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Original Research

^{177}Lu-PSMA vs. cabazitaxel in patients with castration-resistant prostate cancer: Real-world efficacy and safety data from the ARON-3 study

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ABSTRACT

Background: Radioligand therapy with [^{177}Lu]Lutetium-177-PSMA-617 (^{177}Lu-PSMA) was recently introduced in clinical practice in the US, Latin America and in most European countries for progressive, metastatic castration-resistant prostate cancer (mCRPC). However, multicenter real-world data on cancer-control outcomes are scant.
Methods: Real-word data from the ARON-3 collaboration in progressive mCRPC patients treated with ^{177}Lu-PSMA vs. cabazitaxel were collected. A retrospective analysis was performed, including overall survival (OS), progression free survival (PFS), time to treatment failure (TTF) and PSA50/90 rates.
Results: Data from 285 (50.1 %) patients receiving ^{177}Lu-PSMA vs. 283 (49.9 %) cabazitaxel after one or two lines of ARPI and Docetaxel were analyzed. PSA50 and PSA90 rates were higher, and TTF and OS were significantly longer in ^{177}Lu-PSMA patients, even after multivariable adjustment ($p \leq 0.01$). This effect held true for most subgroups such as age < 70 and ≥ 70 years, ECOG 0–1, distant lymph nodes and one vs. two lines of prior ARPI. Incidence of grade 3–4 adverse events were comparable between both treatments (37 % vs. 43 % for ^{177}Lu-PSMA vs. cabazitaxel cohort $p = 0.5$) but differed according to the type of adverse events. Sensitivity analyses with cross-over adjustment showed similar effects.
Conclusions: Analyzing the currently largest real-world cohort comparing ^{177}Lu-PSMA vs. cabazitaxel, we provided robust information of ^{177}Lu-PSMA being at least equally effective or possibly even superior to cabazitaxel regarding cancer-control outcomes with reasonable side effects.

1. Introduction

Prostate cancer is the second most diagnosed cancer and a leading cause of cancer-related death among men [1,2]. Approximately 10–20 % of patients progress to metastatic stage, which is frequently associated with a further progress to metastatic castration-resistant prostate cancer (mCRPC).

Over the last decade, the treatment landscape for mCRPC has significantly changed with the approval of androgen receptor pathway inhibitors (ARPI), taxane-based chemotherapies (docetaxel, cabazitaxel), the alpha-emitter Radium-223 and Poly-(ADP-Ribose)-Polymerase (PARP)-inhibitors and combinational therapies [3–6]. In this scenario, radioligand therapy (RLT) with [^{177}Lu]Lutetium-Prostate-specific membrane antigen (^{177}Lu-PSMA) has progressively emerged as a novel effective treatment for progressive mCRPC, being recently introduced in clinical practice in the US, Latin America and in most European countries.

PSMA is a transmembrane protein normally expressed in prostatic epithelium, small intestine, renal tubule, salivary and lacrimal glands [7,8]. Normal prostate tissue expresses PSMA, but it is notably overexpressed 100–1000 times in prostate cancer cells, with a linear correlation to Gleason score and further increase in metastatic disease and especially in mCRPC [9–11].

PSMA ligands, particularly PSMA-I&T and PSMA-617, have thus emerged as promising agents for both diagnostics and therapy in nuclear medicine ("theranostics"), being conjugated either with β^+-emitting or β^--emitting radioisotopes. After binding to their target, PSMA radioligands are internalized, delivering radiation directly into PSMA expressing prostate cancer cells.

In 2022 the Food and Drug Administration approved ^{177}Lu-PSMA-617 (Lutetium-177-vipivotide tetraxetan) after results from the VISION and TheraP trial demonstrating significant prolongation of radiographic progression-free survival (PFS) and overall survival (OS) compared to best standard of care and cabazitaxel, respectively [12,13].

The ARON-3 (ClinicalTrials.gov NCT06200558) is a multicenter, international, retrospective study designed to collect real-world data from patients with advanced prostate cancer [14]. This subset analysis was aimed to compare the real-world effectiveness and tolerability of ^{177}Lu-PSMA vs. standard of care with cabazitaxel in patients with progressive mCRPC after previous ARPI and docetaxel pre-treatment. We hypothesized that important differences in cancer-control outcomes between both mCRPC treatments may exist.

2. Patients and methods

2.1. Study design and population

We conducted a retrospective analysis of clinical data from patients aged 18 years or older who were diagnosed with mCRPC and received RLT with ^{177}Lu-PSMA (PSMA-I&T or PSMA-617) or cabazitaxel after progression on docetaxel and one or two ARPI between November 1st, 2021, and January 30th, 2025, in 42 Institutions across 16 countries (Figure S1). Eligibility criteria included the availability of information on age, tumor histology, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), metastasis sites, prior surgery, prior therapies [Androgen-Deprivation Therapy (ADT), taxane-based chemotherapies, ARPI, Radium-223], ^{177}Lu-PSMA treatment duration, and prostate-specific antigen (PSA) response to ^{177}Lu-PSMA therapy or cabazitaxel. For ^{177}Lu-PSMA treatment, PSMA-PET positivity without predefined cut-off values such as SUVmax were necessary. Tumor assessment and re-staging was performed according to local clinical practice, without prespecified uniform schedule. Clinical and pathological data were extracted from patient medical and pathology records at each participating center. Patients with missing clinical or outcome data were excluded from the ARON-3 study.

2.1.1. Study objectives

The primary aim of this investigation was to compare the real-world effectiveness of ^{177}Lu-PSMA vs. cabazitaxel in mCRPC patients. Specifically, we assessed Overall Survival (OS), and Time to Treatment Failure (TTF). OS was defined as the period from ^{177}Lu-PSMA or cabazitaxel therapy initiation to death from any cause. TTF referred to the interval between starting ^{177}Lu-PSMA or cabazitaxel and any treatment discontinuation.

