTEE - DEBATE: WILL ALPHA THERAPY BE THE MAIN RADIONUCLIDE THERAPY APPROACH IN THE FUTURE?

SUNDAY, 5 OCT, 15:00 - 16:30

MODERATORS: DR. CHIARA GRANA AND DR. CHRISTOPHE DEROOSE

ALPHA-EMITTER THERAPIES: THE NEXT FRONTIER IN RADIONUCLIDE ONCOLOGY

Speaker: Prof. Désirée Deandreis, Institut Gustave Roussy, University of Turin, Villejuif/Turin, France/Italy

Supporters: Carmela Nappi, University of Naples Federico II, Italy; Tadashi Watabe, Osaka University, Japan

Prof. Désirée Deandreis made a compelling case for alpha-emitter therapies as the next transformative leap in radionuclide oncology. She described alpha radiation as offering "a fundamentally different radiobiology," one defined by high linear energy transfer (LET) and ultra short path length, creating concentrated clusters of DNA double strand breaks that are nearly impossible for tumour cells to repair.[27] This unique microdosimetry, she argued, positions alpha therapy to overcome classic mechanisms of radioresistance, particularly in hypoxic or tumour niches that often evade beta-emitters and external beam strategies.

Prof. Deandreis contrasted the familiar beta-based paradigm with the "precision lethality" of alpha particles: only a few traversals through the nucleus are sufficient to induce irreversible apoptosis, with collateral dose to surrounding healthy tissue kept minimal. She explained that multiple alpha-emitting isotopes now form a versatile toolkit, each with distinctive decay chains, energy profiles, and chemical compatibilities. These can be coupled to small molecule ligands, peptides, or monoclonal antibodies, allowing tailoring of isotope vector pairs to tumour biology, target density, and microenvironment.

She noted that the field now encompasses a diverse "family" of alpha emitting isotopes, which she referred to as the "Holy Eight" – each distinguished by its half-life, decay energy, and production route. This growing isotope toolkit, ranging from short-lived to long-lived emitters, enables tailoring of physical and chemical properties to specific biological targets and therapeutic contexts. When coupled to ligands, peptides, or monoclonal antibodies, these isotopes provide a highly adaptable platform for precision oncology.

Prof. Deandreis presented striking preclinical data to strengthen her argument. Across aggressive models such as neuroblastoma and glioblastoma, alpha-emitters have achieved durable remission and even curative responses where beta therapy fails.[28,29,30] In addition to direct cytotoxicity, Prof. Deandreis emphasised growing evidence that alpha radiation can reshape tumour immunogenicity, turning "cold" tumours "hot" by enhancing antigen presentation, T-cell infiltration, and immune activation. These effects create an emerging rationale for combination regimens uniting alpha therapy with immuno-oncology agents.

Early clinical experiences are encouraging. In advanced prostate, neuroendocrine, and thyroid malignancies, alpha-emitter therapies have produced strong biological and clinical responses in heavily pretreated populations, with meaningful further improvements in survival and acceptable toxicity.[31,32] Similar proof-of-concept signals have been observed across tumour types, including in radioresistant and refractory disease settings.[33]

Prof. Deandreis framed alpha therapy not as a replacement to beta-emitters, but as a qualitatively different tool, capable of addressing biological niches unserved by beta-emitters. In her vision, the future of theranostics is layered and adaptive: beta for bulky and heterogeneous disease, alpha for micrometastatic and resistant clones, and combination strategies for maximal synergy. "The promise of alpha therapy," she concluded, "lies in its precision and potency; not in displacing what already works, but in extending the boundaries of what can be cured."

27 Poty, S., Francesconi, L. C., McDevitt, M. R. et al. (2018). α-Emitters for Radiotherapy: From Basic Radiochemistry to Clinical Studies-Part 2. Journal of Nuclear Medicine: official publication, Society of Nuclear Medicine, 59(7), 1020–1027.

28 Lacerda, S., de Kruijff, R. M., & Djanashvili, K. (2025). The Advancement of Targeted Alpha Therapy and the Role of Click Chemistry Therein. Molecules, 30(6), 1296.

29 Ertveldt, T., Krasniqi, A., Ceuppens, H. et al. (2023). Targeted α-therapy using 225Ac radiolabeled single-domain antibodies induces antigen-specific immune responses and instills immunomodulation both systemically and at the tumor microenvironment. Journal of Nuclear Medicine, 64(4), 564–573.

30 Czernin, J., Current, K., Mona, C. E. et al. (2021). Immune-Checkpoint Blockade Enhances 225Ac-PSMA617 Efficacy in a Mouse Model of Prostate Cancer. Journal of Nuclear Medicine: official publication, Society of Nuclear Medicine, 62(2), 228–231.

31 Kratochwil, C., Bruchertseifer, F., Rathke, H. et al. (2018). Targeted alpha therapy of mCRPC with 225Ac-PSMA-617: Swimmer-plot analysis suggests efficacy regarding duration of tumor control. Journal of Nuclear Medicine, 59(5), 795–802.

32 Sathekge, M., Bruchertseifer, F., Vorster, M. et al. (2019). Predictors of overall and disease-free survival in metastatic castration-resistant prostate cancer patients receiving 225Ac-PSMA-617 radioligand therapy. Journal of Nuclear Medicine, 60(9), 1221–1227.

33 Watabe, T., Mukai, K., Naka, S. et al. (2025). First-in-human study of [211At]NaAt as targeted α-therapy in patients with radioiodine-refractory thyroid cancer (Alpha-T1 trial). Journal of Nuclear Medicine, 66(9), 1401–1409.

BETA THERAPY: THE BACKBONE OF THERANOSTIC ONCOLOGY

Speaker: Prof Clément Bailly, Nantes University Hospital, Nuclear Medicine, Nantes, France

Supporters: Mathilde Colombié, St. Vincent's University Hospital, Ireland; Matteo Bauckneht, University of Genoa, Italy

Taking the opposing stance, Prof. Clément Bailly delivered a measured, evidence-based argument that while alpha-emitters are scientifically exciting, the beta-based backbone of theranostic oncology remains far from obsolete. He began by acknowledging the elegance of alpha physics but warned that clinical medicine advances through validation, not fascination. "We must distinguish biological potential from proven benefit," he said, noting that beta-emitters have already earned regulatory approval through multiple Phase 3 trials and have demonstrated reproducible survival gains across large, heterogeneous patient populations.

Prof. Bailly highlighted the crossfire effect of beta radiation as a pragmatic advantage rather than a limitation. In real tumours, marked by variable perfusion, necrosis, and heterogeneous antigen expression, the millimetre scale path of beta particles provides coverage beyond the cells that physically bind the radiopharmaceutical, sterilising neighbouring malignant cells and compensating for imperfect targeting. He highlighted that in the clinic, heterogeneity is the rule, not the exception. "Crossfire is our ally," he argued.

He then outlined the maturity of the beta therapy ecosystem. Radiolabelled peptide and ligand therapies targeting somatostatin receptors and prostate-specific membrane antigens (PSMA) have already established international standards of care. Robust dosimetry workflows, retreatment protocols, and combination trials integrating beta therapy with DNA repair inhibitors, chemotherapy, and immunotherapy are well underway. In comparison, alpha therapy remains mostly in early phase and compassionate use settings. When scaled to larger patient cohorts, alpha therapy still faces challenges in dosimetry, reproducibility, and manufacturing consistency.

Addressing the technical limitations of alpha-emitters, Prof. Bailly highlighted that recoil of radioactive daughters can cause partial detachment from the targeting vector, redistributing activity and creating uncertainty around absorbed dose and long-term toxicity.[34] He also noted supply constraints, radioactive waste management, and short isotope half-lives that require specialised handling and depend on limited global production capacity. The complex physics of microdosimetry further complicate patient-specific dose estimation compared with beta therapy.

For Prof. Bailly, these challenges reinforce a central thesis: beta therapy is scalable, standardised, and safe — qualities essential for population-level impact. "We cannot yet promise every centre an alpha generator," he remarked, "but we can ensure every patient access to beta therapy." He acknowledged that alpha therapy will serve important niche roles in micrometastatic disease, beta-refractory relapse, and tumours favouring ultra-high LET, but said that, "innovation must meet reproducibility," he concluded. "Until it does, beta therapy remains the anchor of theranostic oncology, while alpha continues its promising but unvalidated ascent."

Discussion Highlights

Moderators Dr. Chiara Grana and Dr. Christophe Deroose led a dynamic discussion with live polling and audience Q&A, reflecting optimism toward alpha therapy without displacing the established beta-therapy backbone.

Dosimetry and Toxicity:

- Prof. Deandreis and Prof. Bailly agreed that dosimetry is essential for both modalities, with beta workflows currently more advanced.
- Prof. Bailly cited robust clinical evidence linking personalised beta dosimetry to improved outcomes.
- Prof. Deandreis highlighted emerging *daughter-aware dosimetry* and *surrogate imaging* techniques for alpha-emitters.
- Discussion on *marrow, renal, and salivary dose constraints* underscored the need for toxicity-centred α dosimetry harmonisation.

Isotope Physics and Production:

- Longer-chain alpha-emitters pose challenges with daughter recoil and redistribution.
- Shorter-lived isotopes simplify waste handling but require localised radiochemistry capacity.
- Prof. Deandreis and Prof. Bailly agreed that expanding *industrial production* and *regulatory coordination* will be key to ensuring future supply stability.

Adjuvant and Early-Stage Settings:

- Prof. Deandreis argued that alpha therapy is biologically suited to micrometastatic disease, pending validation of toxicity thresholds and imaging selection.
- Prof. Bailly added that ongoing adjuvant beta therapy trials show promise, but early-stage use must weigh benefit versus toxicity in low-burden disease.

Audience Polling Results:

- Alpha-emitters were preferred for *micrometastatic or minimal residual disease* due to their short path length and high-LET precision.
- Beta therapy remained favoured for *bulky or heterogeneous lesions*, where crossfire coverage offers greater efficacy.
- Sequential or combination approaches received the most support, highlighting a consensus that alpha and beta therapies are c*omplementary rather than competitive.*

34 de Kruijff, R. M., Wolterbeek, H. T., & Denkova, A. G. (2015). A Critical Review of Alpha Radionuclide Therapy-How to Deal with Recoiling Daughters? Pharmaceuticals (Basel, Switzerland), 8(2), 321–336.

