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Safety Analyses of the Phase 3 VISION Trial of [^{177}Lu]Lu-PSMA-617 in Patients with Metastatic Castration-resistant Prostate Cancer

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Abstract

Background and objective: [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) plus the standard of care (SoC) significantly improved overall survival and radiographic progression-free survival versus SoC alone in patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer in the VISION trial. We evaluated the safety of additional cycles of ^{177}Lu-PSMA-617 and the impact of longer observation time for patients receiving ^{177}Lu-PSMA-617 plus SoC.

Methods: VISION was an international, open-label study. Patients were randomised 2:1 to receive ^{177}Lu-PSMA-617 plus SoC or SoC alone. The incidence of treatment-emergent adverse events (TEAEs) was assessed in prespecified subgroups of patients who received ≤4 cycles versus 5–6 cycles of treatment and during each cycle of treatment. The TEAE incidence was also adjusted for treatment exposure to calculate the incidence per 100 patient-treatment years of observation. This analysis was performed for the first occurrence of TEAEs.

Key findings and limitations: The any-grade TEAE incidence was similar in cycles 1–4 and cycles 5–6. TEAE frequency was similar across all cycles of ^{177}Lu-PSMA-617 treatment. No additional safety concerns were reported for patients who received >4 cycles. The exposure-adjusted safety analysis revealed that the overall TEAE incidence was similar between arms, but distinct trends for different TEAE types were noted and the

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incidence of events associated with ^{177}Lu-PSMA-617 remained higher in the ^{177}Lu-PSMA-617 arm.

Conclusions and clinical implications: Longer exposure to ^{177}Lu-PSMA-617 plus SoC was not associated with a higher toxicity risk, and the extended time for safety observation could account for the higher TEAE incidence in comparison to SoC alone. The findings support a favourable benefit-risk profile for 6 cycles of ^{177}Lu-PSMA-617 in this setting and the use of up to 6 cycles of ^{177}Lu-PSMA-617 in patients who are clinically benefiting from and tolerating this therapy.

Patient summary: For patients with metastatic prostate cancer no longer responding to hormone therapy, an increase in the number of cycles of treatment with a radioactive compound called ^{177}Lu-PSMA-617 from four to six had no additional adverse side effects.

1. Introduction

Despite numerous therapeutic options for metastatic castration-resistant prostate cancer (mCRPC), most patients still experience disease progression and ultimately succumb to their disease [1,2]. Established therapies for mCRPC include taxanes, androgen receptor pathway inhibitors (ARPIs), and bone-targeted α-particle–emitting radioisotope therapy [3]. Newer therapeutic approaches include PARP inhibitors [4], immune checkpoint inhibitors [5], and radioligand therapy [6].

[^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) is a prostate-specific membrane antigen (PSMA)-targeted radioligand [7–14]. In the VISION trial, ^{177}Lu-PSMA-617 prolonged radiographic progression-free survival (rPFS) and overall survival and delayed the time to worsening of patient-reported health-related quality of life and pain and to first symptomatic skeletal event when added to protocol-permitted standard of care (SoC; ^{177}Lu-PSMA-617 arm) versus SoC alone (control arm) in patients with PSMA-positive mCRPC previously treated with at least one ARPI and one or two taxane regimens [6,15]. Although there were no unexpected safety concerns with ^{177}Lu-PSMA-617 treatment and safety was consistent with that reported in previous clinical studies [16–21], the incidence of treatment-emergent adverse events (TEAEs) was higher in the ^{177}Lu-PSMA-617 arm than in the control arm [6]. However, overall treatment exposure was more than three times longer in the ^{177}Lu-PSMA-617 arm than in the control arm because of the prolonged time until rPFS was reached [6]. Thus, between-group differences in TEAE incidence were potentially affected by ascertainment bias.

Although a longer safety observation period generally increases the likelihood of recording a TEAE, it was important to evaluate whether longer exposure to ^{177}Lu-PSMA-617 for up to 6 cycles was associated with greater toxicity. Here, we report a prespecified safety analysis for patients who received 1–4 cycles of ^{177}Lu-PSMA-617 in comparison to those who received 5–6 cycles, an analysis of TEAE incidence during each cycle of ^{177}Lu-PSMA-617 treatment, an analysis of cumulative TEAE incidence, and a post hoc exposure-adjusted safety analysis in both study arms to facilitate comparison between arms.

2. Patients and methods

2.1. Study design and patients

VISION was an open-label, international, randomised, phase 3 trial investigating the efficacy and safety of ^{177}Lu-PSMA-617 in patients with progressive, PSMA-positive mCRPC previously treated with at least one ARPI and one or two taxane-containing regimens [6]. Patients were randomised to receive either ^{177}Lu-PSMA-617 (7.4 GBq, 200 mCi) every 6 wk for up to 6 cycles plus protocol-permitted SoC (^{177}Lu-PSMA-617 arm) or protocol-permitted SoC alone (control arm). Details of the study enrolment criteria and study treatments are provided in the Supplementary material.

