The Potential Contribution of Radiopharmaceutical Therapies in Managing Oligometastatic Disease

Amar U. Kishan[1,2], Shankar Siva[3], Michael S. Hofman[4], James Nagarajah[5], Ana P. Kiess[6], Phuoc Tran[7], and Jeremie Calais[8]

[1]Department of Radiation Oncology, UCLA, Los Angeles, California; [2]Department of Urology, UCLA, Los Angeles, California; [3]Peter MacCallum Cancer Centre and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia; [4]Prostate Cancer Theranostics and Imaging Centre of Excellence, Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia; [5]Roentgeninstitut Duesseldorf, Duesseldorf, Germany; [6]Department of Radiation Oncology and Molecular Radiation Sciences, School of Medicine, Johns Hopkins University, Baltimore, Maryland; [7]Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland; and [8]Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, UCLA, Los Angeles, California

There is a growing understanding of the oligometastatic disease state, characterized by the presence of 5 or fewer lesions. Advanced molecular imaging techniques, such as prostate-specific membrane antigen PET, refines the ability to detect oligometastatic recurrences (oligorecurrences) early. These developments have led to the exploration of metastasis-directed therapy (MDT) in oligorecurrent disease as an alternative to or as a means of delaying systemic therapy. Unfortunately, MDT often does not provide a durable cure, and progression—particularly progression in multiple new areas—remains a concern. Simultaneously, developments in radioligand therapy (RLT) have led to studies showing overall survival benefits with α-emitting and β-emitting RLT in advanced, high-volume, metastatic castration-resistant prostate cancer. The success of RLT in late-stage disease suggests that earlier use in the disease spectrum may be impactful. Specifically, integration of RLT with MDT might reduce progression, including polymetastatic progression, in the setting of oligorecurrent disease.

Key Words: stereotactic body radiotherapy; radioligand therapy; oligometastatic prostate cancer

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As our understanding of the natural history and biology of prostate cancer evolves, we have gained appreciation for the fact that metastatic prostate cancer is a heterogeneous disease entity composed of multiple subgroups with distinct prognoses (*1*,*2*). The most intuitive method of subclassifying metastatic disease—based on the burden or volume of disease—is also the most evidence-based, as a lower burden of disease has consistently been associated with improved overall survival (OS) (*3*–*7*). At the extreme end of this spectrum of disease would be the oligometastatic disease state, formally postulated in 1995 and now considered to be a distinct disease stage characterized by the presence of a limited number of clinically detectable metastases, typically 5 or fewer (*8*,*9*). Oligometastatic disease can be further dichotomized on the basis of the temporal sequence of presentation: de novo oligometastatic disease refers to oligometastatic spread detected at the time of initial diagnosis, and recurrent oligometastatic disease (or oligorecurrent disease) refers to oligometastatic disease detected after prior definitive-intent local therapy. Conceptually alongside increasing evidence, the oligometastatic disease state could be considered a combination of truly indolent disease biology with limited polymetastatic potential, truly aggressive disease biology identified early in the course, or traditionally subclinical disease that has been identified by increasingly sensitive imaging (*10*,*11*).

The recognition of the oligometastatic disease state occurred in synchrony with years of diligent basic, translational, and clinical research that have identified substantial survival benefits with androgen deprivation therapy (ADT) and second-generation androgen receptor signaling inhibitors in metastatic hormone-sensitive prostate cancer (mHSPC) (*12*). Although the improvement in efficacy has been undeniable, ADT alone, let alone with second-generation agents, is associated with significant detriments in quality of life (*13*).

Furthermore, significant imaging advances have led to a substantial improvement in detection of metastatic spread, allowing diagnosis of metastatic disease far earlier—and thus at a substantially lower burden—than previously possible. Chief among these advancements is the development of prostate-specific membrane antigen (PSMA)–based PET/CT. PSMA PET/CT offers substantially improved sensitivity and specificity for the identification of extraprostatic disease in both the de novo and the recurrent settings (*14*). A reasonable conclusion would be that molecular imaging–defined oligometastatic disease represents the lowest potential burden of disease along the metastatic spectrum, and therefore alternative therapeutic strategies to those typically used for conventionally defined mHSPC can and should be pursued.