Best PSA response rate was defined according to the Prostate Cancer Clinical Trials Working Group-3 (PCWG3) as the proportion of patients achieving a ≥ 50 % decline in PSA from baseline (PSA50) [15]. PSA90 was defined as a ≥ 90 % reduction in PSA levels from baseline.

Adverse events (AEs) were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, focusing only on severe AEs (grade 3 or higher). Additionally, any AEs that led to dose modification or discontinuation of ^{177}Lu-PSMA therapy were

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documented.

2.1.2. Statistical considerations

OS and TTF were estimated using the Kaplan-Meier method, and subgroup comparisons were derived using the log-rank test. Median follow-up was calculated using the inverse Kaplan-Meier method. Multivariable analyses using Cox proportional hazard models were performed to assess the effects on survival, including all variables that gained significant p values (<0.05) at univariable analysis, and providing hazard ratios (HRs) and 95 % confidence intervals (CIs). Fisher's exact test was utilized for pairwise comparisons of categorical variables, while chi-square tests were applied for multiple categorical comparisons. A p-value of < 0.05 was considered as statistically significant. All statistical analyses were conducted using MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).

2.1.3. Ethical considerations

The study protocol was approved on April 18, 2024, by the Ethical Committee of the coordinating centre (Marche Region, Italy, No. 2024 20, Study Protocol "ARON-3 Study") and by the Institutional Review Boards of the participating sites. The study adhered to Good Clinical Practice (GCP) guidelines, the International Ethical Guidelines for Biomedical Research, and the principles outlined in the Declaration of Helsinki on human experimentation.

3. Results

3.1. Patient population

A total of 568 mCRPC patients treated with ^{177}Lu-PSMA vs. cabazitaxel (either or both) were included from the ARON-3 dataset (Figure S2, Table 1). The median follow-up duration was 18.9 months (95 % CI 16.1–96.3), 16.9 months (95 % CI 15.0–21.4) for ^{177}Lu-PSMA and 21.0 months (95 % CI 16.1–96.3) for Cabazitaxel ($p = 0.2$); 271 patients (48 %) had died by the time of the analysis.

The study population included 285 men (50 %) treated with ^{177}Lu-PSMA vs. 283 (50 %) with cabazitaxel. Median age was 66 years (range 38–93 years). ECOG-PS was ≥ 2 in 57 patients (10 %). Bone metastases were present in 354 patients (62 %). Radical Prostatectomy and radiation therapy for localized disease were reported in 24 % vs. 15 % of patients with ^{177}Lu-PSMA vs. cabazitaxel, respectively.

In total, 326 mCRPC patients received ^{177}Lu-PSMA or cabazitaxel after progression on docetaxel and one previous ARPI, while 242 patients were treated with ^{177}Lu-PSMA or cabazitaxel after previous treatment with docetaxel and two ARPIs. Further patient characteristics are summarized in Table 1.

3.1.1. PSA kinetics

PSA reductions were observed in 71 % of the overall study population. Patients with any PSA response represented 78 % of ^{177}Lu-PSMA vs. 64 % of cabazitaxel patients ($p = 0.042$). PSA50 and PSA90 rates were 65 % vs 40 % and 41 % vs 19 % (both $p = 0.001$) for ^{177}Lu-PSMA vs. cabazitaxel (Fig. 1).

3.1.2. OS-stratified analyses

The median OS was 20.2 months (95 %CI 18.2–23.3) with ^{177}Lu-PSMA vs. 14.8 months (95 %CI 12.8–17.9) with cabazitaxel ($p = 0.002$, Fig. 2A). Sensitivity analyses of patients who did not receive both treatments revealed virtually similar median OS results (20.2 vs. 15.1 months, Figure S3).

Patients aged $<$ 70years showed a median OS of 21.3 months (95 % CI 18.2–23.6) with ^{177}Lu-PSMA vs. 15.2 months (95 %CI 13.5–17.9) with cabazitaxel ($p = 0.01$, Fig. 2C). Patients aged $\geq$ 70years showed a median OS of 19.8 months (95 %CI 15.0–37.0) with ^{177}Lu-PSMA vs. 8.9 months (95 %CI 4.0–25.2) with Cabazitaxel ($p = 0.02$, Fig. 2E).

In the subgroup of patients with ECOG-PS 0–1, the median OS was 20.7 months (95 %CI 18.6–23.6) with ^{177}Lu-PSMA vs. 16.1 months (95 %CI 14.4–20.4) with cabazitaxel ($p = 0.01$, Figure S4A), while patients with ECOG-PS 2 reported a median OS of 9.0 months (95 %CI 5.7–35.5) with ^{177}Lu-PSMA vs. 2.6 months (95 %CI 2.2–42.9) with cabazitaxel ($p = 0.10$). In mCRPC patients with distant lymph nodes only and those with bone metastases, significant better median OS was observed for ^{177}Lu-PSMA vs. cabazitaxel (both $p < 0.01$, Figure S4), while no statistically significant differences were found in patients with visceral metastases (^{177}Lu-PSMA: 12.1 months, 95 %CI 8.4–34.0; Cabazitaxel: 14.4 months, 95 %CI 3.6–54.2, $p = 0.700$). In multivariable Cox-regression models, ^{177}Lu-PSMA treatment remained an independent predictor of better OS compared to cabazitaxel (Table 2, HR 1.91, $p = 0.01$).