2.2. Endpoints and assessments

In VISION, safety was a secondary endpoint. Safety was analysed in a subset of randomised patients who received at least one dose of study treatment according to the actual treatment received. TEAEs were defined as AEs, regardless of causality, occurring from the first administration of randomised treatment until up to 30 d after the last treatment administration, including SoC, or 1 d before subsequent anticancer treatment, whichever occurred first (treatment-emergent period). Further details on safety assessments are provided in the Supplementary material.

2.3. Prespecified and post hoc safety analyses

2.3.1. Analyses of safety by cycles of ^{177}Lu-PSMA-617 received

The incidence of any-grade and grade ≥3 TEAEs and treatment-related AEs (TRAEs) was analysed for prespecified subgroups of patients who received either 1–4 cycles or 5–6 cycles of ^{177}Lu-PSMA-617. The incidence of TEAEs and TRAEs was also analysed during each cycle of treatment in the ^{177}Lu-PSMA-617 arm. TEAEs and TRAEs for each patient were allocated to a cycle programmatically if the onset date for the event was on or after the start of the current cycle but before the start of the next cycle or within the treatment-emergent period, whichever occurred earlier. Multiple occurrences of the same event in a patient within a cycle were counted only once and reported by maximum grade.

2.3.2. Analysis of time to first occurrence of events

Time to first occurrence of safety events of interest was defined as the time from the start of the study treatment to the date of the first occurrence of an event within a class of safety events of interest for ^{177}Lu-PSMA-617 therapy. In the absence of an event during the treatment-emergent period, the patient was censored at the end of the period, withdrawal of informed consent, death, or the data cutoff date.

Cumulative event probabilities (percentage and 95% confidence interval [CI]) at specific time points were estimated using the Kaplan-Meier method on the basis of all patients in the treatment arm, with censoring of those without an event. Estimates of the median time to occurrence of first event were based on patients with at least one event.

2.3.3. Post hoc exposure-adjusted safety analysis

To account for differences in treatment exposure duration between the treatment arms, TEAE incidence rates was adjusted for the number of patient-treatment years (PTY). The time at risk spanned from the start of randomised treatment to the first occurrence of a given TEAE (any grade or grade ≥3) or until 30 d after last treatment administration (including SoC) or 1 d before subsequent treatment for patients without a given TEAE. The adjusted rate for a given TEAE was calculated as the number of events per 100 PTY = (TEAE incidence [*n*]/PTY) × 100, where PTY was defined as the sum of patient-years at risk for all patients within a treatment arm.

3. Results

3.1. Patient disposition

Overall, 734/831 patients (88%) received at least one dose of the study treatment. In the ^{177}Lu-PSMA-617 arm, 529/551 patients (96%) received ^{177}Lu-PSMA-617 plus SoC; the median duration of treatment exposure (including SoC beyond ^{177}Lu-PSMA-617 therapy), and thus the follow-up period for safety observation, was 7.8 mo (interquartile range [IQR] 4.4–10.6) and patients started a median of 5 cycles of treatment (IQR 3–8). In the control arm, 205/280 patients (73%) received SoC alone; the median duration of exposure was 2.1 mo (IQR 1.4–4.1) and patients started a median of 2 cycles of treatment (IQR 1–3).

Of the 529 patients who received ^{177}Lu-PSMA-617 plus SoC, 240 (45%) received ≤4 cycles and 289 (55%) received 5–6 cycles of ^{177}Lu-PSMA-617 treatment; the median duration of treatment exposure (including SoC beyond ^{177}Lu-PSMA-617 therapy) was 4.2 mo (IQR 2.8–5.5) and 9.7 mo (IQR 8.3–12.8), respectively. Disease progression was the most frequent cause of treatment discontinuation during each cycle apart from cycle 1 (Supplementary Table 1). Similar proportions of patients discontinued ^{177}Lu-PSMA-617 during each cycle because of AEs (Supplementary Table 1). Overall, 30/529 patients (5.7%) had ^{177}Lu-PSMA-617 dose reductions owing to TEAEs, and the incidence for dose reductions were similar across all cycles: 0 patients in cycle 1, ten patients in cycle 2 (1.9%), eight patients in cycle 3 (1.5%), six patients in cycle 4 (1.1%), five patients in cycle 5 (0.95%), and three patients in cycle 6 (0.57%). The most common TEAEs resulting in ^{177}Lu-PSMA-617 dose reductions were thrombocytopenia (*n* = 10; 1.9%); anaemia (*n* = 7; 1.3%); dry mouth, leukopenia, and neutropenia (*n* = 3 each; 0.57%); elevated blood creatinine, fatigue, and lymphopenia (*n* = 2 each; 0.38%); and chronic kidney disease, malignant urinary tract obstruction, and urosepsis (*n* = 1 each; 0.19%).