OVERVIEW OF METASTASIS-DIRECTED THERAPY (MDT) IN PROSTATE CANCER

To this end, MDT has emerged as an attractive option for the growing population of patients diagnosed with molecularly defined mHSPC. The premise for why MDT might significantly impact

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For correspondence or reprints, contact Amar U. Kishan (aukishan@mednet.ucla.edu).
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natural history, rather than simply provide local control for treated lesions, stems from the discovery that metastasis-to-metastasis spread in the same patient is common, either through de novo monoclonal seeding of daughter metastases or through the transfer of multiple tumor clones between metastatic sites (*15*). Indeed, in contrast to the traditional belief in solid oncology that the cancer is no longer curable once it becomes metastatic, aggressive MDT to eliminate all sites of macroscopic disease in a patient with oligometastatic disease has been shown to lead to long-term disease control and possibly even a cure in certain cases (*16–25*).

The development of stereotactic body radiation therapy (SBRT), which involves the delivery of an ablative dose of radiation precisely to the lesions in 5 or fewer treatment sessions, is a critical tool for MDT. Given its biologic advantage of a higher dose per fraction, increased convenience with a shorter treatment course, a high local control rate, and a modest toxicity profile, SBRT has become the radiation modality of choice when delivering MDT. The randomized SABR-COMET trial is one of the earlier trials that tested whether MDT delivered via SBRT could improve outcomes in patients with oligometastatic disease. In this trial, 99 patients with controlled primary malignancies of various histologies who had 5 or fewer metastatic lesions were randomized 2:1 to SBRT to all sites of disease or the palliative standard of care (which included non-SBRT palliative radiation). The most common primary tumor types were breast ($n = 18$), lung ($n = 18$), colorectal ($n = 18$), and prostate ($n = 16$). At a median follow-up of 25 mo, median OS was 41 mo among patients receiving SBRT versus 28 mo in patients receiving the standard of care ($P = 0.09$) (*26*). With longer-term follow-up (median, 51 mo), SBRT was still associated with an increased OS (5-y OS, 42.3% vs. 17.7%; $P = 0.006$) and progression-free survival (PFS) (5-y PFS, not reached vs. 17.3%; $P = 0.001$) (*17*). However, an increased risk of grade 2 toxicity or higher was seen (29% vs. 9%, $P = 0.026$).

For prostate cancer specifically, MDT for oligorecurrent disease has been evaluated in 4 prospective studies, including 2 randomized phase II trials (Table 1). The STOMP trial enrolled 62 men with oligorecurrent disease after prior surgery or radiation who had no more than 3 metastases visible on ^{11}C-choline PET and randomized them to observation versus MDT (*18*). The primary endpoint was ADT-free survival, with ADT starting at the time of polymetastatic progression, local progression, or symptoms. PFS was a composite secondary endpoint, defined by biochemical progression (as per PCWG2 (*27*)), RECIST-based local progression

NOTEWORTHY

- MDT, particularly in the form of SBRT, has been shown to improve PFS and systemic treatment-free survival in men with oligorecurrent prostate cancer in multiple prospective studies.
- Long-term cures after MDT are rare, and a substantial proportion of patients experience polyprogression within 2 y of MDT.
- ^{223}Ra and ^{177}Lu-PSMA RLT have been shown to improve OS in patients with mCRPC, but responses in advanced disease are not durable because of the aggressive natural history and high burden of disease that can become nonresponsive.
- Integrating theranostic therapy with metastasis-directed SBRT may limit polyprogression and improve durable response rates and intervals.