Table 1
Patients' characteristics of 568 metastatic castration resistant prostate cancer (mCRPC) patients receiving Lutetium-177 Prostate-specific membrane antigen radioligand therapy (^{177}Lu-PSMA) vs. cabazitaxel.

Patients	Overall568 (%)	^{177}Lu-PSMA285 (50.1 %)	Cabazitaxel283 (49.9 %)	*p*-value
Age ≥70 years	176 (31)	104 (36)	72 (25)	0.12
ECOG-PS				
0–1	511 (90)	264 (93)	247 (87)	0.2
≥ 2	57 (10)	21 (7)	36 (13)	
Gleason score				
< 8	116 (20)	73 (26)	53 (19)	0.3
≥ 8	388 (68)	189 (66)	189 (72)	0.4
Data missing	64 (12)	29 (8)	25 (9)	>0.9
Metastatic stage				
de novo	345 (61)	167 (59)	178 (63)	0.7
metachronous	223 (39)	118 (41)	105 (37)	
Sites of metastases				
Distant lymph nodes	282 (50)	136 (48)	146 (52)	0.7
Bones	354 (62)	160 (56)	194 (69)	0.060
Visceral	54 (10)	25 (9)	29 (10)	> 0.9
PSA value at start of treatment				
Median	78.1	76.4	79.5	-
Range	0.3–975	2.1–858.3	0.3–975.4	
Radiotherapy for localized HSPC	88 (15)	49 (17)	39 (14)	0.7
Prostatectomy for localized HSPC	135 (24)	69 (24)	66 (23)	> 0.9
Previous treatments				
Docetaxel +1 ARPI	326 (57)	150 (53)	176 (62)	0.3
Docetaxel +2 ARPI	242 (43)	135 (47)	107 (38)	
Treatment with Cabazitaxel in further therapy lines	3 (1)	3 (1)	0 (0)	-
Treatment with 177Lu-PSMA in further therapy lines	74 (13)	0 (0)	74 (26)	-

3.1.3. TTF-stratified analyses

The median TTF was 9.2 months (95 %CI 7.4–37.0) with ^{177}Lu-PSMA vs. 5.1 months (95 %CI 4.0–6.2) with cabazitaxel ($p < 0.001$, Fig. 2B); the six-months- and one-year-TTF rates of ^{177}Lu-PSMA vs cabazitaxel were 62 % vs. 46 % and 40 % vs. 19 %, respectively. Sensitivity analyses excluding patients (crossover-adjusted analyses) who received both treatments revealed virtually similar median TTF results (9.0 vs. 5.1 months, Figure S3).

Patients aged $<$ 70years reported a median TTF of 9.0 months (95 % CI 6.7–36.7) with ^{177}Lu-PSMA vs. 5.8 months (95 %CI 4.4–6.3) with cabazitaxel ($p < 0.001$, Fig. 2D), while patients aged $\geq$ 70years reported a median TTF of 9.6 months (95 %CI 5.8–37.0) with ^{177}Lu-PSMA vs. 4.0 months (95 %CI 3.0–6.2) with Cabazitaxel ($p = 0.001$, Fig. 2E).

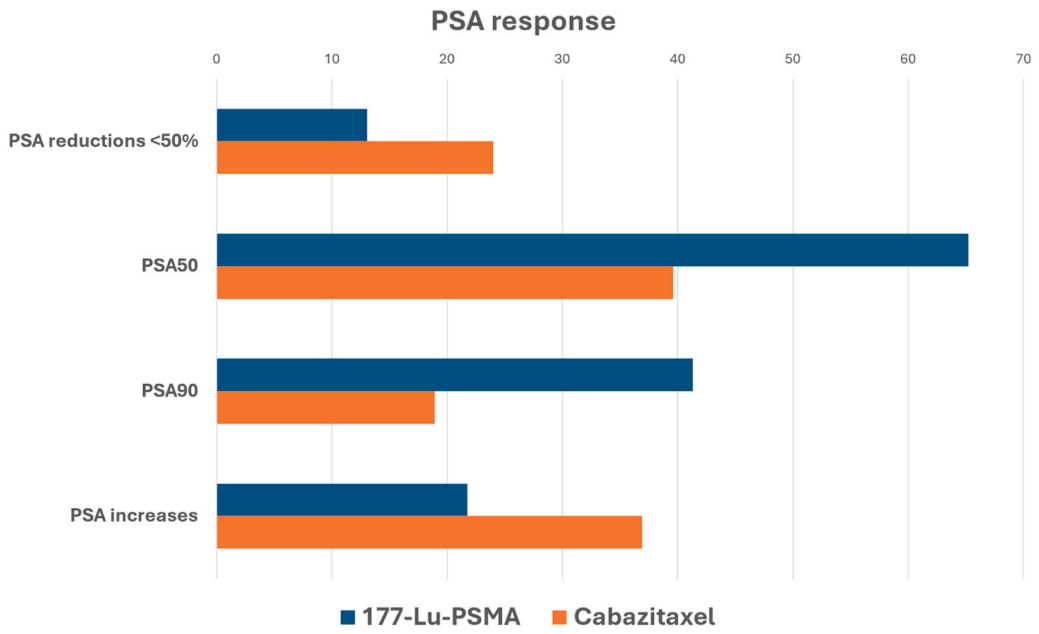


Fig. 1. PSA response rates in metastatic castration resistant prostate cancer (mCRPC) patients treated with ^{177}Lu-PSMA vs. cabazitaxel.

Similarly, sensitivity analyses of mCRPC patients with ECOG-PS 0–1, lymph node only mCRPC disease, as well bone metastatic mCRPC patients revealed significant better TTF outcomes for ^{177}Lu-PSMA vs. cabazitaxel (all $p < 0.001$, Figure S5).

