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Review

PSMA-Targeted Radioligand Therapy for Androgen Pathway Modulation-Resistant Prostate Cancer (APMR) in the Chemotherapy-Naïve Setting: A Narrative Review and Expert Commentary

Di Maria Jiang [1,*], Kim N. Chi [2], Urban Emmenegger [3,4], Sebastien J. Hotte [5], Girish S. Kulkarni [6], Aly-Khan A. Lalani [5,7], Krista L. Noonan [8], Frédéric Pouliot [9,10], Ricardo A. Rendon [11], Christopher J. D. Wallis [12,13,14], Steven M. Yip [15] and Fred Saad [16]

1 Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON M5S 1A1, Canada
2 BC Cancer, University of British Columbia, Vancouver, BC V5Z 4E6, Canada; kchi@bccancer.bc.ca
3 Sunnybrook Odette Cancer Centre and Research Institute, Toronto, ON M4N 3M5, Canada
4 Temerty Faculty of Medicine, University of Toronto, Toronto, ON M5S 1A1, Canada
5 Department of Oncology, McMaster University, Hamilton, ON L8S 1C7, Canada; hotte@hhsc.ca (S.J.H.)
6 Division of Urology, Department of Surgery, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON M5S 1A1, Canada
7 Division of Medical Oncology, Juravinski Cancer Centre, Hamilton, ON L8V 5C2, Canada
8 Department of Medical Oncology, BC Cancer, Surrey, BC V3V 1Z2, Canada
9 Centre Hospitalier Universitaire de Québec, Université Laval, Québec City, QC G1R 2J6, Canada
10 Division d'Urologie, Département de Chirurgie, Université Laval, Québec City, QC G1V 0A6, Canada
11 Department of Urology, Dalhousie University, Halifax, NS B3H 4R2, Canada
12 Division of Urology, Department of Surgery, University of Toronto, Toronto, ON M5S 1A1, Canada; christopher.wallis@sinaihealth.ca
13 Division of Urology, Department of Surgical Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON M5G 2C4, Canada
14 Division of Urology, Department of Surgery, Mount Sinai Hospital, University of Toronto, Toronto, ON M5S 1A1, Canada
15 Arthur J.E. Child Comprehensive Cancer Centre, University of Calgary, Calgary, AB T2N 5G2, Canada
16 Division of Urology, Centre Hospitalier de l'Université de Montréal (CHUM), Université de Montréal, Montréal, QC H3T 1J4, Canada
* Correspondence: di.jiang@uhn.ca

Simple Summary

Prostate cancer is one of the most common cancers among men and is becoming even more prevalent over time. The options for treating advanced prostate cancer are rapidly growing. One newer option is radioligand therapy ("RLT"), which takes advantage of markers on the tumor surface to guide radioactive molecules to cancerous cells in a highly targeted manner. Until recently, this kind of therapy had only been tested and approved for use after the failure of chemotherapy to treat advanced disease. There are now data showing it may be effective earlier in the disease course, and this creates difficulty in choosing who is best suited for which treatment. This review provides a summary of what we know about using RLT before chemotherapy, how it compares to chemotherapy, and our opinion on how to best choose between them for patients with advanced prostate cancer who have not yet received chemotherapy.

Abstract

The treatment landscape for metastatic castration-resistant prostate cancer (mCRPC), more recently termed androgen pathway modulation-resistant prostate cancer (APMR), continues to evolve rapidly with advances in imaging techniques and prostate-specific membrane

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antigen (PSMA)-targeted radioligand therapy (RLT). Following disease progression on androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPIs), treatment selection remains challenging, particularly for patients who are not planned for docetaxel chemotherapy. Although docetaxel remains an important standard treatment, its relatively low real-world uptake and the frequent use of alternative strategies with limited proven efficacy highlight an important unmet need. Recent randomized trials demonstrate that PSMA-targeted RLT has improved response rates compared to an ARPI switch in patients with APMR who are chemotherapy-naïve, with a favorable tolerability profile. However, the optimal treatment sequencing relative to docetaxel chemotherapy remains unestablished. In this review, we examine the emerging evidence supporting the use of PSMA-targeted RLT in select patients with chemotherapy-naïve APMR, its potential role within current treatment pathways, and key considerations for patient selection, treatment sequencing, and the involvement of an experienced medical oncologist within a multidisciplinary team.