TABLE 1
Summary of Prospective Trials of MDT for Oligorecurrent Hormone-Sensitive Prostate Cancer

Trial	Design	Imaging	Patients (*n*)	Lesion distribution	Median follow-up	Result
STOMP (*18*)	Phase II RCT MDT vs. surveillance (80% MDT was SBRT)	Choline PET/CT (1–3 lesions)	62	Bone, 39%; node, 55%; viscera, 2%	36	PFS, 10 vs. 6 mo; ADT-FS, 21 vs. 13 mo
ORIOLE (*19*)	Phase II RCT SBRT vs. surveillance	Conventional imaging (1–3 lesions)	54	Bone, 39%; node, 61%	19	6-mo progression rate: 19% vs. 61%
POPSTAR (*20*)	Phase I SBRT (33% had ADT)	NaF PET/CT (1–3 lesions)	33	Bone, 61%; node, 36%; bone and node, 3%	24	2-y distant PFS, 58%; 2-y ADT-FS, 48%
MRgRT (*23*)	Phase II single MDT (73% SBRT)	Negative conventional and positive PSMA PET/MRI/CT (1–5 lesions)	37	Node, 92%; bone, 8%	16	22% had complete response with PSA < 0.05; ADT-FS, 17.7 mo

RCT = randomized controlled trial; ADT-FS = ADT-free survival.

(*28*), distant progression, and death from any cause. Among patients who received MDT, 81% received SBRT. Initial results at a median follow-up of 36 mo showed that MDT improved ADT-free survival from 13 to 21 mo and improved the median time to biochemical progression from 6 to 10 mo. In an update with longer follow-up, the PFS benefit of MDT was maintained (hazard ratio [HR], 0.48; $P = 0.01$) (*29*).

The ORIOLE trial enrolled 54 patients with oligorecurrent disease after prior surgery or radiation who had no more than 3 metastases visible on conventional imaging (*19*). The primary endpoint was the proportion of men with disease progression at 6 mo, defined as a composite endpoint of a PSA rise of at least 2 ng/dL and 25% above nadir; concern for radiologic progression by either CT, MRI, or bone scanning; symptomatic progression of disease; initiation of ADT for any reason; or death. All patients underwent ^{18}F-DCFPyL PSMA PET/CT as well, though patients and investigators were masked to the results. Overall, SBRT reduced the proportion of men with disease progression from 61% to 19% at 5 mo ($P = 0.005$). With a median follow-up of 18.8 mo, the median PFS with SBRT was not reached, whereas it was 5.8 mo with observation (HR, 0.3; $P = 0.002$). Among the 36 men who underwent PSMA PET/CT, 16 (44.4%) had lesions not seen on conventional imaging. The proportion of progression at 6 mo was only 5% for men with no untreated PSMA-positive lesions, versus 38% for those with any untreated PSMA-positive lesions ($P = 0.03$). Median distant metastasis-free survival was 29.0 mo in men with no untreated lesions, versus 6.0 mo in men with any untreated lesion ($P < 0.001$).

In an update with a median follow-up of 5.3 y, the PFS benefit of MDT was maintained (HR, 0.48; $P = 0.01$) (*29*). In a per-protocol analysis, MDT improved castration-resistant prostate cancer–free survival (HR, 0.51; $P = 0.12$) (*30*).

A pooled analysis of both trials with a median follow-up of 52.5 mo found that MDT significantly improved PFS from 5.9 to 11.9 mo, with a pooled HR of 0.44 ($P < 0.001$) (*29*). However, radiographic PFS, time to castration-resistant prostate cancer, and OS were not improved. Patients whose tumors harbored a high-risk mutational signature (defined by pathogenic somatic mutations within *ATM, BRCA1/2, Rb1,* and *TP53*) had a shorter PFS, though these patients had a significantly larger PFS benefit from MDT as well.