In patients with ECOG-PS ≥ 2 median TTF was 6.0 months (95 %CI 2.1–16.3) for ^{177}Lu-PSMA vs. 3.0 months (95 %CI 2.1–26.7) with cabazitaxel without reaching statistical significance ($p = 0.5$). Similarly, no statistically significant but numerical differences were observed for patients with visceral metastases (^{177}Lu-PSMA: 5.9 months, 95 %CI 3.9–9.0; cabazitaxel: 3.9 months, 95 %CI 3.2–5.9, $p = 0.900$).

3.1.4. Cancer-control outcomes stratified by number of previous ARPI-treatments

The median OS in patients previously treated with one taxane- and one ARPI-based treatment was 23.3 months (95 %CI 18.6–28.3) vs. 15.9 months (95 %CI 13.1–20.4) for ^{177}Lu-PSMA vs. cabazitaxel ($p = 0.01$, Fig. 3A), with 83 % vs 65 % of one-year-OS rate, respectively. Analogously, the median TTF was 9.5 months (95 %CI 6.6–37.0) vs. 6.2 months (95 %CI 4.2–7.1) for ^{177}Lu-PSMA vs. cabazitaxel ($p = 0.002$, Fig. 3B), with of six-months and 1-year-TTF rates of 60 % vs 54 % and 43 % vs 25 %.

In subgroups of mCRPC patients with one previous taxane-based and two ARPI-based treatments, median OS was 19.3 months (95 %CI 14.5–21.9) vs. 13.0 months (95 %CI 9.8–16.0) ^{177}Lu-PSMA vs. cabazitaxel ($p = 0.029$, Fig. 3C). The median TTF was 8.3 months (95 %CI 6.6–36.7) vs. 4.2 months (95 %CI 3.6–5.5) for ^{177}Lu-PSMA vs. cabazitaxel ($p < 0.001$, Fig. 3D).

3.1.5. Safety outcomes

The incidence of G3-G4 SAEs was 40 % in the overall study population, and 37 % vs. 43 % in the ^{177}Lu-PSMA vs. cabazitaxel cohort ($p = 0.471$, Fig. 4). ^{177}Lu-PSMA was characterized by a higher incidence of G3-G4 fatigue (16 % vs 12 %, $p = 0.425$), while Cabazitaxel showed a higher incidence of neutropenia (10 % vs 3 %, $p = 0.082$). The complete list of the incidences of G3-G4 SAEs is illustrated in Fig. 4.

4. Discussion

We initially hypothesized that important differences in cancer-control outcomes between mCRPC patients treated with either ^{177}Lu-PSMA vs. cabazitaxel after previous docetaxel and one or two-line ARPI treatment may exist. We tested this hypothesis within the ARON-3 multicenter and international collaboration working group and made several important observations.

First, when baseline comparisons were made between ^{177}Lu-PSMA vs. cabazitaxel mCRPC patients, we observed clinically meaningful and statistically significant differences, as well as notable similarities. For example, the proportion of patients being 70 years and above were more pronounced within the ^{177}Lu-PSMA cohort (36 % vs. 25 %), while ECOG-PS ≥ 2 was more frequent in the cabazitaxel group (7 % vs. 13 %), despite not reaching statistical significance. The observation regarding age is not new. For example, a previously published real-world outcomes also reported on in median six years older ^{177}Lu-PSMA patients, relative to cabazitaxel mCRPC patients [16]. However, in this report the proportion of patients with ECOG-PS ≥ 2 was also significantly higher in the ^{177}Lu-PSMA group (12 % vs. 5 %). The latter may be explained by a selection bias of treatment physicians and patients' probability expecting less side effects under ^{177}Lu-PSMA other than under chemotherapy. Moreover, within the current study, patients undergoing ^{177}Lu-PSMA more frequently had previous systemic treatment with docetaxel and two ARPIs (47 % vs. 38 %), relative to cabazitaxel patients. However, other important tumor characteristics such as de novo mHSPC or local treatment to the prostate were equally balanced. Nonetheless, the included patients within the current study represented an equally balanced cohort for further cancer-control analyses.

When secondly cancer-control outcome measures were compared, also important observations were made. Specifically, overall PSA response rates, as well as PSA50 and PSA90 rates were significantly higher within the ^{177}Lu-PSMA group, relative to cabazitaxel treated patients. Especially, approximately two thirds of patients undergoing ^{177}Lu-PSMA treatment had a 50 % decrease in PSA. Compared to previous findings from the TheraP trial, our findings are virtually identical. Specifically, in the TheraP trial, PSA response rates were 65 % vs. 37 % for ^{177}Lu-PSMA vs. cabazitaxel [13], showing a very good real-world adherence of the data from the prospective studies. However, within all previous studies comparing selective prostate cancer cell targets such as ARPI- or PSMA-targeting agents, PSA response rates were higher, relative to the more unselective effect of taxane-based chemotherapies [12,17–19].