4 CME 4: CARDIOVASCULAR COMMITTEE - TOTAL BODY IMAGING: THINK BIG, THINK FORWARD! (CARDIO)

SUNDAY, 5 OCT, 16:45 - 18:15, AUDITORIUM

CHAIRS: DR. CARMELA NAPPI AND PROF. STEPHAN NEKOLLA

FROM CARDIAC SPECT TO WHOLE-BODY QUANTIFICATION

Speaker: Dr. Laetitia Imbert, Department of Nuclear Medicine and Nancyclotep Imaging Platform, IADI, INSERM U1254, Université de Lorraine, CHRU Nancy, France

Dr. Laetitia Imbert opened the session by tracing the evolution from traditional scintillation cameras to cadmium–zinc–telluride (CZT) digital detectors, marking a major step forward in nuclear medicine technology. Since their introduction to cardiac SPECT in 2010, CZT systems have overcome the limitations of conventional sodium-iodide detectors by providing direct photon conversion, higher energy resolution, and substantially increased sensitivity.

Dr. Imbert explained how transitioning from analog to pixelated CZT detectors enhances intrinsic spatial resolution and allows for more compact system geometries, which position the detectors closer to the patient. The first generation of dedicated cardiac CZT systems exhibited four- to seven-fold greater sensitivity compared to conventional SPECT systems, resulting in reduced injected activities and faster protocols. This technology is now adapted for whole-body imaging, utilising multiple swivelling detectors to achieve near-simultaneous 360-degree coverage, integrated with CT for tissue characterisation.

Dr. Imbert described two primary acquisition modes: focused single-bed imaging, typically used for a limited field of view, such as in cardiac and dynamic studies, and whole-body multi-bed imaging, which mimics PET workflows. Advanced reconstruction algorithms now incorporate attenuation, scatter, and resolution recovery corrections, allowing for quantitative accuracies with only 5 and 10 percent error for technetium-99m[35] and lutetium-177[36], respectively.

From a clinical point of view, long axial field-of-view CZT systems offer improved performance and a higher image quality, particularly in high body weight patients, and they support absolute quantification using Standard uptake value (SUV)-based analysis. Image quality and quantitative reliability bring SPECT closer to PET standards, expanding its potential from dedicated cardiac studies to total-body functional and theranostic applications. Dr. Imbert concluded that these cameras represent a transformative advance, with high sensitivity, precise quantification, and broad clinical applications in a single platform.

35 Seret, A., & Bernard, C. (2025). A critical phantom study of the energy window used for 99mTc quantitative explorations with a ring CZT SPECT system. EJNMMI physics, 12(1), 79.

36 Danieli, R., Stella, M., Leube, J. et al. (2023). Quantitative 177Lu SPECT/CT imaging for personalized dosimetry using a ring-shaped CZT-based camera. EJNMMI physics, 10(1), 64.

BRIDGING THE QUANTITATIVE GAP IN CARDIOVASCULAR IMAGING

Speaker: Dr. Johanna Diekmann, Department of Nuclear Medicine, Hannover Medical School, Hannover, Germany

Dr. Johanna Diekmann presented on the clinical translation of CZT technology, particularly its role in myocardial perfusion imaging and the quantification of myocardial blood flow (MBF) and myocardial flow reserve (MFR). Over the past decade, advances in detector design, reconstruction, and acquisition have transformed myocardial perfusion SPECT, with CZT solid-state cameras driving this shift through higher energy resolution, lower radiation dose, and dynamic quantitative capability.

Dr. Diekmann reviewed the routine advantages of CZT imaging, highlighting stress-first or stress-only protocols that minimise total scan time and radiation dose. Integrated CT attenuation correction markedly reduces artefacts and enhances diagnostic confidence, particularly in women and individuals with obesity. Quantitative MBF and MFR analyses provide added prognostic value beyond conventional perfusion scores, revealing diffuse or microvascular disease that may not be evident on relative imaging.[37]

Results from multicentre validation studies confirm the reproducibility and clinical reliability of CZT-derived MBF and MFR,[38] although standardisation across tracers, stress agents, and software remains essential. Real-world

data further demonstrates strong correlations between stress MBF, left-ventricular ejection fraction, and disease severity, with attenuation correction improving accuracy without altering flow reserve measurements.[39]

Dr. Diekmann compared CZT SPECT with PET, emphasising that while PET remains the gold standard for absolute quantification, CZT systems deliver comparable diagnostic and prognostic performance with lower cost, greater availability, and substantially lower radiation burden. Looking ahead, she highlighted the role of artificial intelligence in motion correction, input-function extraction, and attenuation correction, including promising results from deep-learning-based virtual attenuation correction that eliminated artifacts and improved specificity.[40]

37 Assante, R., Zampella, E., Cantoni, V. et al. (2023). Prognostic value of myocardial perfusion imaging by cadmium zinc telluride single-photon emission computed tomography in patients with suspected or known coronary artery disease: a systematic review and meta-analysis. European journal of nuclear medicine and molecular imaging, 50(12), 3647–3658.

38 de Souza, A. C. D. A. H., Harms, H. J., Martell, L. et al. (2022). Accuracy and Reproducibility of Myocardial Blood Flow Quantification by Single Photon Emission Computed Tomography Imaging in Patients with Known or Suspected Coronary Artery Disease. Circulation. Cardiovascular imaging, 15(6), e013987.

39 Wieting, W., Bengel, F. M., & Diekmann, J. (2025). Comparison of global and regional myocardial blood flow quantification using dynamic solid-state detector SPECT and Tc-99 m-sestamibi or Tc-99 m-tetrofosmin in a routine clinical setting. The International Journal of Cardiovascular Imaging, 41(1), 537–548.

40 Sprauel, T., Imbert, L., Doyeux, K. et al. (2025). Assessment of sestamibi CZT-SPECT reconstructed using deep-learning-based virtual attenuation correction maps according to coronary artery territory and with comparison to rubidium-PET. Journal of nuclear cardiology: official publication of the American Society of Nuclear Cardiology, 49, 102226.

ENTERING THE FAST LANE WITH WALK-THROUGH PET

Speaker: Prof. Stefaan Vandenberghe, Department of Electronics and Information Systems, Medical Image and Signal Processing (MEDISIP), Ghent University, Belgium

Prof. Stefaan Vandenberghe provided an in-depth overview of the technological frontiers in PET, highlighting how innovation now extends far beyond simply increasing the axial field of view. He outlined advances in deep learning across the PET pipeline, high-resolution detectors with depth-of-interaction capability, ultra-fast time-of-flight systems enabling near-direct image formation, and multi-tracer or positron-lifetime imaging, all converging to enhance image quality and efficiency.

While long axial field-of-view scanners deliver outstanding sensitivity and whole-body dynamic imaging, Prof. Vandenberghe noted their cost and operational constraints. This challenge inspired his team to explore a disruptive alternative: the walk-through PET concept. Similar in form to an airport security scanner, the system uses two opposing flat-panel detectors to capture high-resolution total-body images of a standing patient in under a minute.

Initiated in 2022, modelling studies demonstrate that walk-through PET could achieve component costs approximately 3.3 times lower than long axial systems and throughput nearly three times higher. Compared with short field-of-view scanners performing 28 scans per eight-hour day, walk-through prototypes could exceed 80, while reducing radiotracer costs by up to 66% per patient. These results highlight the potential of walk-through PET as a practical and scalable solution for high-volume clinical environments.[41]

Prof. Vandenberghe concluded that the next generation of PET will pair smarter detectors with intelligent reconstruction to deliver faster, sharper, and more accessible molecular imaging. Walk-through total-body PET, he said, represents a paradigm shift with the potential to transform high-sensitivity imaging from an elite research capability into a routine clinical tool.

41 Vandenberghe, S., Muller, F. M., Withofs, N. et al. (2023). Walk-through flat panel total-body PET: a patient-centered design for high throughput imaging at lower cost using DOI-capable high-resolution monolithic detectors. European journal of nuclear medicine and molecular imaging, 50(12), 3558–3571.

LAFOV PET: THE SWISS-ARMY-KNIFE OF CARDIOVASCULAR AND SYSTEMIC IMAGING

Speaker: Dr. Federico Caobelli, Department of Nuclear Medicine, University of Bern, Bern, Switzerland

Dr. Federico Caobelli concluded the session by describing how long-axial-field-of-view (LAFOV) PET systems are transforming cardiovascular imaging. He explained that modern digital LAFOV PET delivers up to an eight-fold gain in sensitivity over conventional scanners, enabling high-quality imaging with lower radiation exposure and shorter acquisition times. With axial coverage exceeding one metre, these systems can simultaneously visualise all major organs relevant to cardiovascular disease.

Dr. Caobelli characterised LAFOV PET as an advanced "Swiss-army-knife" technology that combines flexibility, sensitivity, and efficiency within a single platform. Its extended coverage supports dynamic, quantitative imaging across organ systems, facilitating the study of inter-organ relationships such as the brain–heart, gut–heart, and kidney–heart axes.[42] This integrated perspective is particularly valuable for understanding systemic processes like atherosclerosis and inflammation.

Enhanced sensitivity enables ultra-fast whole-body scans within two to three minutes, which is significantly faster than conventional 15–20-minute protocols. The result is improved comfort for frail or critically ill patients while maintaining diagnostic quality. Late-time-point imaging further refines the distinction between perfusion and inflammation, aiding evaluation of conditions such as vasculitis and cardiac sarcoidosis. The system's sensitivity also allows detection of subtle or low-grade infections, including prosthetic biofilms and cranial vessel inflammation.

Dr. Caobelli noted that dynamic whole-body imaging now allows detailed kinetic analysis of glucose metabolism, helping differentiate infection from inflammation. LAFOV PET performs consistently well even in technically challenging patients, and its quantitative precision enhances detection of coronary plaque activity and large-vessel vasculitis, although thresholds must be recalibrated for higher sensitivity.

He concluded by emphasising LAFOV PET's potential for dose reduction and workflow optimisation, supporting low-exposure, high-efficiency imaging. Dr. Caobelli believes the future of cardiac PET is dynamic, quantitative, and whole-body in scope, with LAFOV technology serving as a versatile platform that unites cardiovascular and systemic disease imaging.

42 Valenza, G., Matić, Z., & Catrambone, V. (2025). The brain-heart axis: integrative cooperation of neural, mechanical and biochemical pathways. Nature reviews. Cardiology, 22(8), 537–550.

5 JOINT SYMPOSIUM 4 - AI COMMITTEE / EFMOP: TRUSTFUL AI IN THE CLINIC

MONDAY, 6 OCT, 15:00 - 16:30

CHAIRS: EFI KOUTSOUVELI AND DR. DIMITRIS VISVIKIS

PREPARING FOR THE EU AI ACT

Speaker: Selina Zipponi, Global Data Protection Officer, Milan, Italy

Selina Zipponi opened the joint symposium with an overview of the rapidly evolving European regulatory framework for AI in clinical medicine. Centring on the EU Artificial Intelligence Act, adopted in mid-2024, she outlined how this first-of-its-kind legislation will progressively take effect, shaping trust, ethics, and transparency in medical AI.