Keywords: radioligand therapy; chemotherapy; prostate cancer; mCRPC; APMR; PSMA; ^{177}Lu-PSMA-617

1. Introduction

Prostate cancer is the most common cancer among men in Canada (excluding non-melanoma skin cancers), estimated to represent over 20% of cancer diagnoses and 11% of cancer deaths in Canadian men [1]. Metastatic prostate cancer is associated with a 5-year net survival rate of 56.6% in men between 50 and 75 years of age and under 30% in older men; its incidence appears to be rising in Canada [1,2]. For patients with metastatic castration-resistant prostate cancer (mCRPC), more recently termed androgen pathway modulation-resistant prostate cancer (APMR) [3], whose disease has progressed after androgen deprivation therapy (ADT) and an androgen receptor pathway inhibitor (ARPI), real-world Ontario data suggest a median overall survival (OS) of only 18.9 months [4], highlighting the need for effective and well-tolerated therapeutic options in this setting to improve patient outcomes.

^{177}Lu-PSMA-617 (lutetium [^{177}Lu] vipivotide tetraxetan) is currently Health Canada–approved and available at select centers in Canada for patients with prostate-specific membrane antigen (PSMA)-positive APMR following disease progression on ADT, ARPI and docetaxel chemotherapy, based on the phase III VISION trial [5]. More recently, the PSMAfore, SPLASH, and PLUDO (CCTG.PR21) trials evaluated PSMA-targeted radioligand therapy (RLT) earlier in the treatment pathway in chemotherapy-naïve patients with APMR. These data raise important questions regarding how to best integrate PSMA-targeted RLT alongside established systemic therapies and its optimal positioning within current treatment pathways. In this narrative review, we examine the emerging evidence for PSMA-targeted RLT in chemotherapy-naïve APMR and discuss its potential clinical applicability, with particular consideration of patient selection, treatment sequencing, and emphasis on the involvement of an experienced medical oncologist within a multidisciplinary setting.

2. Methodology

This review was prepared by Canadian genitourinary medical oncologists and urologists with clinical experience in advanced prostate cancer, including RLT. The panel was convened by the lead authors, who prepared an initial draft based on publications and conference presentations/abstracts from pivotal phase II and III trials and current regulatory

approvals. The draft was circulated to all authors and refined through iterative written review until all authors agreed on the final text. The listed authors had full editorial control of the content. No formal consensus methodology (e.g., Delphi process or evidence grading) was applied; the recommendations represent the expert opinion of the authors and are intended to complement, not replace, formal clinical practice guidelines.

3. Current Health Canada-Approved Treatments for APMR After Progression on ADT+ARPI

Canadian and other international guidelines recommend several life-prolonging treatment options for APMR after progression on ADT and ARPIs, including docetaxel (a taxane chemotherapy), radium-223 (an alpha-emitting calcium mimetic targeting the bone matrix), olaparib (a poly [ADP-ribose] polymerase [PARP] inhibitor), and pembrolizumab (a PD-1 receptor inhibitor) in biomarker-selected patients (Table 1) [6,7].

Table 1. Current Health Canada-approved systemic therapy options for APMR in a post-ARPI, docetaxel-naive setting [4,6–9].

Disease and Clinical Features	Systemic Therapy Option	Estimated Real-World Utilization Rates [a]
BRCA1/2 or *ATM* mutation	Olaparib	<10%
Mismatch repair-deficient or MSI-high tumors	Pembrolizumab	<5%
Symptomatic, bone-only disease	Radium-223	<10%
Rapid progression, fit for chemo	Docetaxel	30%
Indolent disease trajectory, wish to defer chemotherapy, None of the above	ARPI switch, prednisone to dexamethasone switch	35%

[a] Numbers represent authors' estimates of usage rates among patients who received ARPIs as a first line of therapy based on the cited literature and their own experiences. Rates do not total 100% as some patients are referred for radiation or clinical trials. Abbreviations: MSI, microsatellite instability.

APMR has marked heterogeneity in tumor biology and clinical phenotype, and treatment decisions should be individualized whenever possible. Mutations in genes associated with homologous recombination repair (HRR), particularly involving *BRCA2*, should lead to prioritizing PARP inhibitor monotherapy as the next line of therapy given the significant survival benefit in this subgroup and relatively favorable tolerability profiles [6]. Among HRR-wild type patients, those with rapid progression or significant visceral disease are likely best served with docetaxel chemotherapy. Radium-223 should be considered for patients with symptomatic bone-only metastases, either pre- or post-docetaxel, and has an excellent safety profile [6]. Pembrolizumab is also a treatment option for patients with mismatch repair–deficient (dMMR) or microsatellite instability-high tumors, which occurs in roughly 3% of prostate cancers [8,10].