Two additional single-arm phase II trials have used advanced molecular imaging to investigate MDT in patients with oligorecurrent disease. The POPSTAR trial enrolled 33 men who had up to 3 bony or lymph node lesions seen on a screening ^{18}F-NaF-PET/CT scan (*20*). The primary endpoints were feasibility and tolerability; secondary outcomes included local and distant PFS, with the former scored by RECIST (*28*). Local PFS was 93% at 2 y, whereas 2-y distant metastasis-free survival was 39%. Twenty-two of the patients had hormone-sensitive disease, and among these patients, the freedom from ADT was 48% at 24 mo. The PSMA MRgRT trial enrolled patients with negative results on conventional imaging and 5 or fewer lesions on ^{18}F-DCFPyL PSMA PET/MRI/CT who had a rising PSA of 0.4–3.0 ng/mL (*23*). Ultimately, 37 patients received MDT. At a median follow-up of 15.9 mo, 22% of patients had a complete biochemical response (PSA reduced to <0.05 ng/mL) and 60% of patients had a PSA decline of at least 50%. The median time to PSA progression was 17.7 mo. An update of the initial PSMA MRgRT cohort found that, with an extended follow-up to 40.7 mo, the biochemical response rate was maintained at 59.4%, with a complete biochemical response in 27% (*31*). In a validation cohort of 37 patients with identical enrollment criteria and a median follow-up of 14.3 mo, a biochemical response was seen in 43% of patients, with a complete response in 13.5%.

Taken together, studies confirm that MDT (predominantly delivered with SBRT) for patients with oligorecurrent prostate cancer significantly delays PSA-based progression. Importantly, MDT is safe: across these trials, of the 165 patients who received MDT, only 2 grade 3 toxicities attributable to MDT were seen. This contrasts with SABR-COMET, in which 3 treatment-related deaths were seen. The difference may be explainable by the fact that patients on the 4 prostate trials rarely had visceral metastases, which can be more challenging to irradiate.

Despite the favorable safety profile and overall initial efficacy, however, there are clearly patients who progress after MDT and may benefit from further treatment intensification (*32*,*33*). In a retrospective study of 258 patients with oligorecurrent mHSPC who had a median follow-up time of 25.2 mo, the median time to PSA recurrence after MDT was 15.7 mo and the median distant metastasis-free survival was 19.1 mo. Among patients who did not receive ADT, the median time to PSA recurrence was 10.9 mo and distant metastasis-free survival was 12.4 mo. Another 20 men were treated with a defined course of ADT; after stopping ADT, the median biochemical PFS was 17.6 mo. Overall, bone-only recurrence was the most common form of failure (44.2% of patients with recurrences), with another 24.8% of recurrences involving osseous disease in addition to another site. Node-only recurrences accounted for 26.5% of recurrences. Interestingly, the original site of recurrence was associated with subsequent sites of recurrence. Among patients treated for a bone lesion, most recurrences (86.5%) involved at least 1 osseous structure. For patients treated for a node-only lesion, most recurrences were also node-only (64.5%), though an osseous component was seen in 32.3% of recurrences. Three modes of progression were defined. Class I progressors, accounting for 40.9% of patients overall and 27.6% treated without ADT, had long-term control with no recurrences after 18 mo. Class II progressors, or oligoprogressors, had no more than 3 lesions at recurrence and accounted for 36% of patients overall and 44.8% of those treated without ADT. Class III progressors, or polyprogressors, had more than 3 lesions at recurrence and accounted for 23.1% of patients overall and 27.6% of those treated without ADT. Among patients who had advanced molecular imaging for follow-up, rather than conventional imaging, a lower percentage had long-term control (36.3%) and a higher percentage had polyprogression (26%). Overall, these data suggest that systemic therapy intensification is warranted in some patients with oligorecurrent mHSPC. Given that most men with early oligometastatic disease defined by molecular imaging may be seeking to avoid ADT—which may be primarily cytostatic in this context—alternative forms of systemic intensification warrant investigation.