3.2. Safety and tolerability

3.2.1. TEAEs by number of ^{177}Lu-PSMA-617 cycles received

The incidence of TEAEs and TRAEs was consistent between the groups that received 1–4 cycles and 5–6 cycles of ^{177}Lu-PSMA-617 treatment (Table 1). The frequency of grade ≥3 TEAEs and TRAEs was higher in the group that received 1–4 cycles than in the group that received 5–6 cycles (Table 1). As this subgroup analysis was defined according to a postrandomisation characteristic and thus was influenced by the actual treatment, we analysed the incidence of TEAEs and TRAEs within each treatment cycle to evaluate whether there were additional safety risks for patients who received 5 or 6 cycles of treatment.

Table 1 – TEAEs and TRAEs by prespecified subgroups for the number of ^{177}Lu-PSMA-617 cycles received in the ^{177}Lu-PSMA-617 arm (*N* = 529)

Event	Patients with at least one event, *n* (%)	
	1–4 cycles (*N* = 240)	5–6 cycles (*N* = 289)
Any grade TEAE	234 (98)	285 (99)
Grade ≥3 TEAE	145 (60)	134 (46)
Serious TEAE	100 (42)	92 (32)
Any grade TRAE	205 (85)	246 (85)
Grade ≥3 TRAE	88 (37)	62 (22)
Serious TRAE	33 (14)	16 (6)

PSMA = prostate-specific membrane antigen; TEAE = treatment-emergent adverse even; TRAE = treatment-related adverse event.

3.2.2. TEAEs and TRAEs by cycle of onset

The median cycle duration in the ^{177}Lu-PSMA-617 arm was 6 wk for cycles 1–5. For cycle 6, the median time on treatment was 26.6 wk. Using a cycle duration of 6 wk, the incidence of any-grade TEAEs/TRAEs and of the most common TEAEs, irrespective of seriousness, did not increase during later cycles. Importantly, this was not accompanied by an increase in the incidence of grade ≥3 events (Tables 2 and 3, and Supplementary Fig. 1A, B). Patients had more TEAEs overall in cycle 6 after ^{177}Lu-PSMA-617 treatment than in cycle 6 up to 6 wk, reflecting continued exposure to SoC and the safety observation time (Supplementary Fig. 2).

Grouping the TEAEs into safety classes of interest for the ^{177}Lu-PSMA-617 arm showed that events occurred in earlier cycles of treatment (Supplementary Table 2 and Supplementary Fig. 1C). The overall crude incidence of myelosuppression was higher in the ^{177}Lu-PSMA-617 arm but, importantly, the risk of bone marrow toxicity was not associated with longer exposure to ^{177}Lu-PSMA-617 treatment (Supplementary Table 2 and Supplementary Fig. 1C). There were also consistent rates of recovery and resolution of these events within classes of special interest for each cycle (Supplementary Table 2).

The frequency of renal toxicity was similar between the treatment arms (Supplementary Table 3) and there was a trend for decreasing incidence by cycle of onset in the ^{177}Lu-PSMA-617 arm (Supplementary Table 2). Among patients who started cycle 6, late renal toxicity (onset >6 wk after the start of the cycle) occurred in 7/257 (2.7%; Supplementary Table 4); five patients had acute kidney injury (grade 3 in 4 patients), one patient had both elevated blood creatinine (grade 2) and proteinuria (grade 1), and one patient had a decrease in urine output (grade 3). Treatment-related late renal toxicity was reported for 3/257 patients (1.2%).

Table 2 – TEAEs and TRAEs by cycle of onset in the ^{177}Lu-PSMA-617 arm

Event	Patients with at least one event, *n* (%)[a]											
	Cycle 1 (*N* = 529)[b]		Cycle 2 (*N* = 503)[b]		Cycle 3 (*N* = 447)[b]		Cycle 4 (*N* = 371)[b]		Cycle 5 (*N* = 300)[b]		Cycle 6 (*N* = 257)[c]	
	AG	G ≥3	AG	G ≥3	AG	G ≥3	AG	G ≥3	AG	G ≥3	AG	G ≥3
TEAE												
Any	438 (83)	90 (17)	349 (69)	80 (16)	294 (66)	70 (16)	240 (65)	54 (15)	170 (57)	40 (13)	121 (47)	31 (12)
Serious	55 (10)	47 (8.9)	42 (8.3)	36 (7.2)	32 (7.2)	26 (5.8)	30 (8.1)	23 (6.2)	24 (8.0)	21 (7.0)	15 (5.8)	12 (4.7)
TRAE												
Any	339 (64)	45 (8.5)	222 (44)	45 (8.9)	184 (41)	42 (9.4)	126 (34)	26 (7.0)	92 (31)	17 (5.7)	62 (24)	17 (6.6)
Serious	20 (3.8)	16 (3.0)	12 (2.4)	11 (2.2)	8 (1.8)	8 (1.8)	1 (0.27)	1 (0.27)	6 (2.0)	5 (1.7)	1 (0.39)	1 (0.39)