4. Significant Unmet Need in APMR When Chemotherapy Is Not an Option

While docetaxel chemotherapy is an effective treatment option for APMR, with PSA50 response rates around 40–50% in recent trials [6,11], its use can be limited due to toxicity, including fatigue, nausea, neutropenia, serious infections, and neuropathy. Rarely, docetaxel

can cause treatment-related deaths [12]. In real-world practice, up to 40% of patients require dose reductions, and only about half complete ≥6 cycles [13]. Although some toxicities of docetaxel can be mitigated (e.g., by dose modification and/or primary G-CSF prophylaxis for neutropenia [14]), the overall negative impact on quality of life is a serious concern for patients [15]. The adverse event (AE) profile and patient perceptions of chemotherapy likely underlie its low rate of adoption in Canada. Of the 3575 patients who died of prostate cancer in Ontario from 2013 to 2017, only 776 received taxane chemotherapy; a more recent study shows that only an estimated 32% of patients with advanced prostate cancer ever receive taxane-based chemotherapy [16,17]. This rate was even lower in real-world results from the American Veterans' Affairs database [18].

In scenarios where docetaxel is not feasible or not immediately indicated, there are limited effective options. The presence of extra-osseous disease often precludes radium-223, and the absence of HRR mutations or dMMR limits the use of olaparib and pembrolizumab, respectively. As a result, we estimate that approximately 35% of patients with APMR who experience progression following ARPI treatment are either ineligible or not clinically indicated for life-prolonging systemic therapy options based on current Health Canada approval criteria (Table 1). Real-world data suggests these patients may be relying on alternative treatments with limited efficacy and/or low-level evidence.

After progression on ADT+ARPI, approximately 20% of patients in Ontario receive a second ARPI [4], although this is not widely endorsed by current guidelines due to limited efficacy and the availability of alternative life-prolonging systemic therapies. Notably, the use of enzalutamide after abiraterone has demonstrated modest activity, with a PSA30 response rate of 36% and median PSA progression-free survival of 3.5 months compared to 4% and 1.7 months, respectively, for the sequence of abiraterone after enzalutamide [4,6,19].

Similarly, evidence supporting the use of metastasis-directed therapy (MDT) in oligometastatic or oligoprogressive APMR following ARPIs is very limited. Most evidence supporting MDT currently comes from the mCSPC setting [20]. In APMR, the randomized phase 2 ARTO and GROUQ-PCS 9 trials demonstrated that the addition of MDT to ADT+ARPI provided significant improvements in radiographic progression-free survival (rPFS) in oligometastatic disease (up to 3–5 lesions). Median rPFS was 44 vs. 17 months (HR 0.48 [95% CI 0.32–0.72], $p < 0.001$) in ARTO, and 4.6 vs. 2.3 years (HR 0.48 [95% CI 0.27–0.86], $p = 0.014$) in GROUQ-PCS9 [21,22]. ARTO also reported a significant OS benefit for MDT (not reached vs. 50 months, HR 0.55 [95% CI 0.33–0.92], $p = 0.021$) [22]. However, both trials were relatively small (approximately 80 and 50 patients per arm, respectively) and enrolled patients largely with APMR who had progression on ADT alone (ARPI-naïve), limiting their generalizability to contemporary APMR patients progressing on ADT and ARPIs. The small, phase 2, single-arm RADIANT study supports the feasibility of MDT in this setting, though larger randomized trials are still needed [23]. Several other uncertainties remain regarding the use of MDT, including the optimal definition of oligometastatic APMR and the role of PSMA PET in patient selection.

Common strategies used to delay chemotherapy—including continued ARPI, a switch in ARPI, a switch from prednisone to dexamethasone in patients undergoing abiraterone therapy, or adding radiation therapy—have limited efficacy and supporting data. Although these approaches are relatively well tolerated, their use may lead to some patients missing a "window of opportunity" for more effective therapies upon progression due to declining performance status or marrow reserve. Their frequent use in real-world practice highlights a significant unmet need in these patients.