OVERVIEW OF RADIOLIGAND THERAPY (RLT) AND THERANOSTIC THERAPIES IN PROSTATE CANCER

RLT, also known as radionuclide therapy, refers to the systemic administration of radiolabeled drugs targeting proteins that are specific to abnormal cells, allowing the delivery of localized radiation at the cellular level (*34*). Radioligands can be broadly classified into α-emitting radioligands and β-emitting radioligands. α-particles have short pathlengths of 50–80 μm, possess a linear energy transfer of 100 keV/μm, and can cause significant direct

DNA damage (*35*,*36*). β-particles have a longer pathlength of 0.05–12 mm as well as lower linear energy transfer of 0.2 keV/μm (*37*). β-particles may thus be less directly efficacious, particularly against smaller lesions, and may have more toxicity against nontarget tissues (*38*). Overall, only 1 α-emitter is approved for clinical use, whereas multiple β-emitters are approved across different cancers. Specifically in the context of prostate cancer, 2 older β-emitters were approved for palliative use, but 1 α-emitter, ^{223}Ra-dichloride (^{223}Ra), and 1 β-emitter, ^{177}Lu vipivotide tetraxetan (^{177}Lu-PSMA-617), have been shown to improve OS (*39*). Studies with these agents are summarized below and in Table 2.

^{223}Ra is a targeted α-emitter that, as a calcium mimetic, is preferentially incorporated into the bony matrix in areas of high bone turnover such as osteoblastic or sclerotic metastases (*40–42*).^{223}Ra is thus an attractive RLT for metastatic castration-resistant prostate cancer (mCRPC), a lethal, end-stage form of prostate cancer in which bone-related complications are a leading cause of death (*43*). The benefit of ^{223}Ra was shown in the ALSYMPCA trial (*44*). In this trial, 921 men with progressive mCRPC and 2 or more symptomatic bone metastases with no known visceral metastases were randomized in a 2:1 fashion to receive either 6 doses of ^{223}Ra (dosed at 50 kBq/kg of body weight every 4 wk) or placebo, in addition to the standard of care. The primary endpoint was OS, and this was improved by the addition of ^{223}Ra (median OS, 14.9 vs 11.3 mo; $P < 0.001$). The time to the first symptomatic skeletal event was significantly prolonged as well (median, 15.6 vs. 9.8 mo; $P < 0.001$). No significant differences in adverse events of grade 3 or higher were noted between arms. At the median follow-up of 13 mo, no acute myeloid leukemia, myelodysplastic syndrome, or new primary bone cancers were seen (*45*). Quality of life was also assessed; using an estimation of pain-related symptoms based on the Functional Assessment of Cancer Therapy–Prostate questionnaire, patients receiving ^{223}Ra were found to be more likely to experience meaningful improvements in pain (30.2% vs. 20.1%; $P = 0.010$) (*46*). An earlier randomized phase II trial using a similar dosing regimen, but with only 4 doses total, identified a benefit in terms of time to first bone-related event as well (*47*). A trial-level metaanalysis that included both studies found a pooled HR of 0.70 (95% CI, 0.58–0.83) for improving OS (*48*). Unfortunately, the addition of ^{223}Ra to abiraterone acetate with prednisone failed to improve symptomatic skeletal event–free survival or OS in the evaluation of ^{223}Ra in combination with abiraterone in castration-resistant prostate cancer (ERA 223) trial (*49*). Significantly more fractures were seen in patients receiving ^{223}Ra (9% vs. 3%), particularly in patients not receiving bone protection agents.

Theranostics is a precision medicine approach that uses targeted radioactive compounds to image specific cell surface markers and subsequently uses RLTs to irradiate tissues expressing these markers (*50*). ^{177}Lu-PSMA-617 is a chemically modified DOTA-conjugated PSMA binder that has allowed the first theranostic therapy in prostate cancer. In the VISION trial, 831 patients with mCRPC and at least 1 PSMA-positive lesion were randomized in a 2:1 ratio to either 4 or 6 cycles of 7.4 GBq of ^{177}Lu-PSMA-617 every 6 weeks with standard of care versus standard of care alone (*51*). Specific eligibility criteria were at least 1 PSMA-positive lesion with uptake greater than liver parenchyma and no large PSMA-negative lesions, disease progression after treatment with at least 1 second-generation androgen receptor signaling inhibitor and 1 or 2 taxanes, and life expectance of more than 6 mo. Treatment with ^{177}Lu-PSMA-617 improved OS (median, 15.3 vs.