The first milestone, in February 2025, banned high-risk practices such as social scoring and emotional recognition in workplaces and education. Starting from August 2025, general-purpose model providers must meet transparency obligations, and by August 2027, full requirements for high-risk AI systems, including those used in medical devices, will apply.

Zipponi clarified the Act's definition of providers, distributors or importers, and deployers, stressing that liability and documentation duties differ between these actors. Most AI medical devices will be deemed high risk, requiring conformity assessment, data governance, post-market surveillance, and proof of traceability, bias control, cybersecurity, and human oversight, under both the AI ACT and the Medical Device Regulation (MDR).

Ethically, she underscored the importance of transparency and the continued centrality of clinicians. AI outputs must be explainable and open to human reinterpretation. For example, a lung nodule detector should display confidence levels and allow radiologists to disregard false positives.

Hospitals, acting as deployers, must designate qualified supervisors, maintain audit trails, and report anomalies. Creating AI oversight committees that include medical physicists, data protection officers, and clinicians was recommended as best practice.

In discussion, participants asked how oversight quality and staff training will be evaluated. Zipponi noted that hospitals must define local governance and documentation processes, while European Federation of Organisations for Medical Physics is embedding AI ethics and governance into the medical physicist curriculum.

Zipponi stressed that the AI Act complements the MDR. The MDR ensures safety and performance, while the AI Act secures ethical and trustworthy use. Her key message was that different stakeholders should act now to build oversight structures, training, and reporting systems ahead of the Act's full enforcement in 2027.

EXPLAINABLE AI IN NUCLEAR MEDICINE:

Speaker: Mathieu Hatt, Director of Research, INSERM, LaTIM UMR1101, Brest, France

Mathieu Hatt followed with a technically grounded exploration of explainable AI, a concept central to building clinician trust in automated systems. He distinguished between interpretability, which enables developers to understand internal model behaviour, and explainability, which translates that understanding into clinically meaningful forms. In healthcare, he emphasised, explanation is not a luxury but a necessity: it underpins trust, regulatory compliance, and scientific discovery.

To illustrate the pitfalls of opacity, he invoked the "Clever Hans" analogy—models that appear accurate but rely on spurious correlations, such as background artefacts rather than true information. Explanations, whether visual or textual, are essential to expose such bias in the data or unwanted behaviour.

He described two main strategies for generating explanations: interpretable-by-design models, which make reasoning transparent through explicit rules or sparse representations, and post-hoc methods that analyse black-box networks after training. The latter may use gradients, activations, or perturbation tests to infer which input features drive outputs, though not all saliency or attribution maps are reliable. Some simply highlight edges or noise.

Presenting a case study using CT data, Hatt compared several popular saliency techniques, including integrated gradients and Grad-CAM variants, showing that their outputs can diverge markedly even for identical inputs. To address this, his team developed a fidelity metric that quantifies how faithfully a map reflects true model

dependency: model performance should drop when important pixels are perturbed but remain stable when unimportant ones are altered. This quantitative fidelity index, validated across two architectures, enables objective comparison without relying on comparison with human reference.

Hatt then explained how these principles could be applied to nuclear medicine, where PET and SPECT applications demand trustworthy visualisations that link quantitative outputs to physiological meaning. He emphasised that explanations should be concise, selective, and counterfactual-friendly. For example, "the risk score is high because lesion volume and uptake ratio exceeded thresholds; if uptake were lower, the classification would change." Such clarity allows clinicians to understand and challenge model outputs.

In practical terms, he advised teams to prioritise interpretable models when possible, validate any explainability method with fidelity tests before deployment, ensure perturbations remain realistic, and co-design explanatory interfaces with clinicians. Explanations should be logged and auditable alongside predictions to support traceability and bias monitoring.

During discussion, participants asked how to explain non-image data such as text reports or hybrid imaging outputs. Hatt suggested combining feature-attribution tools for tabular variables with image-based visualisations so that each modality's contribution remains explicit.

He concluded that explainability is inseparable from safety and reliability. In nuclear medicine, where AI increasingly supports complex multimodal analysis, transparent reasoning bridges the gap between computational prediction and clinical judgement, enabling adoption that is both confident and accountable.

BUILDING CLINICAL TRUST IN AI FOR IMAGING

Speaker: Oliver Díaz, Department of Mathematics and Computer Science, University of Barcelona, Spain

Dr. Oliver Díaz concluded the symposium by examining what it truly means for AI in imaging to be trustworthy. He defined trust as a justified belief that a system will act appropriately in a clinical situation. In nuclear medicine and radiology, where AI increasingly informs diagnostic and therapeutic decisions, that belief must rest on transparency, reproducibility, and ethical governance.

He contrasted the vast research output in imaging AI, with over 70,000 publications in the past 25 years, with the relatively few clinically validated systems, only a few hundred with regulatory clearance. Citing a European Radiology analysis, he noted that 64% of AI tools lack published proof of effectiveness and only 18% show potential clinical impact.[43] Approval, he cautioned, does not equal trust. Many commercial tools still lack peer-reviewed evidence of clinical benefit, and their real-world performance remains uncertain.

Dr. Díaz outlined three core principles for establishing trust in clinical AI. The first is model provenance, ensuring clarity on where a model originates and how it was developed. The second is output assurance, providing interpretable confidence scores that help clinicians judge reliability. The third is governance, defining clear accountability for oversight and incident reporting. He illustrated these principles with a mammography example in which an AI tool required the radiologist to interpret probability scores and review an explanatory overlay before confirming a result.

He highlighted the lack of suitable evaluation metrics as a recurring risk. Traditional measures such as Dice coefficients can mask serious failures, as high scores may still miss small but critical lesions. He called for task-appropriate evaluation using lesion-wise sensitivity, calibration, and utility curves, or perceptual and task-based metrics for synthetic imaging that capture diagnostic equivalence better than simple pixel-level similarity.

Dr. Díaz referenced the Metrics Reloaded initiative,[44] which promotes fit-for-purpose assessment, and the FUTURE-AI consensus framework,[45] which defines six pillars of trustworthy imaging AI, including fairness, robustness, and explainability. Within this framework, transparency requires disclosure of dataset biases, subgroup performance, and generalisation tests so users can judge where and when a model can be trusted.

Looking ahead, he introduced the AI Passport, a digital record developed within the EU RadioVal project.[46] This living document captures dataset lineage, training splits, subgroup performance, known failure modes, and change logs, enabling traceability and post-market monitoring. The goal is to make such documentation routine across all clinical AI systems.

In discussion, participants considered the balance between automation and the legal requirement for human oversight under the EU AI Act. Dr. Díaz cautioned that forthcoming autonomous decision-support pilots must align innovation with accountability. Audience questions focused on current regulatory approvals in nuclear medicine and on scaling the AI Passport concept. He confirmed that work is ongoing to refine and standardise the framework for wider adoption.

Closing the symposium, the Chairs summarised that ethical governance, transparency, and explainability form the foundation of clinical trust in AI. The three talks converged on a common vision in which regulatory compliance ensures safety, explainability fosters understanding, and trustworthy design anchors confidence. Together, these pillars define a roadmap toward responsible and sustainable AI integration in nuclear medicine.

43 van Leeuwen, K. G., Schalekamp, S., Rutten, M. J. C. M. et al. (2021). Artificial intelligence in radiology: 100 commercially available products and their scientific evidence. European Radiology, 31(6), 3797–3804.

44 Metrics Reloanded. A framework for trustworthy image analysis validation. https://metrics-reloaded.dkfz.de/

45 Lekadir, K., Frangi, A. F., Porras, A. R. et al. (2025). FUTURE-AI: International consensus guideline for trustworthy and deployable artificial intelligence in healthcare. BMJ, 388, e081554.

46 Radioval. Empowering personalised treatment of breast cancer patients. https://radioval.eu/

6 SPECIAL TRACK 8 - NEUROIMAGING COMMITTEE - ROUND TABLE: TAU PET IMAGING: READY FOR CLINICAL USE

MONDAY, 6 OCT, 16:45 - 18:15

CHAIRS: PROF. ALEXANDER DRZEZGA AND DR. ELSMARIEKE VAN DE GIESSEN

THE CLINICAL READINESS OF TAU PET IMAGING

Speaker: Dr. Ruben Smith, Lund University, Sweden

Dr. Ruben Smith opened the Committee Round Table by addressing the central question of whether tau PET imaging is technically and operationally ready to move from research to clinical use. He began by mapping the global landscape of tracer availability, highlighting significant regional disparities in access, before reviewing first- and second-generation tracers. He noted that while all reliably detect tau pathology, they differ subtly in their kinetics and off-target binding.

Dr. Smith observed that the field has matured rapidly since the first proof-of-concept studies less than a decade ago. Image quality, dynamic range, and radiation exposure have now converged toward clinically acceptable standards. Typical acquisition protocols, involving tracer administration followed by a 60-to-80-minute uptake period and a 20-to-30-minute static acquisition, yield consistent and reproducible images across centres. These improvements, he said, demonstrate the technical readiness of tau PET for clinical application.

The remaining challenge, in his view, is not physics but harmonisation. Dr. Smith highlighted the CenTauR project, an international initiative to create a unified quantitative scale analogous to the Centiloid system for amyloid imaging.[47] By performing head-to-head comparisons between tracers, this framework aims to express tau burden on a common numerical scale independent of the compound used. However, several tracer pairs have not yet been directly compared. Completing this calibration matrix will be essential to ensure reliable comparisons across studies and centres.

He also stressed that implementation depends on harmonised reconstruction parameters, shared quality control standards, and regulatory alignment across jurisdictions. The absence of established commercial distribution channels continues to limit access, even for tracers already approved in selected regions. Dr. Smith called for coordinated action through professional societies to strengthen manufacturing, distribution, and training at a continental level.

Discussion Highlights

- **Access and production:** The panel agreed that the absence of centralised tracer production and inconsistent reimbursement structures across Europe continue to restrict equitable access to tau PET.
- **Professional coordination:** Ms. Vermeiren proposed that professional societies collaborate to advocate for harmonised training on approved tracers.
- **Clinical prioritisation:** Dr. Gregory Mathoux emphasised that Alzheimer's disease should be prioritised as the initial indication before expanding to other non-Alzheimer's tauopathies.
- **Audience perspectives:** Questions focused on the feasibility of early-phase imaging protocols following clinical trials and highlighted reimbursement inconsistencies for the three available tau tracers in Europe, citing Germany and Sweden as examples.
- **Shared consensus:** Panellists agreed that the technology itself is ready. Remaining challenges involve establishing clear regulatory and economic frameworks to support integration into clinical workflows.