5. PSMA-Targeted Radioligand Therapy for APMR After Progression on ADT+ARPI

Table 2 summarizes the data from three key trials evaluating PSMA-targeted RLT for patients with APMR in the post-ARPI, docetaxel-naïve setting. The phase 3 PSMAfore trial compared the efficacy and safety of ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks for 6 cycles) against a switch in ARPIs in 468 patients with PSMA-positive APMR who experienced progression on an ARPI. The study allowed patients who received prior ARPIs (47%) or docetaxel (18%) for metastatic castration-sensitive disease (mCSPC) or recently termed metastatic androgen pathway modulation-naïve or -sensitive (APMN/S), reflecting the contemporary practice of treatment intensification [24]. Compared to a switch in ARPIs, ^{177}Lu-PSMA-617 provided a significant benefit on the primary outcome of radiographic progression-free survival in the primary analysis (third interim OS analysis, median time from randomization to data cut-off 24.11 months) with rPFS of 11.60 months (95% CI 9.30–14.19 months) versus 5.59 months (95% CI 4.21–5.95 months) with an ARPI change (HR 0.49, 95% CI 0.39–0.61). Response rates favored ^{177}Lu-PSMA-617, with objective response rates (ORR) of 50% vs. 15%, and PSA50 response rates of 51% vs. 17% [25]. Median OS, a key secondary endpoint for this study, was 24.48 months (95% CI 19.55–28.94) with ^{177}Lu-PSMA-617 versus 23.13 months (95% CI 19.61–25.53) with an ARPI switch (HR 0.91 [95% CI 0.72–1.14], $p = 0.20$) in the intention-to-treat population. However, the OS data are confounded by a substantial rate of crossover: 141/234 participants (60.3%) randomized to an ARPI switch crossed over to the ^{177}Lu-PSMA-617 arm, representing 75.4% of the 187 who had centrally confirmed radiographic progression. It should be emphasized that this trial selected for patients who were considered to not immediately require docetaxel chemotherapy [24]; however, over half of the patients from either arm received subsequent chemotherapy, suggesting many in this trial were chemotherapy-eligible [25]. A pre-specified secondary analysis reported the crossover-adjusted HR for OS by inverse probability of censoring weighting modeling was 0.59 (95% CI 0.38–0.91; accounting for age, stage at diagnosis, previous ARPI medication, previous radiation, presence of liver metastases, bone involvement, PSA level, initial Gleason score, lactate dehydrogenase level, alkaline phosphatase level, hemoglobin level, lymphocyte count, neutrophil count, time since prostate cancer diagnosis, rPD confirmed by BICR, ECOG performance status, previous ARPI use setting, symptomatology, randomized treatment), suggesting a potential OS benefit with ^{177}Lu-PSMA-617 compared to a switch in ARPIs, although this should be interpreted with caution as an exploratory analysis [25]. ^{177}Lu-PSMA-617 was well tolerated compared to an ARPI switch. The most common AEs with ^{177}Lu-PSMA-617 were dry mouth (59.5%), nausea (32.6%), and asthenia (32.2%). Hematological AEs of any grade were more common with ^{177}Lu-PSMA-617 (39.2%) compared to an ARPI switch (23.7%). Renal toxicity was observed in 6.2% of patients treated with ^{177}Lu-PSMA-617 compared with 8.2% of those treated with an ARPI switch. Grade ≥3 treatment-emergent adverse events (TEAEs) were 35.2% for ^{177}Lu-PSMA-617 versus 49.1% for ARPIs. Serious treatment-related adverse events (TRAEs) occurred in 4.0% of the ^{177}Lu-PSMA-617 arm and 2.6% of the ARPI switch arm [25] and led to treatment discontinuation in 6% and 5% of patients, respectively. There were 4 patients (1.8%) in the ^{177}Lu-PSMA-617 arm who developed a secondary malignancy. There were no reports of myelodysplastic syndrome in either arm. Health-related quality of life (HrQOL) data from this open-label trial showed that ^{177}Lu-PSMA-617 delayed time to the first symptomatic skeletal event and delayed deterioration in overall HrQOL and pain [26]. These results led to FDA approval for the treatment of patients with metastatic APMR who have been treated with ARPI therapy and are considered appropriate to delay taxane-based chemotherapy or have received prior taxane-based chemotherapy. The Health Canada decision is still awaited at the time of writing.

