Sequential and Combination Therapies of $^{223}$RaCl$_2$ and Prostate-Specific Membrane Antigen Radioligand Therapy

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There have been unprecedented strides in theranostics, facilitating the bidirectional “see and treat” concept in precision oncology. The momentous VISION trial inaugurated prostate-specific membrane antigen (PSMA)-targeted, $\beta$-emitter $^{177}$Lu-labeled radioligand therapy (RLT) as a viable treatment strategy in men with metastatic castration-resistant prostate cancer (mCRPC) (1). The experimental arm of the VISION trial entailed patients with prior exposure to at least 2 cycles of taxane-based chemotherapy and at least 1 line of androgen receptor pathway inhibitor. Before PSMA RLT availability and approval, the ALSYMPCA trial established $^{223}$RaCl$_2$ as the first $\alpha$-emitter therapy in men with osteoblastic bone-dominant mCRPC (2).

The overall trial designs and outcomes of the VISION and the ALSYMPCA trials were similar in that both used protocol-permitted standard care as the control arm and both demonstrated an overall survival improvement of about 4 mo with the radiotherapeutic agent plus standard care compared with the standard care only. Both trials were also relatively similar in some aspects of the exclusion criteria. The ALSYMPCA trial excluded patients who received radionuclide therapy within the previous 24 wk, and further, other systemic radionuclide therapies were not permitted during the period from the first injection of $^{223}$RaCl$_2$ to 4 wk after the last injection of $^{223}$RaCl$_2$. In the VISION trial, the protocol-permitted standard care excluded $^{223}$RaCl$_2$. However, $^{223}$RaCl$_2$ was received by 17.4% of patients before PSMA RLT. The safety information for this subgroup has not been reported.

The other notable difference between the 2 trials was related to patients with diffuse marrow disease. The ALSYMPCA trial included patients with superscans on bone scintigraphy in both the experimental arm (9% of cohort) and the control arm (10% of cohort). In subgroup analysis, patients with superscan bone disease benefited from $^{223}$RaCl$_2$ with an incremental improvement in overall survival. In the VISION trial, patients with superscan bone disease were excluded. The exclusion was incited in view of safety considerations in exposing patients with extensive marrow disease to additional myelosuppression stress from PSMA RLT. Nevertheless, a multicenter retrospective study demonstrated that patients with diffuse marrow disease may be treated safely with PSMA RLT (3). The recent consensus statement on the appropriate use of PSMA RLT also indicates that patients with diffuse marrow disease can be considered candidates for PSMA RLT, although these patients should be followed closely and transfused as needed in cases of marked marrow suppression (4).

The question then arises whether PSMA RLT and $^{223}$RaCl$_2$ can be sequenced or combined in the treatment of patients with mCRPC. Although there are no reports on the use of $^{223}$RaCl$_2$ after PSMA RLT, there are a few reports on the safety and efficacy of PSMA RLT after $^{223}$RaCl$_2$ (5–8). The amended RALU study reported by Rahbar et al. in The Journal of Nuclear Medicine is the most recent evidence that PSMA RLT is safe and effective in heavily pretreated men with mCRPC who had previously received $^{223}$RaCl$_2$ (9). In this German multicenter retrospective study that included 133 patients with mCRPC, PSMA RLT was determined to be safe and effective after $^{223}$RaCl$_2$. The baseline characteristics before the start of PSMA RLT depicted all patients receiving $^{223}$RaCl$_2$ and at least 4 prior life-prolonging treatments in most patients (docetaxel in 74%, cabazitaxel in 23%, abiraterone in 71%, enzalutamide in 69%, and both androgen receptor pathway inhibitors in 53%). Further, approximately 43% (57/133) of patients received taxane-based chemotherapy during or after $^{223}$RaCl$_2$ and before PSMA RLT. Taxane-based chemotherapy was used before $^{223}$RaCl$_2$ in 37.5% (50/133) of patients. Most patients (73%) received 5 or 6 $^{223}$RaCl$_2$ injections, and after a median period of 12 mo, most patients (73%) received at least 4 PSMA RLT cycles. The serum prostate-specific antigen declined by 50% or more after PSMA RLT in 42% of these heavily pretreated patients who had received $^{223}$RaCl$_2$. The most common grade 3 or 4 but manageable treatment-related adverse event was anemia in 15% of patients.

The RALU study provided important evidence that the $^{223}$RaCl$_2$–to–PSMA RLT sequence is safe and effective regardless of taxane-based chemotherapy position before, during, or after $^{223}$RaCl$_2$ and whether the patients received PSMA RLT less than 6 mo or at least 6 mo after the last dose of $^{223}$RaCl$_2$. A limitation of the study is that deciphering the comparative efficacy of PSMA RLT without prior exposure $^{223}$RaCl$_2$ in a cohort of patients with similar prior or ongoing nonradioactive therapies cannot be determined. Therefore, whereas it may be safe to use PSMA RLT after $^{223}$RaCl$_2$, we are not informed if $^{223}$RaCl$_2$ before PSMA RLT muted the efficacy of PSMA RLT alone if it was used instead of $^{223}$RaCl$_2$ earlier in the therapeutic algorithm. Nevertheless, the mechanisms of action of PSMA RLT and $^{223}$RaCl$_2$ are nonoverlapping, and as such, it may be justifiably reasonable to consider that the PSMA RLT efficacy may not be impeded by the prior use of $^{223}$RaCl$_2$. If there is an observation of less relative efficacy of PSMA RLT after $^{223}$RaCl$_2$, it may simply be due to progressive evolution of the disease.

The distinct mechanism of action also suggests that combination therapy with $^{223}$RaCl$_2$ and PSMA RLT may be a viable option.
The AlphaBet trial (NCT05383079) is an Australian ongoing, single-center, single-arm, open-label phase I and II study with coprimary objectives to establish the maximum tolerated dose, dose-limiting toxicities, and recommended phase II dose of $^{223}\text{RaCl}_2$ in combination with $^{177}\text{Lu}$-PSMA I&T in patients with mCRPC (10). The inclusion criteria entail patients with progressive disease based on Prostate Cancer Working Group 3 guidelines on one or more second-generation androgen receptor pathway inhibitor agents and at most 1 line of chemotherapy, with at least 2 bone metastases on bone scintigraphy and PSMA expression (defined as a minimum SUV$_{\text{max}}$ of 20 at the site of disease, an SUV$_{\text{max}} > 10$ at sites of measurable disease of $>10 \text{mm}$, and no discordant $^{18}$F-FDG PET–positive disease), and adequate protocol-defined marrow, liver, and renal functions. Patients with a superscan on bone scintigraphy and prior treatment with $^{223}\text{RaCl}_2$ or PSMA RLT were excluded.

As radiopharmaceutical therapy matures rapidly and robustly as a major pillar of cancer therapy among the previously established treatment strategies (surgery, cytotoxic chemotherapy, radiation therapy, molecular targeted therapy, immunotherapy), the understanding of the utility and limitations of radiopharmaceutical therapy in single, sequential, and combination therapeutic regimens becomes paramount for optimal cancer management. The RALU study contributed toward this important objective. Cancer is biologically and clinically complex, and its management as a chronic disease demands multifaceted systematic approaches using all available and future pillars of cancer therapy in innovative evidence-based ways.

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**REFERENCES**