TABLE 2
Summary of Selected Phase II–III Randomized Trials of ^{223}Ra and ^{177}Lu-Based RLTs in Prostate Cancer

Trial	Design	Dosage	Inclusion criteria	Patients (*n*)	Result
ALSYMPCA (*44*)	Phase III RCT; standard of care + 6 doses of ^{223}Ra vs. standard of care	50 kBq per kilogram of body weight every 4 wk	Progressive mCRPC and ≥2 symptomatic bone metastases with no known visceral metastases	921	OS, 14.9 vs. 11.3 mo; time to first symptomatic skeletal event, 15.6 vs. 9.8 mo; meaningful improvements in pain (30.2% vs. 20.1%)
VISION (*51*)	Phase III RCT; 4–6 cycles of ^{177}Lu-PSMA-617 vs. standard of care	7.4 GBq every 6 wk	Progressive mCRPC ≥1 PSMA-positive lesion with uptake greater than liver parenchyma and no PSMA-negative lesions	831	Improved OS, median 15.3 mo vs. 11.3 mo; radiographic PFS, median 8.7 vs. 3.4 mo; time to first symptomatic skeletal event or death, median of 11.5 vs. 6.8 mo
TheraP (*53*)	Phase II RCT; op to 6 cycles of ^{177}Lu-PSMA-617 vs. cabazitaxel	8.5 GBq for first cycle, with 0.5-GBq decrease per subsequent cycle (6 wk between cycles)	Progressive mCRPC ≥1 PSMA-positive lesion with SUV_{max} ≤20 (with all other PSMA-avid sites having SUV_{max} of ≥10) and nondiscordant findings between PSMA and ^{18}F-FDG PET/CT	200	PSA response rate (50% reduction or more), 66% vs. 37%; progression was delayed with ^{177}Lu-PSMA-617 (HR, 0.63)

RCT = randomized controlled trial.

TABLE 3
Summary of Prospective Studies Integrating RLT with External-Beam Radiotherapy in Oligorecurrent Disease

Trial	Inclusion	*n*	RLT and dosage	Timing of RLT	Primary endpoint
Randomized evaluating addition of RLT to SBRT					
LUNAR (NCT05496959)	≤5 lesions outside prostate/prostate bed on PSMA PET/CT	90	^{177}Lu-PNT2002 (6.8 GBq per cycle, 2 cycles given 6–8 wk apart)	Neoadjuvant	PFS: progression defined on basis of PSMA PET/CT scans obtained at 12 mo or at time of PSA-based biochemical progression; initiation of salvage therapy
POPSTAR II (NCT05560659)	≤5 sites of nodal or bony metastases, with at least 1 site with SUV_{max} 2× SUV_{max} liver	92	^{177}Lu-PNT2002 (6 GBq (±10%) per cycle, 2 cycles 6–8 wk apart)	SABR between cycles 1 and 2	PFS: progression defined as biochemical or clinical
RAVENS (NCT04037358)	≤3 metastases with at least 1 bone (on CT or bone scan) or ≤5 metastases with at 1 least 1 bone (on PET/CT); PSADT < 15 mo; PSA ≥ 0.5	64	^{223}Ra (55 kBq per cycle, 6 cycles 4 wk apart)	SABR concurrent with cycle 1	PFS: progression defined as biochemical (PSA increased by ≥2 ng/mL from nadir) or clinical (based on conventional imaging or initiation of ADT)
PSMA-DC (NCT05939414)	≤5 metastases by PSMA PET only with none on CT or bone scan	450	^{177}Lu-PSMA-617 (6.8 GBq per cycle, 4 cycles given 6 wk apart)	Neoadjuvant	Metastasis-free survival: defined as lack of metastasis identifiable on bone scan, CT, or MRI
Phase II single arm evaluating adding radiotherapy to RLT					
ProstACT target (NCT05146973)	Recurrent after prostatectomy; ≤5 nodal lesions, all at or below aortic bifurcation with SUV_{max} > 5; radiotherapy here is conventionally fractionated salvage radiotherapy	50	^{177}Lu-DOTA-TLX591-CHO (2.8 GBq per cycle, 2 cycles given 2 wk apart)	Adjuvant	PSA-based PFS: time from enrollment to time of PSA increase > 25%
NCT03361735	≤4 metastases with at least 1 bone lesion and ≤1 visceral or nodal lesions	24	^{223}Ra 5 (55 kBq per cycle, 6 cycles 4 wk apart)	9 mo of ADT, with SBRT starting on day 1 of ADT and radium starting on day 31 of ADT	Time to treatment failure: time from initiation of ADT for metastatic disease until PSA increase to >pre-ADT level or PSA > 10 (whichever is smaller) or radiographic or clinical progression or resumption of ADT by physician's choice

