EANM 2024 Highlights

Bart Timmermans (2nd year PhD candidate at Radboudumc)

The opening plenary highlights lecture emphasized the growth of the nuclear medicine field and the EANM annual meeting, with more participants and submitted abstracts than ever. During the highlights lecture the diversity of the field was also apparent, showcasing various novel tracers, targets and radionuclide combinations. My PhD research focuses on (pre-therapeutic) dosimetry for PSMA-targeted therapy, so the talks I attended thus also centered around prostate cancer, PSMA, and dosimetry.

Radioligand therapies in prostate cancer

The treatment landscape of prostate cancer is rapidly evolving, as was highlighted in one of the first CME sessions. Dr. Walz and Dr. Sartor (OP-073, OP-074) revisited the well-known TheraP and VISION trials, which have demonstrated the overall survival (OS) and progression-free survival (PFS) benefit of [^{177}Lu]Lu-PSMA-617. They also highlighted other major trials. The recently published PSMAfore trial showed the benefit of [^{177}Lu]Lu-PSMA in taxane-naïve metastatic castrate resistant prostate cancer (mCRPC) patients: a radiographic progression-free survival (rPFS) of 11.60 months in the Lu-PSMA arm versus 5.59 months in the ARPI change arm (HR 0.49; Morris et al., *Lancet* 2024). Similarly, the SPLASH trial reported an rPFS of 9.5 months for [^{177}Lu]Lu-PSMA-I&T versus 6.0 months for ARPI change (presented at ESMO 2024).

Combination therapies were another key focus. The ENZA-P trial showed favorable radiographic and PSA PFS for the combination of [^{177}Lu]Lu-PSMA + enzalutamide versus enzalutamide alone in mCRPC patients (Emmett *et al.,* Lancet Oncol 2024). Similarly the Upfront showed improved PSA PFS, freedom from castration resistance, and rPFS for ADT + 2 cycles of [^{177}Lu]Lu-PSMA followed by six cycles of docetaxel versus ADT + 6 cycles of docetaxel alone (Azad *et al.*, Lancet Oncol 2024). Trials investigating [^{177}Lu]Lu-PSMA in combination with for example PARP inhibitors are also underway (LuPARP, PRINCE).

Ongoing trials investigating [^{177}Lu]Lu-PSMA in earlier disease setting are nearing completion (e.g., Bullseye, PSMAddition, ROADSTER, LuTectomy), while other trials are currently ongoing (PSMA-DC, LUNAR, POPSTAR2, STAMPEDE2). In addition, various trials are investigating other radionuclides i.e. Actinium-225 (NCT04597411, NCT04506567).

For me, the key takeaway was that there is a lot of interesting data emerging, many unanswered questions remain. How can good responders be identified? What is the optimal PSMA-ligand or radionuclide? And what combination therapies should be prioritized?

Progress in dosimetry

On dosimetry, there were also many interesting talks, with an emphasis on the need for standardization and improving the workflow for better clinical implementation. Our own work (OP-355) showed the variability of dosimetry due to the lack of standardized approaches. This message was echoed in other presentations and larger challenges such as the AAPM grand challenge (e.g., OP-214, OP-354). Standardizing dosimetry approaches will be essential to ensure the comparability of reported absorbed dose data, especially as personalized approaches and more novel compounds are introduced. Lessons can also be from radioembolization and [^{177}Lu]Lu-DOTATATE treatments (e.g. OP-715, OP-716), which show the benefits of optimizing tumor dose to improve efficacy.

Most of the progress made was in dosimetry for organs at risk. Population-based kinetic modeling and other methods were proposed to simplify clinical workflows. For example, Post *et al.* (OP-316) demonstrated that SPECT/CT scanning times for [^{177}Lu]Lu-PSMA could be reduced by 75% (1 day post-

injection imaging) and 25% (7 day post-injection imaging) without sacrificing accuracy in kidney dosimetry. The choice of when to image still remains important, Gustafsson and coworkers (OP-151) showed that two-timepoint dosimetry approach (one early + one late timepoint) can outperform three early timepoint dosimetry approaches.

Another interesting talk (OP-254) showed that a therapeutic index based on the ratio of tumor-to-kidney dose which is now proposed often, might not be the best solution to optimize administered activity. Instead they propose a "probability of complication free tumor control" model that optimizes for the ratio between tumor control probability and normal tissue complication probability. However more clinical data is needed to validate and implement such an approach.

Beyond dosimetry, genetic biomarkers could also help identify optimal responders. For example, Nikolic *et al.* (OP-570) showed that homologous recombination repair mutations are associated with poorer responses to [^{177}Lu]Lu-PSMA, highlighting the role of these genetic biomarkers in identifying responders.

Artificial Intelligence

AI was also discussed in the context of nuclear medicine. Regarding dosimetry and response prediction, Tran-Gia (OP-195) presented a comprehensive overview of AI applications, ranging from pre-treatment planning, outcome prediction, accelerated SPECT/CT processing, post reconstruction image enhancement, automatic segmentation, dosimetry modeling and time-activity curve fitting, to dose kernel optimizations. However, many prediction models currently lack large data sets.

Pre-clinical insights

Combination therapies were featured in preclinical settings. Presentations (e.g., OP-022, OP-024, OP-027, OP-524, OP-525, OP-526) explored combinations of radioligand therapy with immune checkpoint inhibitors, DNA repair inhibitors, chemotherapy, and other synergistic drugs. Not only the combination type, but also the timing emerged as a critical factor influencing treatment efficacy.

Other preclinical research provided interesting insights into radionuclides. For instance, on Terbium-161 which is now often mentioned as an alternative to Lutetium-177. Spoormans *et al.* (OP-027) highlighted the limited range of Terbium-161's auger electrons, which might not effectively damage DNA but could impact the cell membrane. Additionally, Zitzmann-Kolbe *et al.* (OP-028) examined the daughter nuclides of Actinium-225 in mouse models, showing that Francium-221, was shown to accumulate in kidneys and salivary glands, , potentially contributing to the observed salivary toxicity in [^{225}Ac]Ac-PSMA therapy.

Novel compounds

Several presentations showcased the journey of novel compounds from synthesis to clinical trials. For example, Tang and coworkers (OP-424) showed impressive translational work on a CD-13 tracer for PSMA-negative prostate cancer. They developed and synthesized a novel tracer CD13-L1, performed pre-clinical imaging and treatment studies, and subsequently translated it into the clinical and imaged 16 patients using this tracer. However, its clinical utility might be limited, only one patient showed a higher SUVmax with this CD-13 tracer compared to traditional PSMA-PET imaging. Despite this limited success, I found it quite impressive work from synthesis to clinical evaluation.

EANM'24 was overall a highly interesting meeting, with many interesting talks!