Table 2. Comparison of selected PSMA-targeting RLT trials for APMR in the post-ARPI, docetaxel-naive setting [24–29].

Trial	SPLASH (NCT04647526)	PLUDO/CCTG PR.21 (NCT04663997)	PSMAfore (NCT04689828)
Design	Multicenter, open-label, randomized phase III trial	Multicenter, open-label, randomized phase II trial	International, open-label, randomized phase III trial
***N*(randomized)**	412	199	468
Patient characteristics/ treatment setting	PSMA PET-positive mCRPC progressing after one ARPI; no previous chemotherapy for mCRPC	PSMA PET-positive mCRPC progressing after ARPIs; chemotherapy-naïve for mCRPC, previous docetaxel for hormone-sensitive > 1 year before enrolment was permitted.	PSMA PET-positive mCRPC progressing once on one previous ARPI; taxane-naïve
Imaging criteria	PSMA PET $SUV_{max} \geq 15$ at ≥1 site and >10 at all measurable sites; in the absence of measurable disease, one site with $SUV_{max} > 10$; no FDG PET criteria	≥50% PSMA-positive lesions with no PSMA-negative lesions > 5 cm in any dimension; no FDG PET criteria	VISION criteria; no FDG PET criteria
Chemo eligibility	Declined or considered unsuitable for chemotherapy	Yes	Considered appropriate for ARPI switch with no immediate need for chemotherapy
Visceral metastases	Liver metastases > 1 cm excluded	21% of total population	6% ^{177}Lu-PSMA-617; 3% ARPI switch
Baseline median PSA, ng/mL	22, range 0.3–701.0 [a]	19.6, range 0.08–2789	18.4, IQR 44.7 ^{177}Lu-PSMA-617; 14.9, IQR 32.4 ARPI switch
Arms	^{177}Lu-PNT2002 vs. ARPI switch (to abiraterone or enzalutamide)	^{177}Lu-PSMA-617 vs. docetaxel	^{177}Lu-PSMA-617 vs. ARPI switch (to abiraterone or enzalutamide)
Crossover	ARPI → ^{177}Lu-PNT2002 after centrally confirmed radiographic progression (84.6% crossover rate)	Bidirectional after progression	ARPI → ^{177}Lu-PSMA-617 after centrally confirmed radiographic progression (60.3% crossover rate; 75.4% of those with confirmed progression)
Primary outcome measure	rPFS	rPFS	rPFS
Primary endpoint result	Median rPFS 9.5 vs. 6.0 months; HR 0.71 (95% CI 0.55–0.92); $p = 0.0088$.	Median rPFS 8.6 vs. 10.7 months; HR 1.01 [90% CI 0.77–1.31], one-sided $p = 0.51$)	Updated analysis: 11.60 vs. 5.59 months; HR 0.49 (95% CI 0.39–0.61).
PSA50 response	35.7% vs. 14.6%; $p = 0.0001$	36% vs. 16%; $p = 0.0015$	51% vs. 17%; p not reported
Objective response rate	38.1% vs. 12.0%; $p = 0.0021$	16% vs. 8%; $p = 0.023$ [b]	50% vs. 15%, p not reported
Median time to FACT-P deterioration	8.1 vs. 5.3 months; HR 0.59	Not reached vs. 15.7 months; $p = 0.75$	7.46 vs. 4.27 months; HR 0.61
Grade ≥ 3 treatment-related AEs	9.7% ^{177}Lu-PNT2002 vs. 11.5% ARPI switch	13% ^{177}Lu-PSMA-617 vs. 34% docetaxel	13.7% ^{177}Lu-PSMA-617 vs. 12.1% ARPI switch

Table 2. *Cont.*

Trial	SPLASH (NCT04647526)	PLUDO/CCTG PR.21 (NCT04663997)	PSMAfore (NCT04689828)
TEAEs leading to discontinuation	1.9% ^{177}Lu-PNT2002 vs. 6.2% ARPI switch	Not reported	5.3% ^{177}Lu-PSMA-617 vs. 5.2% ARPI switch
Most common AEs in treatment group, any grade (grade ≥ 3), %	Fatigue 53.5 (NR), dry mouth 37.2 (NR), nausea 31.2 (NR)	Anemia 95 (10), dry mouth 75 (5), LDH elevation 55 (0), fatigue 50 (2), alkaline phosphatase 50 (10) [c]	Dry mouth 59.5 (0.9), nausea 32.6 (0), asthenia 32.2 (0.9), anemia 27.3 (6.2), fatigue 23.8 (0.4)

[a] Based on available data from the lead-in cohort. [b] Combined complete and partial response. [c] Estimated based on figure; numeric results unavailable. Abbreviations: ARPI, androgen receptor pathway inhibitor; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; NR, not reported; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival.