AG = any grade; G ≥3 = grade ≥3; PSMA = prostate-specific membrane antigen; TEAE = treatment-emergent adverse even; TRAE = treatment-related adverse event.
[a] Percentages are based on the number of patients that started the cycle and are reported to two significant figures.
[b] Number of patients with at least one event with an onset date on or after the current cycle but before the start of the next cycle.
[c] Number of patients with at least one event with an onset date on or after cycle 6 up to 6 wk after the start of cycle 6 and within the treatment-emergent period.

Table 3 – Most common TEAEs (reported in ≥4% patients in cycle 1) and other TEAEs of interest by cycle of onset in the ^{177}Lu-PSMA-617 arm

TEAE preferred term[a]	Patients with at least one TEAE, *n* (%)[b]											
	Cycle 1 (*N* = 529)[c]		Cycle 2 (*N* = 503)[c]		Cycle 3 (*N* = 447)[c]		Cycle 4 (*N* = 371)[c]		Cycle 5 (*N* = 300)[c]		Cycle 6 (*N* = 257)[d]	
	AG	G ≥3	AG	G ≥3	AG	G ≥3	AG	G ≥3	AG	G ≥3	AG	G ≥3
Most common TEAEs												
Fatigue	127 (24)	11 (2.1)	56 (11)	6 (1.2)	44 (9.8)	5 (1.1)	24 (6.5)	2 (0.54)	13 (4.3)	1 (0.33)	18 (7.0)	2 (0.78)
Nausea	117 (22)	3 (0.57)	51 (10)	0	27 (6.0)	1 (0.22)	18 (4.9)	1 (0.27)	13 (4.3)	1 (0.33)	14 (5.4)	0
Dry mouth	104 (20)	0	47 (9.3)	0	34 (7.6)	0	19 (5.1)	0	22 (7.3)	0	9 (3.5)	0
Anaemia	63 (12)	15 (2.8)	49 (9.7)	21 (4.2)	45 (10.1)	16 (3.6)	34 (9.2)	10 (2.7)	27 (9.0)	10 (3.3)	15 (5.8)	3 (1.2)
Decrease in appetite	62 (12)	4 (0.76)	29 (5.8)	3 (0.60)	17 (3.8)	1 (0.22)	8 (2.2)	0	4 (1.3)	0	8 (3.1)	0
Constipation	57 (11)	1 (0.19)	29 (5.8)	2 (0.40)	17 (3.8)	0	13 (3.5)	0	11 (3.7)	1 (0.33)	4 (1.6)	0
Vomiting	54 (10)	3 (0.57)	21 (4.2)	0	15 (3.4)	0	12 (3.2)	1 (0.27)	10 (3.3)	0	5 (1.9)	0
Lymphopenia	43 (8.1)	17 (3.2)	27 (5.4)	13 (2.6)	22 (4.9)	10 (2.2)	16 (4.3)	10 (2.7)	6 (2.0)	1 (0.33)	8 (3.1)	6 (2.3)
Back pain	41 (7.8)	4 (0.76)	29 (5.8)	5 (1.0)	24 (5.4)	2 (0.45)	19 (5.1)	1 (0.27)	12 (4.0)	2 (0.67)	11 (4.3)	0
Diarrhoea	41 (7.8)	1 (0.19)	31 (6.2)	0	14 (3.1)	3 (0.67)	14 (3.8)	0	5 (1.7)	0	7 (2.7)	0
Arthralgia	32 (6.0)	3 (0.57)	30 (6.0)	2 (0.40)	26 (5.8)	0	19 (5.1)	0	6 (2.0)	0	14 (5.4)	1 (0.39)
Leukopenia	32 (6.0)	3 (0.57)	14 (2.8)	2 (0.40)	18 (4.0)	1 (0.22)	14 (3.8)	2 (0.54)	10 (3.3)	2 (0.67)	4 (1.6)	1 (0.39)
Thrombocytopenia	30 (5.7)	11 (2.1)	24 (4.8)	8 (1.6)	30 (6.7)	9 (2.0)	19 (5.1)	9 (2.4)	12 (4.0)	5 (1.7)	6 (2.3)	3 (1.2)
Bone pain	23 (4.3)	4 (0.76)	8 (1.6)	1 (0.20)	9 (2.0)	2 (0.45)	5 (1.3)	1 (0.27)	11 (3.7)	3 (1.0)	6 (2.3)	1 (0.39)
Peripheral oedema	22 (4.2)	0	8 (1.6)	1 (0.20)	9 (2.0)	0	2 (0.54)	0	3 (1.0)	0	1 (0.39)	0
Dizziness	21 (4.0)	3 (0.57)	6 (1.2)	0	5 (1.1)	0	5 (1.3)	0	4 (1.3)	1 (0.33)	4 (1.6)	0
Dyspnoea	21 (4.0)	4 (0.76)	17 (3.4)	1 (0.20)	11 (2.5)	1 (0.22)	5 (1.3)	0	3 (1.0)	0	1 (0.39)	0
Neutropenia	21 (4.0)	6 (1.1)	12 (2.4)	4 (0.80)	8 (1.8)	1 (0.22)	11 (3.0)	3 (0.81)	5 (1.7)	2 (0.67)	9 (3.5)	1 (0.39)
UTI	21 (4.0)	7 (1.3)	18 (3.6)	7 (1.4)	10 (2.2)	2 (0.45)	9 (2.4)	1 (0.27)	5 (1.7)	0	6 (2.3)	3 (1.2)
Other TEAEs of interest												
Hypokalaemia	14 (2.6)	1 (0.19)	7 (1.4)	0	8 (1.8)	0	6 (1.6)	2 (0.54)	1 (0.33)	0	4 (1.6)	1 (0.39)
Increase in bCR	13 (2.5)	0	10 (2.0)	1 (0.20)	2 (0.45)	0	3 (0.81)	0	3 (1.0)	0	0	0
Increase in AST	12 (2.3)	1 (0.19)	6 (1.2)	2 (0.40)	1 (0.22)	0	2 (0.54)	0	1 (0.33)	1 (0.33)	2 (0.78)	0
Increase in ALT	10 (1.9)	1 (0.19)	3 (0.60)	1 (0.20)	1 (0.22)	0	1 (0.27)	0	0	0	1 (0.39)	0
Pain	11 (2.1)	1 (0.19)	5 (1.0)	1 (0.20)	7 (1.6)	2 (0.45)	3 (0.81)	2 (0.54)	3 (1.0)	0	4 (1.6)	0
Falls	9 (1.7)	0	6 (1.2)	0	7 (1.6)	1 (0.22)	7 (1.9)	0	5 (1.7)	0	2 (0.78)	0
Dry eye	8 (1.5)	0	3 (0.60)	0	0	0	2 (0.54)	0	2 (0.67)	0	1 (0.39)	0
Acute kidney injury	5 (0.95)	4 (0.76)	3 (0.60)	3 (0.60)	2 (0.45)	1 (0.22)	2 (0.54)	2 (0.54)	1 (0.33)	1 (0.33)	1 (0.39)	1 (0.39)