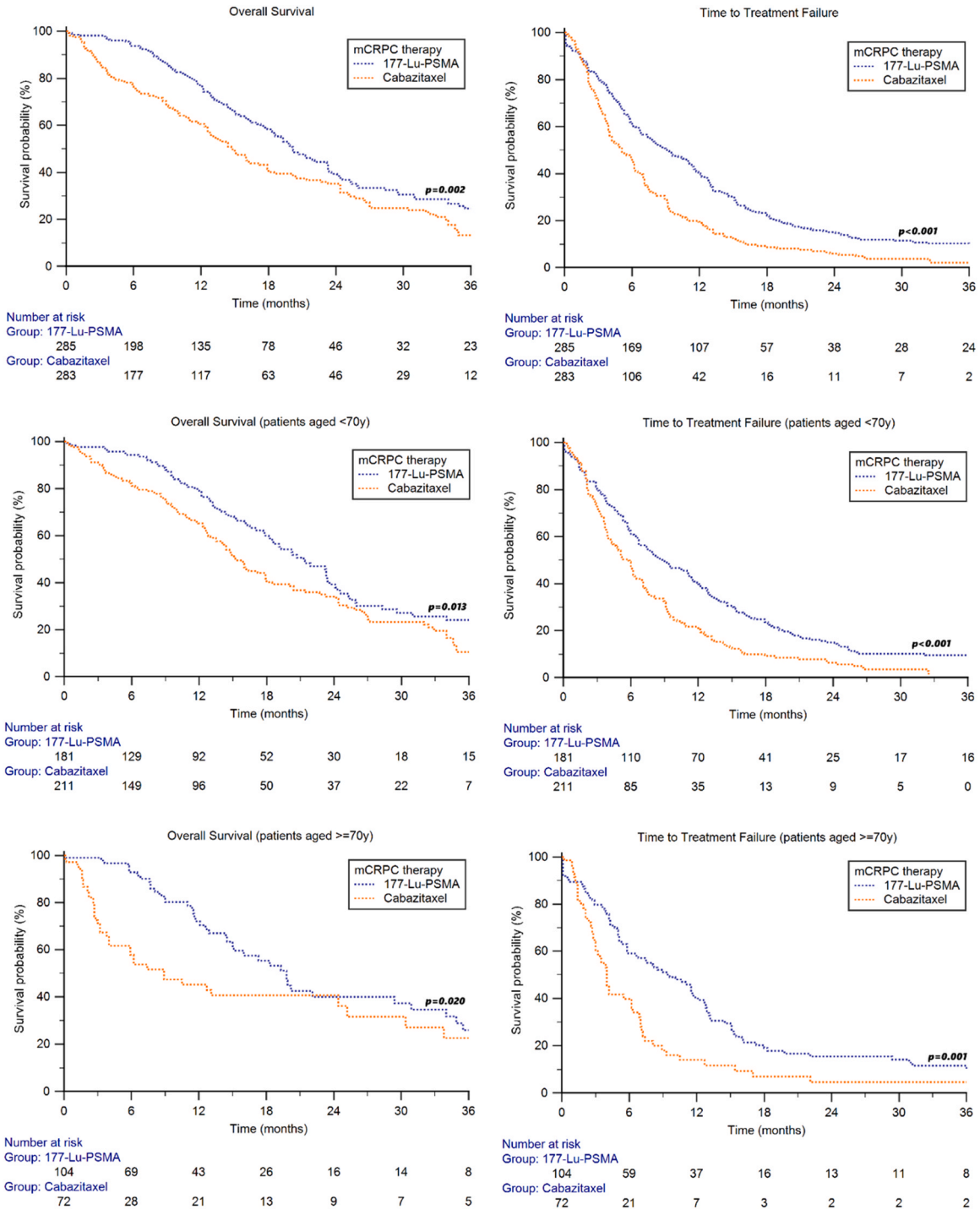


Fig. 2. Overall Survival (OS) and Time to Treatment Failure (TTF) in metastatic castration resistant prostate cancer (mCRPC) patients treated with Lutetium-177 Prostate-specific membrane antigen radioligand therapy (^{177}Lu-PSMA) vs. cabazitaxel (A and B). Subsequent subgroup analyses for patients $<$ 70 years (C and D) and $\geq$ 70 years (E and F) were made.

Nonetheless, when further TTF and OS outcomes were compared between ^{177}Lu-PSMA vs. cabazitaxel mCRPC patients, ^{177}Lu-PSMA treatment was associated with longer TTF and OS compared to cabazitaxel in most subgroups. For ECOG-PS $\geq$ 2 patients clinically meaningful longer duration of TTF and OS for ^{177}Lu-PSMA vs. cabazitaxel was observed, however not reaching significance mostly due to sample size limitations (n = 7 vs. n = 13). All of the above findings underline the potential of ^{177}Lu-PSMA treatment as highly potent across specific subgroups (such as frail patients) and more effective than cabazitaxel after previous docetaxel and ARPI treatment and are in line with previous randomized controlled trials, as well as smaller sized real-world cohorts [20]. For example, compared to the VISION trial with median TTF rates 8.7 vs. 3.4 months and OS rates 15.3. vs. 11.3 months for ^{177}Lu-PSMA vs. cabazitaxel were quite comparable to the findings of the current study [12]. When comparing our data with the TheraP trial, TTF is also comparable. In contrast, regarding OS, in the present real-world study also a significant benefit favoring ^{177}Lu-PSMA was present, even after multivariable adjusting [21]. Similarly, real-world cohorts also reported on similar median TTF and OS rates [22,23]. Moreover, the subgroup analyses revealing better cancer-control

Table 2
Univariable and multivariable analysis for overall survival.