47 Villemagne, V. L., Leuzy, A., Bohorquez, S. et al. (2023). CenTauR: Toward a universal scale and masks for standardizing tau imaging studies. Alzheimer's & dementia (Amsterdam, Netherlands), 15(3), e12454.

INTERPRETING TAU PET: FROM BINARY READS TO BIOLOGICAL CONTINUUM

Speaker: Dr. Gregory Mathoux, University of Geneva, Switzerland

Dr. Gregory Mathoux focused on the interpretive dimension of tau PET, presenting current methodologies for visual reading and the evolving challenge of defining positivity across the disease continuum. He began by outlining the regulatory landscape, noting that only one tracer currently holds formal approval with a validated visual read procedure, while newer agents have proposed but not yet endorsed methods. This gap underscores the need for harmonised interpretation across tracers and centres.

Using illustrative cases, Dr. Mathoux demonstrated typical features of normal and abnormal scans and explained how reader training can mitigate the influence of off-target binding. Physiological uptake in structures such as the basal ganglia, choroid plexus, and meninges can mimic pathology if not properly recognised. Modern high-resolution scanners combined with reader experience allow reliable differentiation between genuine cortical signal and artefactual spill-in. He emphasised that reproducibility between trained readers now approaches that of other neuroimaging modalities, supporting clinical scalability.

Dr. Mathoux described the principles of the standard visual read algorithm, which involves defining a cerebellar reference, applying a consistent threshold, and systematically assessing four temporal quadrants before determining whether neocortical involvement is present. This structured approach, he said, provides high sensitivity and specificity for detecting advanced tau deposition corresponding to later Braak stages. However, he cautioned that its binary outcome, positive or negative, fails to capture the earliest manifestations of disease.

A key focus of his talk was the debate surrounding mesial temporal-only uptake. Current regulatory guidance requires that scans showing isolated signal in this region be classified as negative. Yet longitudinal studies demonstrate that such individuals, particularly those who are amyloid-positive, have an increased risk of cognitive decline and progression to mild cognitive impairment or dementia.[48] Dr. Mathoux argued that rigid binary classification does not reflect biological reality and advocated for descriptive terminology acknowledging early or limited tau pathology. He suggested that a report phrased as "not consistent with advanced Alzheimer-type tauopathy" better conveys clinical nuance without over-interpreting early findings. He also emphasised that clinicians should interpret negative results in the context of tracer sensitivity, disease stage, and complementary biomarker data.

Discussion Highlights

- **Interpretation of early-stage findings:** The discussion focused on how clinicians should interpret ambiguous or early tau PET results. Dr. Mathoux explained that his centre classifies isolated mesial temporal uptake as "possibly consistent with early Braak I–III pathology" and recommends follow-up after approximately two years.
- **Prognostic value:** Dr. Smith emphasised that even subtle medial temporal signals can refine prognosis when interpreted alongside amyloid or plasma p-tau biomarkers.
- **Tracer sensitivity:** It was noted that second-generation tracers show greater sensitivity to early pathology and cautioned that a "tau-negative" report can therefore be misleading. Chair Prof. Alexander Drezga agreed, suggesting reports use the phrasing "not consistent with advanced Alzheimer-type tauopathy" rather than simply "negative."
- **Consensus:** The panel agreed that tau PET interpretation should move away from binary classification and toward a biologically continuous model that reflects both disease stage and therapeutic context. Dr Mathoux proposed that future reading guidelines adopt graded categories such as limited, moderate, and extensive involvement, integrating visual reads with quantitative metrics for greater consistency. He concluded that tau PET interpretation should evolve from a dichotomy to a continuum that mirrors the biology of neurodegeneration.

48 Ossenkoppele, R., Pichet Binette, A., Groot, C. et al. (2022). Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. Nature medicine, 28(11), 2381–2387.

QUANTITATIVE TAU PET STAGING: INTEGRATING VISUAL INTERPRETATION WITH QUANTITATIVE METRICS

Speaker: Dr. Elena Doering, Research Centre Juelich, Germany

Dr. Elena Doering advanced the discussion by presenting a framework for quantitative staging of tau PET images designed to complement rather than replace visual interpretation. She argued that while visual reads provide rapid and clinically intuitive assessments, they compress a biologically continuous process into coarse categories (e.g., positive and negative). Quantitative staging restores nuance, potentially allowing more precise longitudinal tracking and closer alignment with disease progression models.

She presented studies that adapt the classical Braak framework into an in vivo metric by mapping predefined regions of interest corresponding to successive stages of tau spread. Each subject is assigned the highest consecutively positive stage, yielding an intuitive Braak in vivo score that parallels post-mortem neuropathology. Longitudinal data from one- and two-year follow-ups show that this staging increases predictably with clinical progression, supporting its biological validity.[49,50]

Dr. Doering noted that Alzheimer's disease is not always characterised by the same spatial pattern. Recent studies have revealed variant tau topologies ('subtypes'), such as posterior predominant, temporoparietal, asymmetric, and medial temporal sparing forms, each linked to distinct clinical trajectories.[51] To reflect these phenotypic differences, she proposed subtype-aware metrics or lateralised staging may provide valuable information, enabling clinicians to monitor not only total tau burden but also evolving spatial patterns in a patient-centric manner.

Beyond stage assignment, she introduced continuous spatial extent quantification, illustrated by the "fill state" metric, which measures the percentage of brain volume affected by tau pathology relative to a normative reference. Tau fill states demonstrated a stronger association with cognitive impairment severity than mean uptake values, suggesting their potential to enhance early detection and monitoring of Alzheimer's disease. Dr. Doering further noted that the concept of fill states is versatile and could potentially be extended to quantify the degree of affectedness of any brain region of interest.[52]

For molecular imaging reports, Dr. Doering proposed a structured reporting workflow. First, a visual summary should specify whether the scan is positive, negative, or limited to medial temporal regions and highlight any atypical or asymmetric pattern. Second, a quantitative section should detail tracer and protocol parameters, the derived Braak in vivo stage, spatial extent markers such as fill states, and optionally mean uptake ratios for key regions, especially in atypical presentations. Third, an interpretive statement could integrate these findings with complementary findings such as amyloid PET and relevant clinical characteristics, providing diagnostic and prognostic context.

Discussion Highlights

- **Quantitative metrics in clinical workflows:** The panel and audience discussed the practical challenges of integrating quantitative metrics into routine tau PET interpretation. While many of the solutions presented in research are available on open-source platforms, visual approximations of them may be required until they are readily integrated in imaging software available to clinicians.
- **Sensitivity to progression:** Dr. Smith and Dr. Doering discussed that while changes in mean intensity are rather small over the time course of 1-2 years, spatial extent increases may be more evident and thus more sensitive to disease progression and treatment response.
- **Asymmetry:** The audience asked about the potential utility in monitoring spatial extent in only one hemisphere in highly asymmetrical cases, while it was agreed that tau spread across hemispheres may still represent an important clinical milestone and should not be disregarded.
- **Standardisation across tracers**: It was emphasised that standardising extent measures across tracers would reduce inter-tracer variability and that harmonising CE-marked implementations could accelerate clinical adoption. The audience further suggested that inter-tracer variability of spatial extent may be smaller compared to mean intensity values, thereby potentially mitigating the need for harmonisation.
- **Consensus:** The panel concluded that quantitative staging represents the bridge between research-level precision and clinical interpretability, particularly for longitudinal assessment, treatment outcome monitoring, and standardised communication across centres. The future of tau imaging, Dr. Doering said, lies in combining visual expertise with quantitative precision within harmonised frameworks.

49 Therriault, J., Pascoal, T. A., Lussier, F. Z. et al. (2022). Biomarker modeling of Alzheimer's disease using PET-based Braak staging. Nature aging, 2(6), 526–535.

50 Therriault, J., Schindler, S. E., Salvadó, G. et al. (2024). Biomarker-based staging of Alzheimer disease: rationale and clinical applications. Nature reviews. Neurology, 20(4), 232–244.

51 Fleisher, A. S., Pontecorvo, M. J., Devous, M. D. et al. (2020). Positron Emission Tomography Imaging With [18F]flortaucipir and Postmortem Assessment of Alzheimer Disease Neuropathologic Changes. JAMA neurology, 77(7), 829–839.

52 Doering, E., Hoenig, M. C., Giehl, K. et al. (2025). "Fill States": PET-derived Markers of the Spatial Extent of Alzheimer Disease Pathology. Radiology, 314(3), e241482.

OP-023 HARMONISING VISUAL READS ACROSS TRACERS AND THE PATH TOWARD CLINICAL INTEGRATION

Speaker: Ms. Marie R. Vermeiren, Amsterdam UMC, The Netherlands

Ms. Marie R. Vermeiren concluded the round table by addressing one of the field's most urgent needs: a unified visual read framework applicable across the growing family of tau PET tracers. She noted that current protocols, developed independently for different compounds, vary in scaling, thresholding, and categorical structure. While each performs well within its own context, this diversity hinders comparison between centres.

Presenting early results from the multicentre HEAD study, Ms. Vermeiren described a harmonisation effort grounded in direct head-to-head comparisons. Approximately 200 paired scans were evaluated across several tracers, with visual ratings performed by multiple experienced readers. Preliminary analyses show excellent inter-rater reliability, with agreement coefficients around 0.9, supporting the feasibility of a harmonised classification. The emerging system employs five intuitive categories (negative, low, moderate, high and non-AD) that can be mapped across tracers while retaining sensitivity to biological gradation.

Ms. Vermeiren emphasised that harmonisation should not obscure the distinctive sensitivity profiles of individual tracers but instead align interpretive language so that a patient's classification remains consistent regardless of tracer or scanner. Achieving this requires visual calibration, harmonised reconstruction parameters, recognition of scanner characteristics, and prospective validation against neuropathology.

Ms. Vermeiren drew parallels with the evolution of cerebrospinal fluid biomarker assays, cautioning against the early fragmentation that delayed their clinical acceptance. She emphasised that a unified reading framework would facilitate multicentre trials, support regulatory approval, and provide the consistency needed for reimbursement. Integration of quantitative descriptors such as spatial extent or stage within the visual read form is the logical next step, bridging categorical and continuous assessment.