PSADT = PSA doubling time; RCT = randomized controlled trial.

11.3 mo; $P < 0.0001$) and radiographic PFS (median, 8.7 vs. 3.4 mo; $P < 0.001$). Grade 3 or higher adverse events were higher in the experimental group (52.7% vs. 38.0%), but overall quality of life was not impacted. The most common adverse events included fatigue, dry mouth, anemia, and back pain. Time to first symptomatic skeletal event or death was also prolonged (median, 11.5 vs. 6.8 mo; $P < 0.001$). A subsequent quality-of-life analysis found that time to worsening of quality of life by the Functional Assessment of Cancer Therapy–Prostate metric was prolonged with ^{177}Lu-PSMA-617 (*52*). Hematologic adverse events of grade 3 or higher included decreased hemoglobin (15% vs. 6%), lymphocyte concentrations (51% vs. 19%), and platelet counts (9% vs 2%).

The phase II TheraP trial randomized 200 patients with mCRPC and prior docetaxel treatment to ^{177}Lu-PSMA-617 or cabazitaxel (*53*). Patients were required to have at least 1 ^{68}Ga-PSMA–positive lesion with an SUV_{max} of at least 20 (with all other PSMA-avid sites having an SUV_{max} of $\geq$10) and nondiscordant findings between PSMA and ^{18}F-FDG PET/CT. The dosage schedule for ^{177}Lu-PSMA-617 was 8.5 GBq for the first cycle with a 0.5-GBq decrease per each subsequent cycle (maximum of 6 cycles with 6 wk between cycles). The primary endpoint was the PSA response rate ($\geq$50% reduction), and treatment with ^{177}Lu-PSMA-617 did significantly improve this (66% vs. 37%, $P < 0.0001$). The effect of treatment on PFS was not constant with time, and the impact appeared to be more pronounced after 6 mo. However, when a Cox model was used, progression was delayed with ^{177}Lu-PSMA-617 (HR, 0.63; $P = 0.0028$). ^{177}Lu-PSMA-617 did not increase the rate of overall toxicities of grade 3 or higher (33% vs. 53%), though thrombocytopenia was more common with ^{177}Lu-PSMA-617 (11% vs. 0%). Improvements in quality of life and symptoms were seen with ^{177}Lu-PSMA-617 with respect to diarrhea, fatigue, social functioning, and insomnia, and deterioration-free survival for global health status was better for men receiving ^{177}Lu-PSMA-617 at 6 mo (9% vs. 13%, $P = 0.0002$). A post hoc analysis found that ^{68}Ga-PSMA-PET SUV_{mean} was predictive of a higher likelihood of a favorable response and a high ^{18}F-FDG PET metabolic tumor volume associated with a lower response regardless of randomly assigned treatment (*54*).

^{177}Lu-PSMA-I&T (also known as ^{177}Lu-PNT2002) is the second PSMA-targeting RLT that has been studied in large clinical trials. It has more kidney uptake, but less lacrimal uptake, than ^{177}Lu-PSMA-617 (*55–57*) and has shown anticancer activity in the compassionate-use setting for patients with heavily pretreated mCRPC (*58*). It is being studied in 2 phase III randomized trials in the mCRPC space: SPLASH (NCT04647526) and ECLIPSE (NCT05204927). Preliminary results from both were expected in late 2023.