Overall Survival	Univariable Cox Regression		Multivariable Cox Regression	
	HR (95 % CI)	*p-value*	HR (95 % CI)	*p-value*
Age (≥70yrs vs <70yrs)	1.09 (0.86-1.38)	0.487		
ECOG-PS (≥2 vs <2)	3.46 (2.64-4.57)	**< 0.001**	7.17 (4.49-11.47)	**< 0.001**
Grade Group 4–5 vs 1–3	1.18 (0.90-1.56)	0.227		
De novo vs metachronous mHSPC	1.07 (0.86-1.34)	0.530		
Prostatectomy (yes vs no)	0.80 (0.52-1.23)	0.316		
Radiotherapy (curative intent, yes vs no)	0.66 (0.44-0.98)	**0.040**	0.63 (0.41-0.95)	**0.029**
Metastases to distant lymph nodes (yes vs no)	1.16 (0.93-1.45)	0.182		
Bone metastases (yes vs no)	1.19 (0.94-1.49)	0.142		
Visceral metastases (yes vs no)	1.44 (1.03-2.02)	**0.033**	0.81 (0.48-1.34)	0.407
Cabazitaxel vs^{177}Lutetium-PSMA	1.45 (1.15-1.82)	**0.002**	1.91 (1.14-3.19)	**0.013**

outcomes in frail and older patients, as well as also for specific metastatic sites such as lymph node only mCRPC or bone disease indicate a broad and generalizable applicability for ^{177}Lu-PSMA within the mCRPC setting, while cabazitaxel chemotherapy may be expected with severe AEs in frail and old patients. The fact, that in our analyses the effect of ^{177}Lu-PSMA and cabazitaxel is not decreased if the other drug was also given in subsequent lines (“crossover”), may lead to the conclusion, that as many systemic drugs as possible should be offered to each patient, but ^{177}Lu-PSMA might be given prior to cabazitaxel chemotherapy. Still, one has to keep in mind, that some patients with PSMA-PET negative lesions might not have undergone ^{177}Lu-PSMA but rather cabazitaxel and these patients might have a worse prognosis. This could have biased our results in favor of ^{177}Lu-PSMA. In TheraP trial patients with PSMA-negative lesions who were excluded from ^{177}Lu-PSMA accounted for over 30 % of the screened population [13].

Finally, when sAE rates were compared, also important findings were made, with slightly higher rates of G3-G4 AEs (37 % vs. 43 %) within the cabazitaxel cohort and its rate of specific sAEs such as neutropenia or diarrhea. Conversely, fatigue and dry mouth was more pronounced within the ^{177}Lu-PSMA cohort. However, the overall incidence rate of G3–4 AEs is lower than the rate reported within the VISION trial with 53 % of any sAEs [12]. This might be attributed to the retrospective character of the present study. Unfortunately, no longitudinal laboratory data regarding recovery of hematological parameters were constantly available, similar as G2 data.

The current study is not free of limitations. First, the results must be interpreted in the light of its retrospective design. Moreover, some missing data, as well as other not reported variables may have influenced cancer-control outcomes. Further, no information regarding other blood values besides PSA was available, similar to possible dose reductions or adjustments in treatment schedules. Moreover, different PSMA ligands (PSMA-I&T or PSMA-617) might have been used with different activities.

Staging modalities may have introduced a selection bias, since ^{177}Lu-PSMA requires sufficient PSMA expression in PSMA-PET/CT scan and no strict predefined SUVmax cut-off values have been used. Conversely, cabazitaxel patients may have harbored a PSMA-negative or discordant disease, which may be associated with worse prognosis. Finally, some of the reported subgroup analyses may lack sample size and therefore may limit the findings.

5. Conclusions

Taken together the current study is to the best of our knowledge the largest real-world study so far, comparing ^{177}Lu-PSMA vs. cabazitaxel in mCRPC patients who have undergone docetaxel plus at least one ARPI. We provide evidence, that in these patients the use of ^{177}Lu-PSMA is at least equally effective or might even be superior to cabazitaxel in terms of cancer-control outcomes with reasonable side effects.

CRediT authorship contribution statement

Thomas Büttner: Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Javier Molina-Cerrillo:** Writing – review & editing, Validation, Supervision. **Amir Sabet:** Writing – review & editing, Conceptualization. **Linda Danielli:** Writing – review & editing, Validation, Supervision. **Maria T. Bourlon:** Writing – review & editing, Data curation, Conceptualization. **Deniz Tural:** Writing – review & editing, Supervision, Formal analysis. **Pasquale Rescigno:** Writing – review & editing, Validation, Supervision. **Frank Grünwald:** Writing – review & editing, Supervision. **Martin Ignacio Zapata Laguado:** Visualization, Supervision, Conceptualization. **Daniel Groener:** Investigation, Formal analysis, Data curation. **Enrico Sammarco:** Writing – review & editing, Validation, Supervision. **Philipp Mandel:** Writing – original draft, Investigation, Formal analysis, Conceptualization. **Jawaher Ansari:** Validation, Supervision. **Yüksel Ürün:** Writing – review & editing, Supervision, Methodology. **Luca Galli:** Writing – review & editing, Validation, Supervision. **Giulia Follacchio:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Martin Bögemann:** Writing – review & editing, Formal analysis, Conceptualization. **Marc R Matrana:** Validation, Supervision, Conceptualization. **Giandomenico Roviello:** Writing – review & editing, Validation, Supervision. **María Natalia Gandur Quiroga:** Writing – review & editing, Validation, Data curation. **Matteo Santoni:** Writing – original draft, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Vincenza Conteduca:** Writing – review & editing, Validation, Conceptualization. **Georgia Anguera Palacios:** Writing – review & editing, Validation, Supervision. **Gaetano Aurilio:** Writing – review & editing, Validation, Supervision. **Francesco Massari:** Writing – review & editing, Validation, Supervision, Conceptualization. **Gaetano Facchini:** Validation, Supervision, Resources. **Andrey Soares:** Writing – review & editing, Validation, Supervision. **Felix KH Chun:** Writing – review & editing, Validation, Supervision. **Francesca Capoccetti:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Emmanuel Seront:** Writing – review & editing, Validation, Supervision. **Mike Wenzel:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Zin W Myint:** Writing – review & editing, Methodology, Formal analysis. **Diogo Assed Bastos:** Writing – review & editing, Validation, Supervision. **Sati Coskun Yazgan:** Supervision, Formal analysis, Data curation. **Fernando Sabino Marques Monteiro:** Formal analysis, Data curation, Conceptualization. **Tarek Taha:** Supervision, Methodology, Investigation. **Abdul Rahman Jazieh:** Validation, Supervision, Investigation. **Ray Manneh Kopp:** Writing – review & editing, Validation, Supervision.