Discussion Highlights

- **Unified categorical framework:** The panel and audience discussed the feasibility of cross-tracer harmonisation, with the panel agreeing that adopting a shared categorical scale – such as negative, low, moderate, high – would enhance consistency across centres.
- **Technology considerations**: The audience noted that harmonisation should also encompass scanner technology, as newer digital PET systems influence image resolution and threshold behaviour.
- **Neuropathological and regulatory alignment:** Audience members highlighted the need for neuropathological correlation and regulatory recognition to support broader clinical adoption.
- **Clinical usability:** Dr. Mathoux stressed maintaining clinical practicality, cautioning against overly technical reporting formats that could hinder day-to-day interpretation.
- **Consensus:** Scientific readiness has been achieved, but harmonisation and coordinated integration are the next frontier.

7 EU POLICY SYMPOSIUM 1 - FROM POLICY TO PATIENTS: BUILDING READINESS FOR NUCLEAR MEDICINE INNOVATION IN EUROPE

TUESDAY, 7 OCT, 08:00 - 09:30

CHAIRS: PROF. WIM OYEN AND PROF. PAOLA ANNA ERBA

SIMPLERAD: ADVANCING HARMONISATION IN THERAPEUTIC RADIOPHARMACEUTICALS

Speaker: Prof. Michael Lassmann, University Hospital Würzburg, Germany

Prof. Michael Lassmann opened the symposium via webcam with an in-depth presentation on the outcomes and legacy of the EU-funded SIMPLERAD project, which has played a pivotal role in shaping the regulatory and practical landscape for therapeutic radiopharmaceuticals across Europe. He explored how SIMPLERAD addresses inconsistencies in radiation protection, pharmaceutical regulation, and clinical implementation, providing an evidence-based foundation for harmonised standards and future policy initiatives.

The project, organised with input from EURADOS, EANM, and multiple professional societies, conducted a comprehensive legislative review and a major survey with almost 200 responses from 40 countries[53]. The results demonstrate ongoing inconsistencies in the implementation of the Basic Safety Standards Directive (BSSD), variability in patient release criteria, ambiguity in professional roles such as the Medical Physics Expert, and inequities in clinical practice and regulatory interpretation across Member States.

Prof. Lassmann explained that these findings, along with other open topics identified by the consortium and confirmed by stakeholders, resulted in the project's ten key recommendations, as outlined in the project's 137-page final report.[1] This document also includes practical guidance on treatment planning and verification for five therapeutic use cases and refers to an EANM guidance document on dosimetry for first-in-human studies and early clinical trials.

The key findings of the SIMPLERAD project form the technical backbone for upcoming harmonisation work led by the European Medicines Agency (EMA) and the European Commission. Prof. Lassmann also referenced the EMA's forthcoming guidelines on the clinical evaluation of therapeutic radiopharmaceuticals, planned for 2026, as well as the complementary work by the Directorate-General for Energy on theranostics and clinical dosimetry integration.

Beyond its technical achievements, Prof. Lassmann emphasised the project's educational legacy, noting that SIMPLERAD recommendations are now being integrated into revised European curricula for medical physicists and radiopharmacists. He concluded by underscoring the need for sustained coordination between national authorities, regulators, and the nuclear medicine community to ensure personalised, dosimetry-guided therapy can be delivered safely, ethically, and efficiently across Europe.

53 Krause, B.J., Lassman, M., Bardiès, M. et al. (2024). SAMIRA Study on the Implementation of the Euratom and EU Legal Bases with Respect to the Therapeutic Uses of Radiopharmaceuticals. https://eanm.org/wp-content/uploads/2025/02/SIMPLERAD_Final-Guidelines-and-Recommendations_FinalReport.pdf

PRISMA AND FUTURE SAMIRA: STRENGTHENING QUALITY AND SAFETY IN EUROPEAN NUCLEAR MEDICINE

Speaker: Senior Inspector Sampsa Kaijaluoto, Finnish Radiation and Nuclear Safety Authority (STUK)

Sampsa Kaijaluoto provided a forward-looking overview of the Preparatory Activities to Support Implementation of Quality and Safety for Medical Ionising Radiation Applications (PrISMA) and Future SAMIRA Joint Action, cornerstone project within the European Commission's Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA). These initiatives, under DG ENER, aim to bring tangible and sustainable improvements in quality and safety in medical uses of ionising radiation in EU Member States.

PRISMA, launched in 2024 as an 18-month preparatory action involving 18 organisations from 12 countries, is mapping key national actors and jointly producing a proposal for future work on priority areas. Its work directly feeds into the larger €11.5 million Future SAMIRA Joint Action, announced in the EU4Health programme in 2025. That effort will promote consistent application of the BSSD across Member States, with one of its six mandatory deliverables focused specifically on the optimisation and dosimetry of therapeutic nuclear medicine.

Kaijaluoto described how these actions build upon the evidence and recommendations of earlier projects such as SIMPLERAD and QuADRANT, translating policy frameworks into operational measures. For therapeutic nuclear medicine, this could mean a future project on regulatory training and convergence, alongside work on reimbursement and patient release criteria.

Speaking also on behalf of HERCA (Heads of the European Radiological Protection Competent Authorities), Kaijaluoto noted ongoing efforts to produce guidance on dose constraints for carers, comforters, and the general public, expected by 2026, as well as a position paper on BSSD implementation in therapeutic contexts. He concluded by urging Member States and professional societies to join these coordinated efforts, emphasising that early participation will shape Europe's future framework for quality, safety, and innovation in nuclear medicine.

FORECASTING THE FUTURE DEMAND FOR RADIOLIGAND THERAPY IN EUROPE

Speaker: Dr Uwe Holzwarth, Joint Research Centre, European Commission

Dr. Uwe Holzwarth presented for the first time publicly the Joint Research Centre's projections on the expected growth of patients eligible for radioligand therapy (RLT) across the European Union. The modelling, conducted in collaboration with industry and academic partners, provides policymakers with the most comprehensive forecast to date of future demand, resource needs, and isotope requirements. Using data from the European Cancer Information System (ECIS) and the Institute for Health Metrics and Evaluation (IHME), the model estimates that eligibility will rise sharply across the EU-27 and UK, with the largest increases expected in France, Germany, Italy, and Spain.

Based on incidence data and evolving clinical indications for approved and emerging RLT agents, annual eligible patient numbers are projected to increase from approximately 15,000 today to as many as 200,000 by 2035—a more than tenfold rise. Growth is anticipated across multiple cancer types, including neuroendocrine, prostate, renal, and haematological malignancies, reflecting both new indications and earlier-line use of existing therapies. By 2030, between 40,000 and 100,000 patients could require treatment annually, with significant implications for imaging capacity, radiopharmaceutical supply, and workforce readiness.

Dr. Holzwarth highlighted that around 70% of future patients will depend on lutetium-labelled compounds, requiring an estimated 3,000 to 4,300 TBq of Lu-177 annually by 2035. Meeting this demand will necessitate robust isotope supply chains, expanded production capacity, and coordinated infrastructure planning. He emphasised that while the Commission can support through research and data, implementation rests with Member States. The data should now guide national planning on workforce, facilities, and reimbursement structures to ensure timely access for all patients.

Closing his presentation, Dr. Holzwarth reiterated that Europe stands on the brink of a transformative expansion in nuclear medicine, one that will only succeed through proactive collaboration between regulators, hospitals, and industry partners.

FROM STRATEGY TO IMPLEMENTATION: STRENGTHENING EUROPE'S RADIOLIGAND THERAPY INFRASTRUCTURE

Speaker: Prof. Karolien Goffin, University Hospital Leuven, Chair of Oncology & Theranostics Committee EANM

Prof. Karolien Goffin expanded on the previous presentation by assessing Europe's capacity to meet the rising demand for radioligand therapy (RLT), noting that with the field projected to grow at a compound annual rate of around 13% through 2035, it poses a systems challenge requiring coordinated progress across six fronts: diagnostic readiness, workforce growth, infrastructure investment, supply chain resilience, regulatory alignment, and standardisation.

She highlighted key bottlenecks, including limited PET/CT and SPECT/CT access, fragmented referral pathways, and workforce shortages. Across Europe, only 15–20% of eligible patients currently receive appropriate diagnostic imaging, reflecting a lack of standardised multidisciplinary pathways. Theranostic centres report a median of one nuclear medicine physician per 50 administrations and one medical physicist per 138, with little available data on radiopharmacy or nursing support.

To address these gaps, Dr. Goffin proposed targeted investment in diagnostic infrastructure, modular treatment facilities, and accelerated training programmes, alongside embedding RLT pathways in national cancer plans and establishing clear referral algorithms. She also called for harmonised European policies and funding to strengthen isotope supply

chains, particularly for lutetium-177 and actinium-225, through redundancy and automated production.

Financial and regulatory fragmentation was also identified as a major barrier to sustainable access. Current fee-for-service models often lead to disjointed care, whereas bundled or value-based payment models could provide a more coordinated and equitable reimbursement framework.

Dr. Goffin concluded with a strategic roadmap calling for six concrete actions: expanding PET/CT capacity and referral pathways; accelerating workforce development through modular curricula; mobilising funding for shielded rooms and waste management; reinforcing isotope supply chain resilience; reforming reimbursement through, for example, bundled payments; and standardising dosimetry and imaging procedures.

Her final message was clear: Europe now has the data, evidence, and tools to act. What is needed next is the translation of readiness into implementation. "We know the value," she said, "now we must ensure delivery."

PUTTING THE PATIENT AT THE CENTRE OF RADIOLIGAND THERAPY ACCESS

Speaker: Dr Anne-Laure Giraudet, Léon Bérard Cancer Center, Lyon, France

Dr. Anne-Laure Giraudet concluded the session with a perspective on patient access and referral bottlenecks, emphasising that Europe's success in radioligand therapy (RLT) will depend on connecting innovation with clinical reality. She illustrated how RLT is evolving from a niche intervention to a core pillar of multimodal oncology, with expanding clinical indications and increasing investment across the therapeutic landscape.

Referencing national data from France, Dr. Giraudet highlighted the widening gap between patient eligibility and treatment capacity. In 2024, based on VISION criteria, only around 2,200 of 5,700 eligible patients with prostate cancer could be treated across the country's 40 active RLT centres, underlining significant infrastructure and workforce constraints.

Dr. Giraudet explained that outcomes improve when RLT is introduced earlier in the treatment pathway, citing data demonstrating gains in progression-free survival, overall survival, and quality of life.[54,55,56] Delays in eligibility or referral therefore represent missed opportunities for both survival and symptom control. These findings reinforce the importance of early identification and coordinated referral systems to ensure patients receive treatment at the optimal stage.