COMBINING RLT WITH MDT

Overall, the data suggest that although MDT for mHSPC is effective at controlling individual lesions, its potential as a curative option is limited because of the existence of occult disease at the time of treatment. The use of advanced molecular imaging for patient selection may increase the percentage of patients with a long-term response, but ultimately most patients will still experience progression. RLT possesses significant antineoplastic activity even in the most advanced setting of mCRPC but ultimately is not a curative option given the natural history of CRPC and a limit to the number of cycles that can safely be administered (*59*). The ultimate limitation after RLT may also depend on the emergence of PSMA-negative, ^{18}F-FDG–positive disease that is no longer effectively targeted. Earlier administration of RLT therapy before such clones can emerge and when the burden of disease is lower may increase the effectiveness of RLT in durably controlling disease. A logical synergy between MDT and the theranostic approach might be achieved using both MDT and RLT in patients with oligorecurrent mHSPC. The disease setting would by definition include a low burden of disease, and we would not expect the presence of PSMA-negative ^{18}F-FDG–positive occult disease, which would improve the efficacy of the RLT. Similarly, the addition of RLT and the use of imaging to select patients with lower-volume disease would improve the efficacy of MDT by reducing the rates of oligo- and polyprogression.

The potential benefit of this synergy also rests on the hypothesis that RLT would be effective, without combination with ADT, in mHSPC. This was tested in the randomized multicenter phase II BULLSEYE trial (*60*). In this trial, men with mHSPC and 5 or fewer lesions, with an SUV_{max} of more than 15 for all lesions and a PSA doubling time of no more than 6 mo were randomized in a 1:1 fashion to 2–4 cycles of 7.4 GBq of ^{177}Lu-PSMA-617 versus deferred ADT. The primary endpoint is progression within 24 wk of cycle 2, with progression defined as a 100% increase in PSA or radiographic or clinical progression. Early results based on the first 42 patients enrolled on the study indicated a promising effect from the treatment (*34*). The median PSA was 4.5 ng/dL at inclusion. At 6 mo of follow-up, 10% of patients on the treatment arm versus 77% of patients on the control arm had experienced progression. The median PFS was not reached in the treatment arm, versus 4 mo in the control arm ($P < 0.001$). Overall, 24% of patients had a complete biochemical and imaging response. Only 3 grade 3 adverse events were seen. Though early, these interim results support the concept that RLT agents are active in the setting of mHSPC as well.

The direct question of whether the integration of RLTs with MDT will improve outcomes in mHSPC is being tested in 3 randomized phase II trials and 2 single-arm phase 2 studies. These are summarized in Table 3. The RAVENS and LUNAR trials will be fully accrued by the end of 2023. The phase III PSMA-DC study (NCT05939414) is also planned to open to accrual in late 2023 for patients with only molecular oligometastatic disease. As data supporting RLT in earlier disease states matures, more studies integrating RLT with MDT are likely on the horizon.

CONCLUSION

An increased appreciation of the oligometastatic state in prostate cancer has led to a paradigmatic shift in approaches to managing selected patients with low-volume or oligorecurrent mHSPC. Among the most promising is the use of MDT, particularly via SBRT, to significantly prolong progression and the initiation of ADT. In tandem, clinical trials have shown survival benefits to the use of α-emitting ^{223}Ra and β-emitting ^{177}Lu-PSMA agents in more advanced mCRPC. Given that progression, particularly polyprogression, remains a common pattern of progression after MDT for oligorecurrent disease, the integration of RLTs with MDT seems a rational approach. Several clinical trials, including 3 randomized phase II trials, have already been launched evaluating this concept. The results of these studies are eagerly anticipated, and further clinical studies will be necessary to define the optimal integration and sequencing of these agents.

DISCLOSURE

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