The phase III SPLASH trial had a similar patient population and study design compared to the PSMAfore trial. Prior ARPIs could have been administered in either the APMN/S or APMR. This trial evaluated ^{177}Lu-PNT2002 (6.8 GBq every 8 weeks for 4 cycles) against a switch in ARPIs and also allowed crossover. The primary endpoint of rPFS was positive, favoring ^{177}Lu-PNT2002 (9.5 months versus 6.0 months, HR 0.71 [95% CI 0.55–0.92], $p = 0.0088$), based on results presented at the 2024 European Society of Medical Oncology (ESMO) Annual Meeting. Patients treated with ^{177}Lu-PNT2002 also had a higher ORR (38.1% versus 12%, $p = 0.0021$) and PSA50 response rate (35.7% vs. 14.6%). Interim OS analysis suggested no significant difference between treatment arms (20.8 months vs. NE, HR 1.11 [95% CI 0.73–1.69], $p = 0.6154$). However, the OS data from SPLASH were similarly impacted by a substantial crossover rate of 84.6%. The exploratory IPCW crossover-adjusted OS analysis at the first interim showed an HR of 0.72 (95% CI 0.48–1.12). Grade ≥3 TRAEs were 9.7% for ^{177}Lu-PNT2002 versus 11.5% for ARPIs. Serious TEAEs leading to treatment discontinuation were 1.9% and 6.2% respectively. In this open-label trial, time to deterioration of the FACT-P score favored the ^{177}Lu-PNT2002 arm (8.1 months versus 5.3 months, HR 0.59 [95% CI 0.44–0.80], $p = 0.0005$) [27].

Assessing against a guideline-recommended control, the phase 2 CCTG PR21 (PLUDO) trial compared ^{177}Lu-PSMA-617 to docetaxel in 199 patients with PSMA-positive APMR after progression on ARPIs, with a built-in optional crossover design in both arms. This trial included patients deemed eligible and appropriate for chemotherapy, with 21% of patients having visceral metastases. The primary endpoint of rPFS was numerically longer with docetaxel, though this difference did not achieve statistical significance (median 8.6 months for ^{177}Lu-PSMA-617 vs. 10.7 months for docetaxel, HR 1.01 [90% CI 0.77–1.31], one-sided $p = 0.51$), based on results presented at the 2025 ESMO Annual Meeting. Response rates favored ^{177}Lu-PSMA-617, with an ORR of 16% vs. 8% ($p = 0.023$) and PSA50 response rates of 36% vs. 16% ($p = 0.0015$) [28]. Notably, PSA50 response rates in PLUDO were lower than the 40–50% observed in other trials such as KEYNOTE-921 [12]. This may reflect important differences in patient populations across trials, given PSMA PET was used to select eligibility in PLUDO [28]. PR21 notably also had a higher proportion of visceral metastases. In the docetaxel arm, 77.5% (62/80) of patients with disease progression crossed over to receive ^{177}Lu-PSMA-617, and 53% (42/79) in the ^{177}Lu-PSMA-617 arm crossed over to receive docetaxel; this imbalance did not appear to be related to worse HrQOL or AEs at the time of first progression [29]. Patients who did not cross over to receive a second treatment had worse OS compared to those who did (HR 3.18 in the ^{177}Lu-PSMA-617 arm, HR 4.73 in the docetaxel arm). Among patients who crossed over and received both

treatments, there were no significant differences in rPFS2 (18.5 months for ^{177}Lu-PSMA-617 followed by docetaxel vs. 15.8 months for the reverse sequence) or OS (23.2 vs. 20 months, respectively). PSA50 responses to second-line treatment were higher in the ^{177}Lu-PSMA-617 to docetaxel sequence compared to the inverse (69% vs. 40%, $p = 0.004$), indicating that both agents remain active regardless of either sequencing strategy [29]. In PLUDO, incidence of dry mouth was higher with ^{177}Lu-PSMA-617 relative to docetaxel, with comparable levels of fatigue, nausea, anorexia, and vomiting. Importantly, this trial showed that ^{177}Lu-PSMA-617 is better tolerated than docetaxel: grade 3–4 treatment-related AEs were more common in the docetaxel arm (34% vs. 13%), and two treatment-related deaths occurred in the docetaxel arm compared to none with ^{177}Lu-PSMA-617 [28]. There was no difference in median time to deterioration in total FACT-P scores between treatment arms (^{177}Lu-PSMA-617 not reached, 90% CI 8.08 months-not reached; docetaxel 15.7 months, 90% CI 4.9 months-not reached; 2-sided $p = 0.75$) [28].