Dr. Giraudet called for structured, multidisciplinary referral networks supported by eligibility algorithms and shared registries to improve coordination. She emphasised the need for harmonised radiation protection policies to enable outpatient treatment and greater efficiency, highlighting European initiatives such as PrISMA, SAMIRA, JANE and the EANM Radioligand Therapy Academy, along with international collaborations like the IAEA CLAUD-IT programme and the joint EANM–SNMMI–IAEA guide as key frameworks for implementation and quality assurance.

Dr. Giraudet closed with a powerful call for a "virtuous, multidisciplinary ecosystem" centred around the patient and uniting nuclear medicine physicians, oncologists, physicists, radiopharmacists, regulators, industry partners, and patient representatives.

54 Strosberg, J., El-Haddad, G., Wolin, E. et al. (2017). Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. The New England journal of medicine, 376(2), 125–135.

55 Sartor, O., de Bono, J., Chi, K. N. et al. (2021). Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. The New England journal of medicine, 385(12), 1091–1103.

56 Strosberg, J., Wolin, E., Chasen, B. et al. (2018). Health-Related Quality of Life in Patients with Progressive Midgut Neuroendocrine Tumors Treated With 177Lu-Dotatate in the Phase III NETTER-1 Trial. Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology, 36(25), 2578–2584.

8 PROSTATE CANCER THERAPY: NEW TRACER (SESSION 1506) - ORGANISED BY ONCOLOGY & THERANOSTICS COMMITTEE

TUESDAY, 7 OCT, 15:00 - 16:30

CHAIRS: DR. LENA UNTERRAINER AND DR. ANDREI GAFITA

A first-in-human, Phase 1 dose-escalation and expansion study evaluating the safety, tolerability, and anti-tumour activity of [^{225}Ac]Ac-FL-020, and anti-PSMA radioconjugate in patients with mCRPC

Speaker: Dr Stanley Ngai, Brisbane, Australia

Dr Stanley Ngai presented preliminary data from a first-in-human, Phase 1 dose escalation and expansion study, named the PROTACT Phase 1 Trial, evaluating [^{225}Ac]Ac-FL-020, a novel anti-PSMA radioconjugate, in patients with mCRPC. His presentation offered insights into a new therapeutic approach for this challenging patient population.

Background

Dr Ngai began by outlining the ongoing need for advanced treatment options in mCRPC, noting that a subset of patients continues to progress despite significant advancements in chemotherapy, targeted therapy, immunotherapy, and existing β-emitter RLTs like [^{177}Lu]Lu-PSMA. He highlighted the potential of α-emitters, such as actinium-225, to offer potent, short-range cytotoxicity for deeper tumour control. However, he acknowledged that traditional α-emitter therapies have faced challenges with xerostomia and haematologic toxicity.

[^{225}Ac]Ac-FL-020 was introduced as a next-generation PSMA-targeted ligand specifically engineered to address these concerns. Its design incorporates a plasma-protein-binding domain and a cleavable linker, aiming for higher tumour uptake, prolonged tumour retention, and reduced salivary-gland exposure through accelerated clearance from normal tissues.

Study Design

The study enrolled PSMA-positive mCRPC patients who had received prior Androgen receptor pathway inhibitor (ARPI), and may have received taxane chemotherapy, or [^{177}Lu]Lu-PSMA, but excluded those with prior [^{225}Ac] therapy. The trial employed a Bayesian logistic regression model for dosing, administered every 6 weeks for up to 6 cycles. The study is actively recruiting across seven sites in Australia, the United States, and Turkey, with an additional five sites planned in China and the United States.

Results

As of September 27, 2025, 7 patients have been treated, reaching up to the 4 MBq dose level. The early safety data are particularly noteworthy, with 90% of treatment-emergent AEs being Grade 1-2. Crucially, no xerostomia, no Dose-limiting toxicities (DLT), no discontinuations, and no treatment-related Serious adverse events (SAE) have been observed to date. Additionally, indium-labelled dosimetry demonstrated low initial parotid uptake with rapid washout, alongside high and durable tumour retention visible for up to 168 hours post-dose. These findings support the design's intent for targeted delivery and reduced off-target effects.

Discussion

Dr Ngai emphasised that these early results demonstrate a favourable safety and tolerability profile, coupled with encouraging tumour targeting and minimal salivary-gland involvement. The trial is continuing its dose escalation, currently progressing to 5 MBq, to clarify the Maximum tolerated dose (MTD), determine the recommended Phase 2 dose, and further evaluate its efficacy potential.

During the Q&A, it was highlighted that xerostomia is being rigorously monitored and no cases have been observed, even at higher dose levels, reinforcing the promising safety profile.

Conclusion

In conclusion, Dr Ngai's presentation indicated that [^{225}Ac]Ac-FL-020 shows early promise as a differentiated α-emitter PSMA radioconjugate. Its potential for improved safety, strong tumour retention, and preserved QoL warrants continued clinical evaluation in mCRPC, offering a potential new option for patients with this advanced disease.

EVALUATION OF THE SAFETY AND EFFICACY OF 225AC-PSMA-CY313 IN MCRPC: PRELIMINARY RESULTS

Speaker: Dr Yan Wu, Chengdu, China

Dr Yan Wu presented preliminary results from an ongoing Phase I trial investigating [^{225}Ac]Ac-PSMA-CY313 for mCRPC. The research focuses on this novel, next-generation radiopharmaceutical, and the initial findings indicate a promising new treatment avenue.

Background

Dr Wu began by outlining the increasing incidence of prostate cancer in China and the critical demand for more effective treatment options for mCRPC. He introduced [^{225}Ac]Ac-PSMA-CY313 as an α-emitting radiopharmaceutical designed for high precision. This agent combines an actinium-225 payload with a chelator–linker system and a PSMA-binding ligand (PSMA-CY313), enabling the delivery of potent, short-range α-particle cytotoxicity directly to PSMA-positive tumour cells while aiming to spare surrounding healthy tissue.

Study design

The trial's primary objective was to assess the safety and tolerability of [^{225}Ac]Ac-PSMA-CY313, with secondary objectives evaluating efficacy through metrics such as PSA response, Objective response rate (ORR), Disease control rate (DCR), PFS, and OS. Twenty patients with histologically confirmed mCRPC after failure of standard therapies were enrolled and categorised into three groups based on prior treatments: Group A (prior ARPI + docetaxel), Group B ([^{177}Lu]Lu-PSMA with/without ARPI or docetaxel, and Group C (prior ARPI only). Patients received 200 µCi intravenously every 8 weeks for 4-8 cycles, with potential for investigator-discretionary dose escalation to 300 µCi.

Results

Baseline characteristics were generally comparable across groups in age, Eastern Cooperative Oncology Group Performance Status (ECOG) score, and disease burden. However, Group A patients tended to have higher baseline PSA due to more advanced disease and heavier prior treatment exposure (≥ 3 lines in 78% of cases).

A key finding highlighted was the favourable safety profile of [^{225}Ac]Ac-PSMA-CY313. The most common AE reported was mild, transient xerostomia, which typically resolved within 4 weeks. Significantly, no patients discontinued treatment due to toxicity, and there were no reports of treatment-related SAEs or permanent xerostomia. Only 1 case of Grade 3 anaemia was observed (minor Haemoglobin (Hb) drop from 8.0 g/dL to 7.9 g/dL).

The preliminary efficacy data presented by Dr Wu demonstrated encouraging responses. The PSA-50 response rate was 81.8% and the PSA-80 response rate was 63.6%, suggesting a notable biochemical benefit. Furthermore, the ORR was approximately 60%, and the DCR was approximately 80%. An illustrative case demonstrated a patient's PSA decreasing from approximately 160 to near zero after four cycles, accompanied by a significant reduction in a measurable lesion from 17.3 mm to 3.8 mm.

Discussion

During the discussion, Dr Wu noted that early progression in 2 Group C patients may have been associated with lower PSMA uptake or biological heterogeneity. The initial 200 µCi dose was selected based on prior global α-therapy experience, and investigators planned an optional escalation to 300 µCi for patients with insufficient response and tolerating four cycles without toxicity. The consistent absence of permanent xerostomia was also emphasised.

Conclusion

In conclusion, Dr Yan Wu's presentation indicated that [^{255}Ac]Ac-PSMA-CY313 demonstrated encouraging safety and efficacy in heavily pre-treated mCRPC patients. The therapy was characterised by minimal xerostomia and robust biochemical and radiographic responses. While further dose optimisation and longer follow-up are necessary to confirm durability and optimal dosing, these preliminary results position CY313 as a promising next-generation α-emitter PSMA-targeted therapy. Offering high tumour activity and a manageable safety profile, this therapy can potentially expand treatment options for mCRPC patients resistant to conventional and β-emitter RLTs.

FIRST-IN-HUMAN STUDY OF A NOVEL PSMA-TARGETED RADIOTHERAPEUTIC AGENT: SAFETY, PRELIMINARY EFFICACY, AND DOSIMETRY OF [^{177}LU] LU-PSMA-XT IN PATIENTS WITH MCRPC

Speaker: Dr Yachao Liu (on behalf of Prof Yachao Liu, Beijing, China)

Dr Yachao Liu, presenting on behalf of Prof Yachao Liu, delivered insights from a first-in-human multicentre, dose-escalation and expansion trial evaluating a novel PSMA-targeted radiotherapeutic agent, [^{177}Lu]Lu-PSMA-XT, in patients with mCRPC. The presentation focused on the safety, preliminary efficacy, and dosimetry of this new compound.

Background

Dr Liu began by reaffirming PSMA as a validated target for mCRPC. Building upon the encouraging results observed with existing β-emitters like [^{177}Lu] Lu-PSMA-617, he explained that a new PSMA-targeted radioligand, PSMA-XT, has been developed, and that two companion agents have been created:

1. **68Ga-PSMA-XT** for Positron emission tomography (PET) imaging, which has demonstrated stronger tumour uptake than PSMA-11.
2. **177Lu-PSMA-XT**, a therapeutic agent that was specifically designed to improve tumour retention and reduce off-target exposure, particularly to salivary glands and kidneys.

Study design

The study was conducted in China and enrolled 26 patients with PSMA-positive mCRPC who had progressed after at least one prior systemic therapy. Notably, 70% of these patients were heavily pre-treated, having received more than three prior lines of therapy. Dose-escalation was undertaken from 50 mCi to 200 mCi, with primary endpoints including DLT, dosimetry, PSA response, and radiologic efficacy. Imaging was performed at multiple time points (30 minutes, 4 and 24 hours, and 6 days post-injection), with dosimetry derived via SPECT/CT.