AG = any grade; bCR = blood creatinine; ALT = alanine aminotransferase; AST = aspartate aminotransferase; G ≥3 = grade ≥3; PSMA = prostate-specific membrane antigen; TEAE = treatment-emergent adverse event; UTI = urinary tract infection.
[a] Coded using Medical Dictionary for Regulatory Activities v23.1 and Common Terminology Criteria for Adverse Events v5.0.
[b] Percentages are based on the number of patients that started the cycle and are reported to two significant figures.
[c] Number of patients with at least one event with an onset date on or after the current cycle but before the start of the next cycle.
[d] Number of patients with at least one event with an onset date on or after cycle 6 up to 6 wk after the start of cycle 6 and within the treatment-emergent period.

Second primary malignancies (SPMs) were reported for 11/529 patients in the ^{177}Lu-PSMA-617 arm and 2/205 patients in the control arm. In the ^{177}Lu-PSMA-617 arm, SPMs mainly occurred in early cycles (Supplementary Table 2). The estimated probability of SPM at 24 wk was 2.0% (95% CI 1.1–3.7%) in the ^{177}Lu-PSMA-617 arm and 4.6% (95% CI 1.2–17.2%) in the control arm (Supplementary Table 3). One treatment-related SPM (grade 2 squamous cell carcinoma) occurred in cycle 6 after ^{177}Lu-PSMA-617 treatment, approximately 11 mo after the start of treatment (Supplementary Table 4).

3.2.3. *Time to first onset of safety events of interest*

Assessment of safety classes of interest for all treated patients revealed that the risk of having a first event was greatest early in treatment (Fig. 1 and Supplementary

Table 3). Events occurred earlier in the ^{177}Lu-PSMA-617 arm than in the control arm. In the ^{177}Lu-PSMA-617 arm, for patients with at least one event for each safety class of interest, the median time to first occurrence ranged from 1.9-10.5 weeks, when 1-2 cycles of treatment would have been received. However, although still relatively early, time to first onset of a grade ≥3 event was generally later than the occurrence of any grade events (Supplementary Table 3).