Additional data from other phase III trials evaluating ^{177}Lu-PSMA-I&T (NCT05204927) and TLX591-Tx (^{177}Lu rosopatamab tetraxetan, NCT06520345) for chemotherapy-naïve APMR are also awaited.

6. Discussion

Long-term real-world data from Ontario indicate that more than 70% of patients with APMR receive only one line of therapy [4]. More contemporary data from the US suggest that this remains the case for 60–70% of patients [9,30]. Consequently, treatment selection following progression on ARPIs is particularly important and should involve medical oncologists experienced with all available systemic therapy options, including taxane-based chemotherapy (Figure 1), ideally within a multidisciplinary setting.

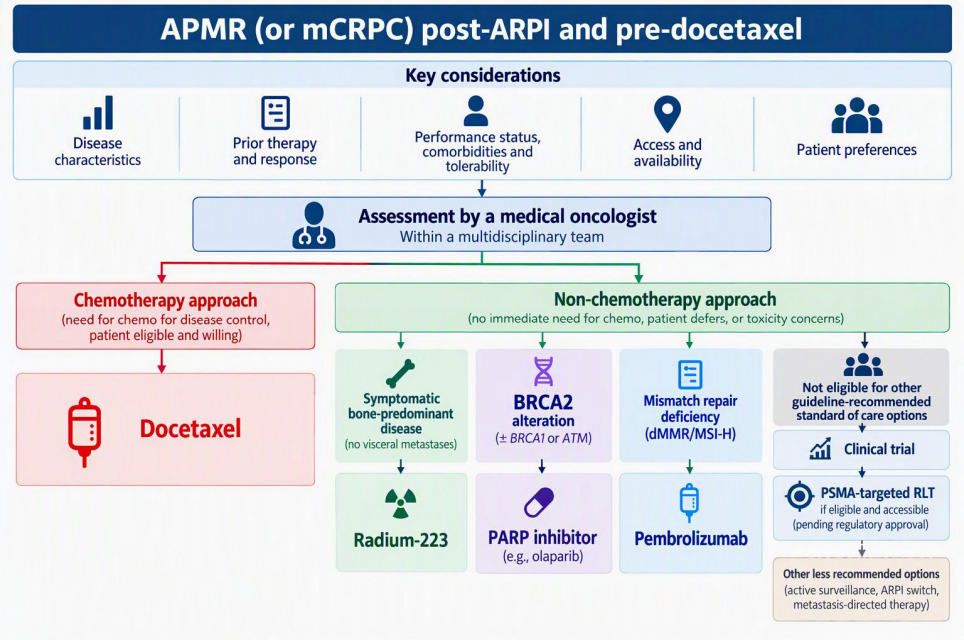


Figure 1. Proposed clinical decision framework for chemotherapy-naïve APMR (or mCRPC) following disease progression on ADT and ARPIs.

Docetaxel remains an important, effective treatment option for APMR [12,31,32]. Toxicity concerns can be mitigated by dose modification, primary G-CSF prophylaxis [14], appropriate anti-emetics, and other supportive measures. Nevertheless, many patients do not immediately proceed to docetaxel after progression on ARPIs because of a rela-

tively indolent disease trajectory, tolerability concerns, and/or patient preferences to defer chemotherapy. Other effective treatment options remain limited in this setting. In this context, emerging randomized data support ^{177}Lu-PSMA-617 as an effective treatment option for appropriately selected patients with PSMA-positive, chemotherapy-naïve APMR. These findings are particularly relevant given that an ARPI switch and other strategies intended to defer chemotherapy continue to be used in clinical practice in an estimated 20–30% of patients, despite very limited efficacy. ^{177}Lu-PSMA-617 provides improved response rates and delays in symptomatic deterioration while maintaining HrQOL, which are clinically meaningful endpoints for patients, though the magnitude of benefit and durability of response remain modest and OS results have been difficult to interpret. In Canada, ^{177}Lu-PSMA-617 is not currently approved in the chemotherapy-naïve APMR setting. If regulatory approval and funding are obtained, its availability may help address an important unmet need for effective therapies in appropriately selected patients.