Preliminary results

The preliminary results presented a favourable safety profile and encouraging efficacy signals:

- **Safety:** AEs were reported in less than 30% of patients. The most common AE was mild, transient xerostomia, affecting approximately 20% of patients. Significantly, no grade ≥3 treatment-related toxicities or therapy discontinuations were reported.
- **Efficacy:** The PSA-50 response rates demonstrated a dose-dependent effect: 67% at 50 mCi, 50% at 100 mCi, and a notable 100% at 200 mCi among all evaluable patients. Two patients achieved radiographic PFS exceeding 13 months, including one at the lowest dose of 50 mCi.
- **Dosimetry:** Analysis revealed high tumour uptake combined with comparatively low absorbed doses in the kidneys and salivary glands, resulting in a favourable tumour-to-organ ratio when compared to the benchmark PSMA-617.

Discussion

During the Q&A, Dr Liu elaborated on the comparison with PSMA-617, emphasising that PSMA-XT demonstrated lower absorbed doses in kidneys and salivary glands while maintaining strong tumour accumulation. He indicated that, given the encouraging tolerability and tumour-to-organ selectivity, investigators are now exploring the potential use of PSMA-XT in earlier-line treatment settings or in combination therapies.

Conclusion

Dr Liu concluded his presentation by stating that this study indicates that [^{177}Lu]Lu-PSMA-XT appeared safe, well-tolerated, and highly active in early clinical testing. With its improved tumour targeting and reduced off-target dosimetry relative to existing β-emitters, PSMA-XT may represent a promising next-generation radioligand for mCRPC. These findings warrant further evaluation in dose-expansion and front-line studies to fully ascertain its therapeutic potential.

HEAD-TO-HEAD DOSIMETRY, SAFETY AND PRELIMINARY EARLY RESPONSE EVALUATION OF [^{161}TB] TB-SIBUDAB VERSUS [^{177}LU]LU-PSMA-I&T IN PATIENTS WITH MCRPC: PROGNOSTICS PHASE 1A

Speaker: Dr Alin Chirindel (on behalf of the PROGNOSTICS consortium, PSI/Basel, Switzerland)

Dr Alin Chirindel, presenting on behalf of the PROGNOSTICS consortium from PSI/Basel, Switzerland, delivered insights from the PROGNOSTICS Phase 1a study. This research conducted a first-in-human, head-to-head intrapatient comparison of a novel terbium-161-based radioligand, [^{161}Tb]Tb-PSMA-CBz, against its lutetium-177 counterpart, [^{177}Lu]Lu-PSMA-CBz, in patients with mCRPC.

Background

Dr Chirindel began by acknowledging [^{177}Lu]Lu-PSMA RLT as an established treatment for mCRPC. However, he noted that disease relapse can occur from micrometastatic lesions that may escape β-particle irradiation due to its limited range and suboptimal energy transfer.

Dr Chirindel then introduced Terbium-161 ([^{161}Tb]), a next-generation therapeutic radionuclide. He stated that while Terbium-161 ([161Tb]) shares similar decay properties with Lutetium-177 ([177Lu]), it uniquely emits additional low-energy Auger and conversion electrons. These deliver higher LET and up to twice the nuclear dose, offering the potential for enhanced eradication of micrometastases and circulating tumour cells. Consequently, PSMA-CBz, a ligand designed with albumin-binding characteristics for prolonged circulation and enhanced tumour uptake, was devised to optimise delivery.

Study design

This study sought to directly compare [177Lu]Lu-PSMA-CBz and [161Tb]Tb-PSMA-CBz. Ten patients with stable mCRPC who had previously received at least two cycles of standard [177Lu]Lu-PSMA therapy were recruited. A randomised crossover design was employed, with each patient receiving 1 GBq of each compound, separated by a 3-week washout period. Primary endpoints focused on tumour absorbed dose comparison, while secondary endpoints included organ absorbed doses (kidney, salivary glands, and bone marrow), safety, and PSA response. Dosimetry was derived, and quantitative SPECT imaging was performed at 3, 24, 48 hours, and up to 7 days post-injection.

Results

The results highlighted several significant findings:

- **Tumour uptake:** [161Tb]Tb-PSMA-CBz achieved approximately double the tumour absorbed dose compared to [177Lu]Lu-PSMA-CBz. The peak uptake for terbium shifted later (48 hours vs. 24 hours for lutetium), consistent with the prolonged circulation from albumin binding.
- **Organ dosimetry:** While slightly higher kidney and bone marrow doses were observed with terbium, these remained within established safe limits.
- **Toxicity:** The safety profile was favourable, with no grade ≥3 AEs reported. No differences in haematologic, renal, or symptomatic toxicity were observed between the two agents, and both test injections were well tolerated.
- **Imaging:** Representative 7-day SPECT imaging confirmed a stronger and more durable tumour signal for [^{161}Tb]Tb-PSMA-CBz compared to its lutetium counterpart.

Discussion

During the Q&A, Dr Chirindel clarified that each patient received both agents in an alternating order (6 started with lutetium, 4 with terbium). Only acute toxicity from the test injections was analysed, and background AEs from prior RLT cycles were excluded. Patients were selected for stable disease to minimise confounding effects from tumour progression or regression during the crossover period.

Conclusion

In conclusion, Dr Chirindel's presentation demonstrated that [^{161}Tb]Tb-PSMA-CBz delivered approximately double the tumour radiation dose of [^{177}Lu]Lu-PSMA-CBz in this study without any additional toxicity. These findings provide strong support for the 3 GBq safety entry dose for the ongoing Phase 1b dose-escalation study.

Key takeaway:

Terbium-161–based PSMA-CBz showed significant potential to enhance RLT efficacy in mCRPC by increasing nuclear dose delivery, particularly for micrometastatic disease, while maintaining a favourable safety profile comparable to lutetium-based therapy.

SATISFACTION TRIAL-IN-PROGRESS: A PHASE 1/2 STUDY OF [^{255}AC] AC-PSMA-R2 IN PATIENTS WITH METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC) OR MCRPC

Speaker: Dr Armelle Vinceneux (on behalf of the SatisfACtion investigators, Basel, Switzerland)

Dr Armelle Vinceneux, presenting on behalf of the SatisfACtion investigators, provided an overview of the ongoing SatisfACtion multicentre, open-label, trial-in-progress; a Phase 1/2 study evaluating [^{225}Ac]Ac-PSMA-AIR2, a novel α-emitting radioligand, in patients with mHSPC or mCRPC.

Background

Dr Vinceneux began her presentation by acknowledging the significant advancements in prostate cancer treatment brought about by RLT targeting PSMA. However, she stated that while [^{177}Lu]Lu-PSMA-617 has demonstrated improved radiographic PFS and OS with a manageable safety profile in both pre- and post-taxane mCRPC populations, α-emitters like actinium-225 offer distinct advantages. These include higher LET and shorter particle range, which could lead to greater cytotoxicity within tumour sites while potentially limiting collateral tissue exposure.

Dr Vinceneux then introduced [^{225}Ac]Ac-PSMA-AIR2, a novel α-emitting ligand specifically engineered to deliver lower absorbed radiation doses to risk organs, notably the salivary glands, while maintaining effective tumour targeting. She stated that the SatisfACtion trial aims to explore its safety, Pharmacokinetics (PK), and preliminary efficacy across both mHSPC and mCRPC settings.

Study design

The trial has the following phased objectives:

1. **Phase 1:** To define safety, tolerability and DLTs, and establish the Recommended dose for expansion (RDE).
2. **Phase 2:** To evaluate antitumour activity (radiographic and biochemical response), PKs, and QoL.

The study will recruit PSMA-positive patients, confirmed by central 68Ga-PSMA PET/CT review, with an ECOG performance status of 0-2 and adequate organ function. Key exclusion criteria include prior actinium-based RLT or other investigational therapies within 6 weeks. The study is structured into three distinct cohorts:

1. **Group 1:** mCRPC patients who are post-ARPI, post-taxane, and post-lutetium therapy.
2. **Group 2:** mCRPC patients who are post-ARPI only (lutetium-naïve).
3. **Group 3:** Minimally treated or untreated mHSPC patients (androgen-deprivation only).

Each group includes a Phase 1 dose escalation segment, utilising a Bayesian logistic regression design with 3-6 patients per cohort. Phase 2 dose expansion will commence after the RDE is defined in Phase 1. The starting dose is 7 MBq [^{225}Ac]Ac-PSMA-AIR2 administered intravenously every 6 weeks for up to 6 cycles, with an evaluation window of the first 42 days. The dose for Group 3 will be determined following a review of safety data from Groups 1 and 2.

Each phase has primary and secondary endpoints:

- **Phase 1:** Primary endpoints include safety, DLTs, and MTD/RDE determination, while secondary endpoints include PSA decline, radiographic response, and PK profiling.
- **Phase 2:** Primary endpoints include ORR per Prostate Cancer Working Group (PCWG) 3 criteria, while secondary endpoints include PSA response, radiographic PFS, OS, QoL, treatment modifications, and organ dosimetry.

Discussion

During the Q&A, it was clarified that PSMA positivity is defined solely by central 68Ga-PSMA PET review, without a predefined SUV threshold or comparison to liver uptake. No salivary protection strategies are planned, as the trial aims to evaluate whether AIR2's inherent lower off-target dose mitigates xerostomia. Combination with standard of care is scientifically motivated, allowing patients to continue androgen deprivation ± optional ARPI per investigator discretion.

Conclusion

In conclusion, the SatisfACtion trial represents the first global Phase 1/2 study of [^{225}Ac]Ac-PSMA-AIR2 across both mHSPC and mCRPC populations. Its primary objective is to establish the compound's safety, dose parameters, and biological activity, potentially offering an α-emitter PSMA therapy with a more favourable therapeutic window; thus, preserving efficacy while reducing the risk of xerostomia. The study is currently ongoing, with active recruitment across multiple international sites.

ADAPTIVE DESIGN AND DOSE OPTIMISATION IN A DOSE ESCALATION AND EXPANSION STUDY OF 212PB-ADVC001 IN MCRPC: THERAPB - PHASE 1B/2 STUDY

Speaker: Dr Stanley Ngai, Brisbane, Australia

Dr Stanley Ngai presented an overview of the TheraPb Phase 1/2 study, which evaluated [^{212}Pb]Pb-ADVC001, a novel PSMA-targeted radioligand, in mCRPC. The study highlights an adaptive design and dose optimisation strategy for this α-emitting agent.