3.2.4. *Comparison of treatment arms: exposure-adjusted safety analysis*

The exposure-adjusted incidence of TEAEs per 100 PTY generally appeared to be similar in the ^{177}Lu-PSMA-617 arm

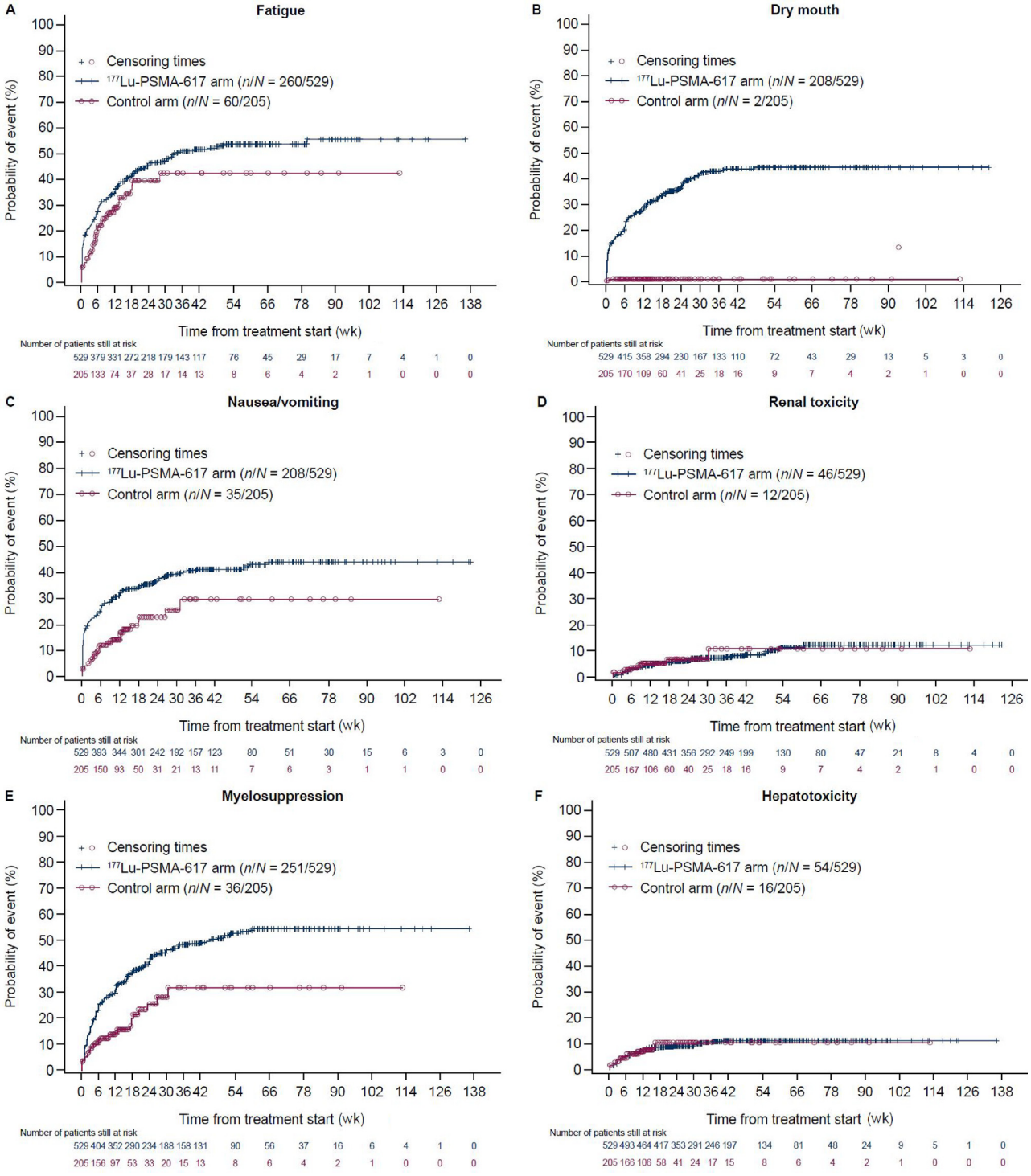

Fig. 1 – Time to first occurrence of any-grade safety events of interest. Analyses were for the 734 patients who received at least one dose of randomised treatment. Second primary malignancies are not shown owing to their low incidence. *n*/*N* = number of events/number of patients in treatment arm; PSMA = prostate-specific membrane antigen.

and control arm (Table 4). Fatigue, dry mouth, and nausea were the most common exposure-adjusted TEAEs in the ^{177}Lu-PSMA-617 arm, and were mainly mild to moderate in severity.