An important caveat is that patients who are unfit for chemotherapy are likely not well represented in the trials detailed above. For example, PSMAfore included mostly patients with ECOG performance status 0–1, and many patients subsequently received chemotherapy, suggesting a predominantly chemotherapy-eligible study population. Patients who are relatively "chemo fit" but have not received or opt to defer chemotherapy likely have inherently different disease characteristics and functional status compared to those who are deemed chemotherapy ineligible. The optimal positioning of PSMA-targeting RLT may differ between these two subgroups; however, available trials so far have not distinguished these populations. Moreover, defining which patients are truly chemotherapy ineligible is difficult in clinical practice, as dose modifications and supportive measures may significantly improve chemotherapy tolerability. For patients who are eligible and willing to receive chemotherapy, the PLUDO trial provided the only randomized direct comparison of ^{177}Lu-PSMA-617 with docetaxel, and both agents had disease activity irrespective of treatment sequence; however, ^{177}Lu-PSMA-617 does not have supportive evidence to routinely replace docetaxel in the second-line setting.

More recently, ^{177}Lu-PSMA-617 received FDA approval for mAPMS/N based on the PSMAddition trial results. Whether ^{177}Lu-PSMA-617 will be adopted even earlier in real-world practice and how it will impact response to subsequent therapies remains to be seen. Ongoing trials are also assessing the utility of PSMA-targeted RLT rechallenge, including VECTRA-01 (NCT07611110), RE-LuPSMA and the REALITY Registry Study (NCT04833517). Long-term toxicity, including rare risks of therapy-related myeloid neoplasms, also requires further characterization given that patients in earlier disease states have longer survival compared to the late-line setting. It is important to note that the use of ^{177}Lu-PSMA-617 earlier in the treatment journey may preclude its use in later stages, as there is no evidence to date supporting the efficacy of RLT re-challenge. In the current Canadian landscape, use in chemotherapy-naïve disease is almost certain to prevent access and reimbursement for ^{177}Lu-PSMA-617 in the post-chemotherapy setting.

Taken together, these data suggest that ^{177}Lu-PSMA-617 likely has an important role in select patients with PSMA-positive, chemotherapy-naive APMR. In Canada, it is still pending regulatory approval for this setting. If regulatory approval and funding are obtained, its access will help to address the current need for effective therapies in this space. Treatment selection should incorporate disease characteristics, toxicity profile, urgency to start systemic therapy, anticipated eligibility for subsequent therapies and patient preferences. Patients should engage in shared decision-making with an experienced medical oncologist to discuss all available treatment options and support individualized treatment selection.

Many unanswered questions remain, including the risk of long-term toxicities with integration in earlier treatment settings, the optimal dosing strategy and treatment duration,

and optimal approaches to response assessment and biomarker-guided treatment sequencing, which also warrant further research. Finally, the broader adoption of PSMA-targeted RLT has implications for cost, treatment capacity, and equitable access in a publicly funded health care system.

7. Conclusions

There remains a significant unmet need for patients with APMR who experience disease progression on ADT and ARPIs, with real-world data demonstrating that most patients receive only one line of therapy and never receive docetaxel chemotherapy. ^{177}Lu-PSMA-617 currently represents one of the options best supported by evidence for selected patients with PSMA-positive, chemotherapy-naïve APMR in whom it is considered appropriate to delay, or who do not wish to pursue, other established life-prolonging therapies, including docetaxel chemotherapy, and who are not eligible for other guideline-recommended standard of care options; randomized trial data demonstrate superior efficacy compared with an ARPI switch. Our recommendation applies where approval and access are in place, considering that the use of ^{177}Lu-PSMA-617 in chemotherapy-naïve disease is not yet approved in Canada. For patients who are candidates for docetaxel, the optimal sequencing of PSMA-targeted RLT relative to chemotherapy should be individualized. Treatment selection should consider disease characteristics, available standard therapies and clinical trials, treatment-related toxicity, access, and patient preferences through shared decision-making with an experienced medical oncologist, ideally within a multidisciplinary setting.

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