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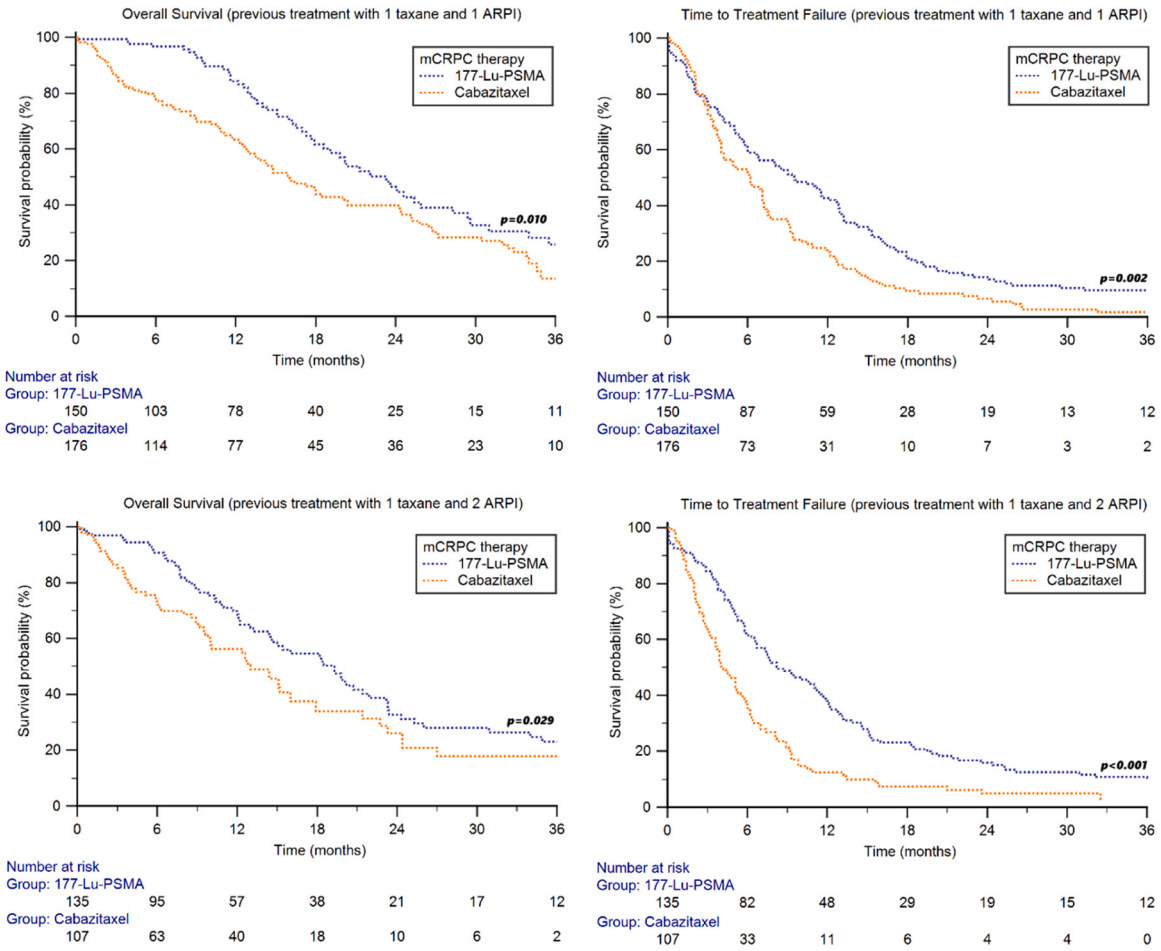


Fig. 3. Overall Survival (OS) and Time to Treatment Failure (TTF) in metastatic castration resistant prostate cancer (mCRPC) patients treated with Lutetium-177 Prostate-specific membrane antigen radioligand therapy (^{177}Lu-PSMA) vs. cabazitaxel, stratified by previous treatments.