Background

Dr. Ngai began by acknowledging the transformative impact of PSMA-targeted RLT on mCRPC management. He stated that while [^{177}Lu]Lu-PSMA prolongs survival and improves QoL, up to 30% of patients show minimal response and all patients ultimately progress, maybe due to the limited energy of beta-emitters. Dr. Ngai informed attendees that αalpha-emitters, in contrast, deliver higher LET over a shorter range, yielding enhanced tumour cytotoxicity while sparing healthy tissue. He presented 212Pb as a promising isotope due to its 10.6-hour half-life, which allows for flexible, short-interval dosing. Its built-in SPECT visibility allows for direct imaging and dosimetry within 24 hours post-infusion with no surrogate tracer required, and its generator-based production supports reliable supply and multi-ligand conjugation.

Study Design

The study evaluates [^{212}Pb]Pb-ADVC001, a small-molecule PSMA ligand, in men with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). Phase 1 was designed to assess safety, tolerability, and determine the recommended Phase 2 dose (RP2D). Phase 2 will focus on optimising the dosing schedule through an adaptive, biomarker-guided approach.

This Phase 1/2 trial aligns with the Food and Drug Administration's (FDA) Project Optimus framework and recent draft guidance on radiopharmaceutical dose optimisation. The Phase 1 population closely mirrors that of the Phase 3 VISION trial. Dose escalation in Phase 1 has been completed using an interval 3 + 3 escalation design. The adaptive dosing strategy explored both dose level escalation and treatment-interval intensification, with a total of seven cohorts receiving treatment every 6, 4, 2, and 1 week, respectively. The short half-life of the isotope enabled evaluation of these condensed regimens. Phase 2 is expected to initiate in Q4 2025 across Australia.

Results

Post-therapy SPECT imaging demonstrated strong and durable tumour uptake and retention, alongside low renal uptake with rapid clearance. Critically, minimal salivary gland accumulation was observed, consistent across all doses (16-200 MBq).

Discussion

Dr. Ngai emphasised that [^{212}Pb]Pb-ADVC001 combines potent alpha particle cytotoxicity with real-time imaging capability. Early data indicate strong tumour targeting, low off-target uptake, and robust PSA declines without clinically significant xerostomia. The adaptive design has allowed for interval-based optimisation and accelerated data generation, achieving a Phase 1 to major conference read-out in under 12 months. Phase 2 will dose regimens across mCRPC and mHSPC cohorts, integrating imaging and biomarker feedback.

During the Q&A, Dr. Ngai confirmed that PSMA positivity is defined per VISION criteria on 68Ga or 18F -PSMA PET and that full Phase 1 results are to be presented at European Society for Medical Oncology (ESMO) 2025, with Phase 2 commencing in Q4.

DOSE ESCALATION STUDY FOR TARGETED RADIONUCLIDE THERAPY WITH [^{161}TB]TB-SIBUDAB IN MCRPC - PROGNOSTICS PHASE 1B STUDY

Speaker: Dr Alin Chirindel, Basel, Switzerland

Dr Alin Chirindel presented interim results from the PROGNOSTICS Phase 1b study. This trial is a dose-escalation and de-escalation study for targeted radionuclide therapy with [^{161}Tb]Tb-SibuDAB in patients with mCRPC, building upon the findings of the earlier PROGNOSTICS-1a study.

Background

Dr Chirindel began by referencing the encouraging results from the PROGNOSTICS-1a head-to-head comparison, which indicated that [^{161}Tb]Tb-PSMA-CBz delivered approximately twice the tumour dose of [^{177}Lu]Lu-PSMA-CBz with a comparable safety profile. This led to the initiation of the PROGNOSTICS-1b trial, designed to establish the Optimal biological dose (OBD) for terbium-161–based PSMA RLT. He reiterated that terbium-161 [^{161}Tb] is a unique radionuclide that emits both β-particles and short-range Auger/conversion electrons. This dual emission provides higher LET, offering the potential to eradicate micrometastases that may evade β-emitters such as lutetium-177.

Study design

This study includes patients with progressive mCRPC who are on Antigen deprivation therapy (ADT) ± ARPI and are either post-chemotherapy or ineligible for chemotherapy. Key inclusion criteria require PSMA-positive disease confirmed by 68Ga-PSMA PET/CT (with at least three lesions, each ≥1.5 cm, and SUVmax > 10), along with adequate marrow and organ reserve. Exclusion criteria include PSMA-negative lesions, uncontrolled comorbidities, and extensive bone-marrow involvement. The study design involves a short 10-minute infusion, followed by quantitative SPECT imaging at 3, 24, 48, and 168 hours, plus 2 weeks for refined dosimetry. Blood-derived marrow dosimetry, PSA monitoring, and safety assessments are conducted according to PCWG3 criteria.

Preliminary results

As of October 2025, the study has progressed through several dose levels. The trial commenced at 3 GBq and escalated to 4.5 GBq without observing any DLTs. Dosing is currently underway at 5.5 GBq, with three patients enrolled at this level.

- **Efficacy:** At the 3 GBq dose level, preliminary results indicated one progression, one stable disease, and one partial response, suggesting potential under-dosing for optimal efficacy. However, at the 4.5 GBq dose level, all evaluable patients demonstrated PSA decline and partial radiographic response after two cycles.
- **Safety:** To date, no grade ≥3 haematologic, renal, or systemic toxicities have been reported. Safety Review Boards have confirmed continuation after each cohort, reinforcing the favourable tolerability profile.

Discussion

During the Q&A, Dr Chirindel clarified that the specific activity remained constant, with only the radioactivity dose increasing. Preliminary renal dosimetry shows an absorbed kidney dose of approximately 0.06 Gy/GBq (compared to 0.09 Gy/GBq in the 1a study), suggesting improved safety and lower renal exposure. Bone-marrow exposure is similar to that observed in the 1a study and remains within acceptable limits.

Conclusion

In conclusion, preliminary results from the PROGNOSTICS-1b study confirm the favourable tolerability and early efficacy of [^{161}Tb]Tb-PSMA-CBz at the 4.5 GBq dose level, with continued escalation to 5.5 GBq underway. The trial's continued objective is to define an OBD that balances tumour control with organ safety. The absence of DLTs reinforces terbium-161's potential as a next-generation RLT isotope capable of delivering higher intratumoural energy while maintaining a low toxicity burden.

DOSIMETRY AND DOSE-ESCALATION STUDY OF A NOVEL LONG-ACTING RADIOPHARMACEUTICAL [^{177}LU]LU-LNC1011 IN MCRPC PATIENTS

Speaker: Dr Jiarou Wang, Department of Nuclear Medicine, MC University (in collaboration with the National University of Singapore)

Dr Jiarou Wang presented findings from an ongoing Phase 1 dosimetry and dose-escalation trial of [^{177}Lu]Lu-LNC1011 (also referred to as A1C-1011), a novel long-acting radiopharmaceutical for mCRPC.

Background

Dr Wang began by acknowledging [^{177}Lu]Lu-PSMA-617 as a benchmark therapy for mCRPC, which has demonstrated improvements in survival and QoL. However, she highlighted that its full therapeutic potential can be restricted by factors such as limited tumour uptake and relatively short tumour retention.

Dr Wang then introduced A1C-1011, a next-generation PSMA-targeted radioligand specifically designed to overcome these limitations. She explained that its design incorporates densely acetylated amino acids and an albumin-binding moiety, intended to extend circulation time, enhance tumour accumulation, and maintain safety. Dr Wang also revealed that preclinical work has shown approximately 8-fold higher tumour uptake compared to PSMA-617, and that early human PET imaging has confirmed prolonged tumour retention with comparable diagnostic performance.

Study design

This study involves nine patients with mCRPC, divided into three cohorts of 3 patients each. Doses of [^{177}Lu]Lu-A1C-1011 have been administered intravenously at 1.85 GBq, 2.78 GBq, and 3.7 GBq per cycle. Endpoints include safety, organ dosimetry, PKs, and PSA. Imaging-based responses are assessed per PCWG3, RECIST 1.1, and PERCIST criteria.

So far, patient characteristics have indicated a median age of 72 years and a mean baseline PSA of 149 ng/mL. Most patients have a history of both bone and nodal metastases and have undergone prior prostatectomy, radiation, ADT, and/or chemotherapy.

Preliminary results

The preliminary results demonstrate a favourable safety profile and encouraging efficacy signals:

- **Safety:** No DLTs or treatment-related deaths have been reported. A single case of Grade 3 thrombocytopenia has been observed, which was asymptomatic and resolved. Importantly, no renal or hepatic toxicity, nor xerostomia, has been reported.
- **Dosimetry:** The agent exhibits high tumour uptake within 2 hours, persisting for over 7 days (168 hours). The tumour effective half-life is approximately 128 hours, compared to 49 hours for whole-body clearance. Kidneys receive the highest organ dose, followed by salivary glands and bone marrow, but all remain within low and acceptable limits. Liver uptake peaks early and declines rapidly by 24 hours.
- **Efficacy:** All patients in the highest dose cohort (3.7 GBq) show PSA decline, with 66% achieving a partial response by RECIST criteria. The DCR is 100%.

Discussion

During the Q&A, Dr Wang explained that the use of lower activity compared to PSMA-617 was justified by preclinical data demonstrating 8-fold greater tumour uptake, suggesting equivalent efficacy at a reduced administered dose. The affinity for other tumour types is currently unknown, and further molecular profiling is planned. Patient selection criteria remain consistent with standard PSMA therapy (PSMA-positive PET).

Conclusion

Dr Wang concluded her presentation by reiterating that [^{177}Lu]Lu-A1C-1011 appears safe, well-tolerated, and highly tumour-avid, producing strong and durable responses at lower administered activities. Its extended tumour retention and low off-target exposure suggest a favourable therapeutic index and the potential for improved efficacy over existing β-emitters. Cohort expansion and additional efficacy analyses are currently underway.

Key takeaway

A1C-1011 may represent a next-generation long-acting PSMA radioligand, combining high tumour uptake, prolonged residence time, and excellent tolerability, promising a new benchmark for β-emitter RLT in mCRPC.

USEFUL CONTACTS

SOCIAL MEDIA

@officialEANM
@officialEANM
@EANM_NucMed
@officialEANM
@eanm_NucMed
@officialEANM

USEFUL LINKS

EANM WEBSITE
https://eanm.org

EANM'25 ABSTRACT BOOK
https://www.sciencedirect.com/science/article/pii/S3051291325000047

EANM OFFICE

Executive Office

EANM Executive Office
Schmalzhofgasse 26
1060 Vienna, Austria
Phone: +43 1 890 44 27
E-mail: **office@eanm.org**
Website: **www.eanm.org**

EANM26
WORLD LEADING MEETING

39th
Annual Congress of the
European Association of Nuclear Medicine

VIENNA

OCTOBER 17 – 21, 2026

eanm26.eanm.org