This exposure-adjusted analysis revealed three distinct patterns for TEAEs (Fig. 2). First, the exposure-adjusted incidence per 100 PTY for any-grade acute myelosuppression events, dry eyes, and dry mouth remained higher in the ^{177}Lu-PSMA-617 arm than in the control arm (Fig. 2A, B). Second, the exposure-adjusted incidence per 100 PTY for any-grade fatigue and gastrointestinal events was generally similar between the ^{177}Lu-PSMA-617 and control arms; however, the incidence of diarrhoea and vomiting remained higher in the ^{177}Lu-PSMA-617 arm (Fig. 2C, D). Third, the exposure-adjusted incidence per 100 PTY for any-grade musculoskeletal, renal, and liver events and dyspnoea was lower in the ^{177}Lu-PSMA-617 arm than in the control arm (Fig. 2E, F).

4. Discussion

In VISION, analyses of TEAE incidence in each dosing cycle and by subgroups for the number of treatment cycles received demonstrated that greater exposure to ^{177}Lu-PSMA-617 for 5 or 6 cycles was not associated with additional toxicity risk in patients who remained on treatment beyond 4 cycles. It must be noted that these analyses were not designed to draw comparative conclusions about the relative safety of 1–4 cycles versus 5–6 cycles of ^{177}Lu-PSMA-617 treatment. A post hoc exposure-adjusted safety analysis of the incidence of TEAEs according to treatment exposure time, and thus accounting for longer follow-up time in the ^{177}Lu-PSMA-617 arm because of prolonged rPFS, revealed that TEAE incidence was generally similar between the treatment arms. However, rates of specific toxicities associated with ^{177}Lu-PSMA-617 treatment, such as dry mouth, dry eyes, myelosuppression, nausea/vomiting, and diarrhoea, remained higher in the ^{177}Lu-PSMA-617 arm than in the control arm.

In a prespecified safety analysis of TEAE incidence for patients who received 1–4 cycles of ^{177}Lu-PSMA-617 treatment (45% patients) and those who received 5–6 cycles (55%), similar incidence rates for TEAEs and TRAEs, regardless of grade or severity, was observed. These results should be interpreted with caution, as this subgroup analysis was

Table 4 – Exposure-adjusted TEAE incidence in VISION[a]

TEAE	Incidence per 100 patient-treatment years (n)[b]			
	^{177}Lu-PSMA-617 arm (N = 529)		Control arm (N = 205)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	1415.7 (519)	91.1 (279)	1137.0 (170)	135.1 (78)
Frequent TEAEs[c]				
Fatigue	79.7 (228)	7.4 (31)	77.2 (47)	4.1 (3)
Dry mouth	75.1 (205)	0	1.4 (1)	0
Nausea	62.9 (187)	1.7 (7)	55.0 (34)	1.4 (1)
Anaemia	47.7 (168)	16.7 (68)	40.8 (27)	14.0 (10)
Back pain	34.0 (124)	4.0 (17)	44.7 (30)	9.7 (7)
Arthralgia	32.5 (118)	1.4 (6)	40.6 (26)	1.4 (1)
Decrease in appetite	30.0 (112)	2.3 (10)	46.6 (30)	1.4 (1)
Constipation	29.3 (107)	1.6 (6)	33.6 (23)	1.4 (1)
Diarrhoea	27.5 (100)	0.9 (4)	8.5 (6)	1.4 (1)
Vomiting	26.8 (100)	1.2 (5)	18.5 (13)	1.4 (1)
Thrombocytopenia	23.0 (91)	10.0 (42)	12.6 (9)	2.8 (2)
Lymphopenia	19.6 (75)	10.2 (41)	11.3 (8)	1.4 (1)
Leukopenia	16.9 (66)	3.1 (13)	5.6 (4)	1.4 (1)
Bone pain	14.8 (59)	3.1 (13)	24.5 (17)	6.9 (5)
Urinary tract infection	14.6 (58)	4.8 (20)	2.8 (2)	1.4 (1)
Decrease in weight	14.2 (57)	0.5 (2)	26.2 (18)	0
Dyspnoea	13.1 (53)	1.6 (7)	28.9 (20)	4.1 (3)
Peripheral oedema	12.7 (51)	0.5 (2)	19.6 (13)	0
Neutropenia	11.1 (45)	4.3 (18)	4.2 (3)	1.4 (1)
Haematuria	11.1 (45)	3.1 (13)	12.6 (9)	1.4 (1)
Extremity pain	11.0 (45)	0.7 (3)	17.1 (12)	0
Dizziness	10.9 (44)	1.2 (5)	13.2 (9)	0
Cough	10.4 (42)	0	18.8 (13)	0
Other TEAEs of interest				
Hypokalaemia	9.8 (40)	11.3 (8)	11.3 (8)	0
Falls	9.4 (38)	0.2 (1)	17.6 (12)	2.8 (2)
Pain	8.0 (33)	1.6 (7)	12.7 (9)	1.4 (1)
Increase in blood creatinine	6.8 (28)	0.2 (1)	6.9 (5)	1.4 (1)
Increase in AST	5.3 (22)	0.9 (4)	7.0 (5)	1.4 (1)
Acute kidney injury	4.5 (19)	3.8 (16)	11.2 (8)	6.9 (5)
Dry eye	3.8 (16)	0	2.8 (2)	0
Increase in ALT	3.6 (15)	0.5 (2)	8.4 (6)	2.8 (2)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PSMA = prostate-specific membrane antigen; TEAE = treatment-emergent adverse event.
[a] Analyses for the 734 patients who received at least one dose of randomised treatment.
[b] n is the number of patients with an event.
[c] TEAEs with an incidence >10 per 100 patient-treatment years in the ^{177}Lu-PMSA-617 arm.