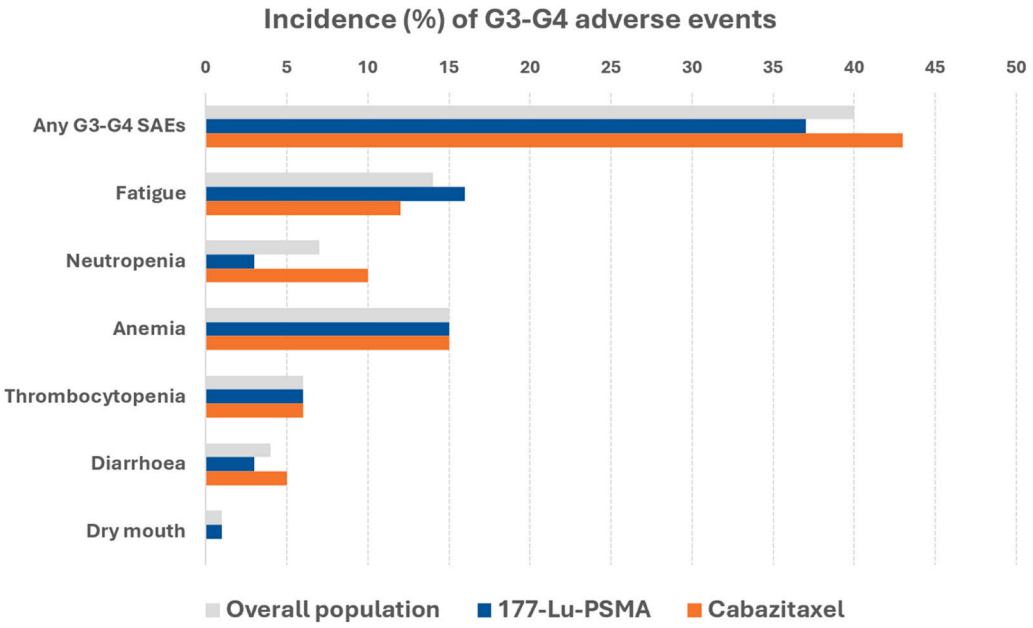


Fig. 4. Incidence of G3-G4 adverse events (SAEs) in metastatic castration resistant prostate cancer (mCRPC) patients treated with ^{177}Lu-PSMA vs. cabazitaxel.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mike Wenzel reports payments or honoraria from presentations, speaker bureaus, consulting or travel expenses for Accord, Astellas, Johnsen&Johnsen, Pfizer, MSD, Astra Zeneca, Ipsen, BayerPhilipp Mandel reports payments or honoraria from presentations, speaker bureaus, consulting or travel expenses from Johnsen&Johnsen, Novartis, Orion, Bayer, Astellas, Ipsen, Amgen, AstraZeneca, Pfizer, MSD Felix Chun reports advisory boards for Astellas, Bayer, Janssen, Lumenis (KOL), Molecular Health, Olympus, Pfizer and speaker honoraria from Novartis, Astellas, Astra Zeneca, Janssen, Lumenis, Olympus, Ipsen Daniel Groener reports honoraria from presentations for Sanofi Aventis. Fernando Sabino M. Monteiro: Research support was provided by Merck Sharp Dome and Foundation Medicine. Honoraria from Janssen, Ipsen, Bristol Myers Squibb, Novartis, Astra-Zeneca, Bayer, ADIUM and Merck Sharp Dome. Travel expenses by Novartis, Bayer, ADIUM, Merck, and Merck Sharp Dome. Ownership: BIO, Brazilian Information Oncology. All are unrelated to this study. Vincenza Conteduca reports a consultant/advisory board role for Johnson & Johnson, Astellas, Merck, AstraZeneca, Amgen, Eisai, Recordati, Novartis, Ipsen, and Bayer; and speaker honoraria or travel support from Astellas, Janssen, Ipsen, Bayer, Gilead, Novartis, and Bristol-Myers SquibbFrancesco Massari has received research support and/or honoraria from Advanced Accelerator Applications, Astellas, Astra Zeneca, Bayer, BMS, Janssen, Ipsen, Merck, MSD, Pfizer. Martin Ignacio Zapata Laguado: Advisory, consultancy: Bayer, wama pharma, Pfizer,Aztraseneca, Astellas, Janssen MSD, BMS, IPSEN, Merck, MSN, adium; Travel, accommodations and expenses: Abbot, Aztraseneca, MSD, astellas, BMS, Bayer, IPSEN, Merck, adium; Clinical trials and research: MSD, BMS, Aztraseneca Gaetano Facchini consultant/advisory board role for Astellas, Johnson & Johnson, MSD, AstraZeneca, Eisai, Recordati, Ipsen, and Bayer; and speaker honoraria or travel support from Astellas, Janssen, Ipsen, BayerTarek Taha reports institutional support for attending meetings and/or travel from Pfizer, and receiving honoraria from BMS, MSD, Merck-Serono and Pfizer. Maria T Bourlon: Honoraria Merck Sharp Dome. Ipsen, Bristol Myers Squibb, Novartis, Astra-Zeneca, Bayer, ADIUM, Novartis, Bayer, ADIUM, Astellas, Asofarma. Thomas Büttner received honoraria from Astellas, unrelated to the present workRay Manneh has received research support and/or honoraria from: Amgen, Astellas, AstraZeneca, Adium, Bayer, BMS, GSK, Ipsen, Jannsen, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche. Martin Boegemann reports serving in an advisory role for Pfizer und receiving honoraria by, Bristol Myers Squibb, Merck Serono, MSD, Astellas, Johnson&Johnson, Astra Zeneca, Bayer, Novartis, Sanofi, Recordati, Lilly, Exelixis, Amgen, EUSApham, Roche, and Ipsen; travel expenses from Johnson&Johnson, Merck Serono, Astra Zeneca, Roche, Bayer, Bristol Myers Squibb, Amgen. Maria Natalia Gandur Quiroga has received payments or honoraria from presentations, speaker bureaus, consulting, or travel expenses from Bayer, Astellas, Novartis, MSD, Merck Serono, Adium, Pfizer, Gador, and Elea. Andrey Soares: Honoraria from Janssen, Pfizer, Bayer, Merck Serono, Novartis. Consulting or Advisory Role from Janssen, Bayer, AstraZeneca, MSD, Pfizer, Novartis. Research Funding from Bristol-Myers Squibb (Inst), Astellas (Inst), AstraZeneca (Inst). Travel, Accommodations, Expenses from Bayer, Janssen, MSD, Merck Serono. Ownership: BIO, Brazilian Information Oncology. All are unrelated to this study. Nonfinancial with no other potential conflicts of interest were reported. ORCID: 0000-0003-4980-6729 Matteo Santoni has received research support and honoraria from Janssen, Bristol Myers Squibb, Ipsen, MSD, Astellas, A.A.A. and Bayer, all unrelated to the present paper.

All remaining authors have declared no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115789.

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