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Bringing VISION to Nuclear Medicine: accelerating evidence and changing paradigms with theranostics

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I first became excited about prostate specific membrane antigen (PSMA) as a game changing target for nuclear medicine at the 2011 European Association of Nuclear Medicine (EANM) meeting in Birmingham. The target had been identified two decades prior(*1*)(*2*). A new approach using radiolabeled small molecule ligands that target the extra-cellular domain of the PSMA receptor, however, showed striking tumor-to-background contrast in both preclinical models with ^{99m}Tc and ^{124}I/^{131}I and in a ^{68}Ga first-in-human image in a patient with prostate cancer. I recorded PSMA as my “image of the conference”. The images provided the clarity needed for groups to rapidly adopt in clinical practice and trials in both imaging and therapy. A decade has passed, and we now have two FDA approved PSMA ligands, ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL. And we also have VISION, a phase 3 trial of radioligand therapy, that has led to FDA Breakthrough Approval of ^{177}Lu-PSMA-617.

The VISION trial, presented at the ASCO 2021 meeting and recently published in NEJM(*3*) included men with metastatic castration resistant prostate cancer who had previous treatment with at least one taxane chemotherapy and one androgen receptor pathway inhibitor. 13% were excluded after ^{68}Ga-PSMA-11 PET/CT selection. 551 men were randomized to ^{177}Lu-PSMA-617 and 280 to standard-of-care. Whilst the standard-of-care can be criticised for being protocol-defined and potentially limiting optimal clinical care options, the trial was designed with a goal of FDA approval and the results will enable widespread availability for men with prostate cancer globally. This is expected to follow given the improvement in overall survival of 15.3 months with ^{177}Lu-PSMA-617 compared to 11.3 months with SOC. This was consistent across pre-specified stratification factors including LDH, liver metastases or androgen-receptor pathway inhibitors planned as part of SOC. Other endpoints such as response on CT (RECIST response 42% vs. 3%) and PSA decline over 50% (46% vs 7%) also impressively favor ^{177}Lu-PSMA-617.

Like many other types of radionuclide therapy that are now widely available, ^{177}Lu-PSMA-617 has followed a development pathway that is unusual compared to conventional pharmaceuticals. The very first treatments were compassionate access treatments at Bad Berka(*4*) and University of Heidelberg(*5*) in Germany in men who had progressed after standard therapies. The unique ability to see what you treat with theranostics enabled the confidence to administer a treatment never tested before in a human. Years of experience with ^{68}Ga/^{177}Lu-DOTATATE in neuroendocrine tumours enabled estimation of an appropropriate administered radioactivity. Post treatment dosimetry instantly validated high tumor targeting with low normal organ uptake(*6*). Such a direct mechanistic treatment paradigm has features more analogous to external beam radiotherapy enabling rapid translation to the clinic.

At the Peter MacCallum Cancer Centre, we designed a prospective phase II study in 2014. Our vision was that a small prospective trial would provide the type of evidence required to evaluate activity, safety, and move this treatment into the mainstream. The results of this 30 patient trial was published in Lancet Oncology(*7*), and is currently in the top ten most highly cited manuscripts in the journal since 2008. Without a commercial sponsor but with support from ANZUP Clinical Trials Group and grant funding, this led directly to the first randomised controled trial of ^{177}Lu-PSMA-617, the TheraP trial. ABX (Radeburg, Germany), manufacturer and owner of the PSMA-617 intellectual property at the time, and ANSTO who manufacture ^{177}Lu in

Australia, kindly agreed to the support trial. Our expanded 50 patient cohort(*7*) provided Endocyte with compelling phase 2 evidence contributing to their purchase of PSMA-617 and design of the phase 3 VISION trial(*8*). A little of a year later, Novartis purchased Endocyte and spearheaded global commercialization.

We now have two randomised trials of ^{177}Lu-PSMA-617 providing complementary evidence. VISION provides definitive survival data in men who have exhausted current therapeutic options. TheraP trial places PSMA theranostics once step earlier by comparing to cabazitaxel(*9*) showing greater efficacy, lower toxicity and better patient reported outcomes. VISION demonstrates efficacy in a broader population whilst TheraP employed quantitative PET and also FDG PET/CT for patient selection. It remains an open question whether men with relatively low intensity PSMA uptake or FDG-positive PSMA-negative disease benefit from this treatment.

We recently celebrated the first administration of radio-iodine by Saul Hertz on March 31, 1941. Eighty years later, the nuclear medicine community continues to innovate with truly personalised medicine. As a last line of treatment, outcomes with ^{177}Lu-PSMA remain modest for many men, although some experience truly exceptional and durable responses. I'm hopeful that multiple efforts are also underway to evaluate novel combinations and use of ^{177}Lu-PSMA earlier, even as a first-line of treatment(*10*,*11*), will further improve outcomes for men with prostate cancer.

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