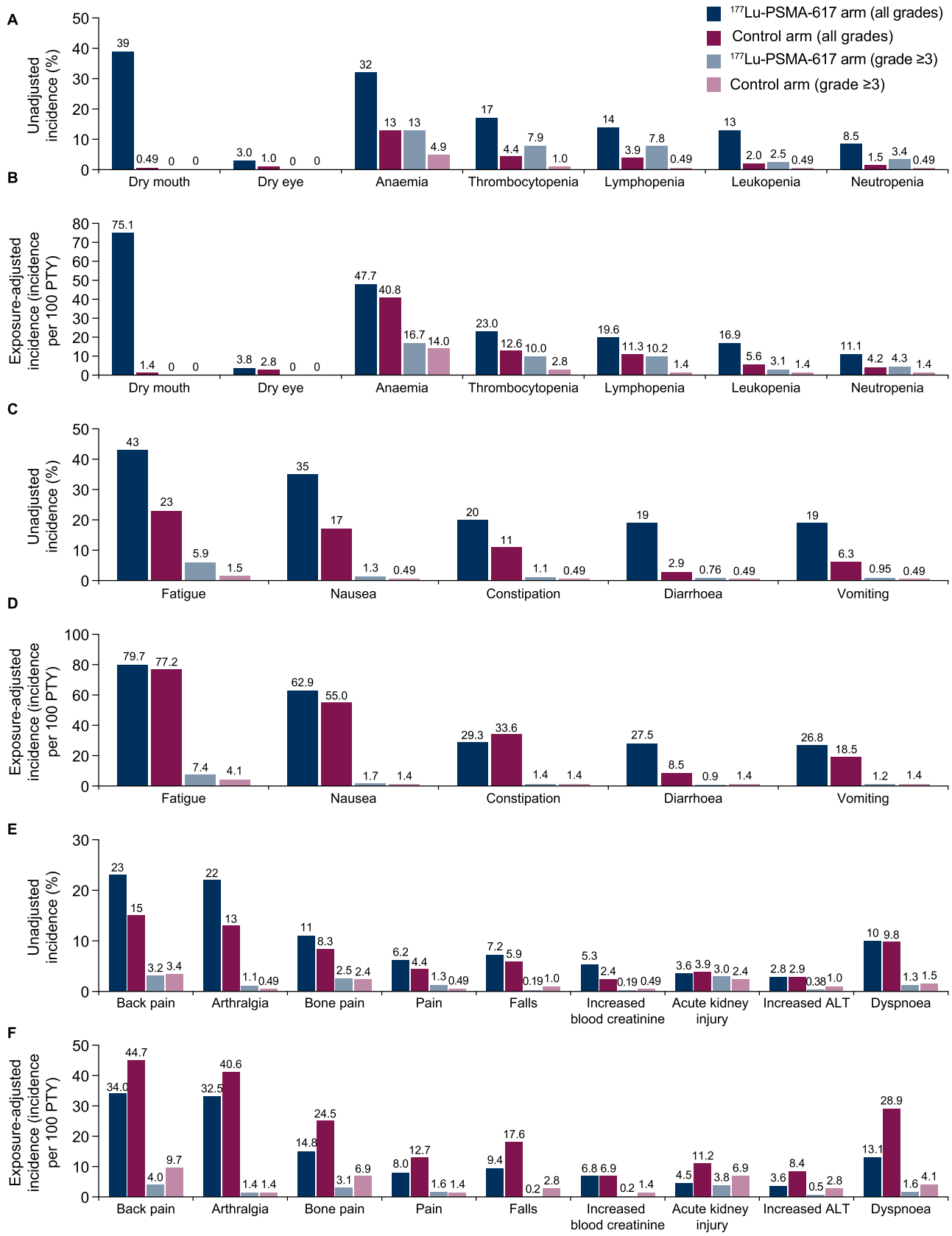

Fig. 2 – Unadjusted and exposure-adjusted incidence of (A,B) dry mouth, dry eye, and acute myelosuppression events, (C,D) fatigue and gastrointestinal events, and (E,F) musculoskeletal, renal, and liver events, and dyspnoea. Analyses were for the 734 patients who received at least one dose of randomised treatment. ALT = alanine aminotransferase; PSMA = prostate-specific membrane antigen; PTY = patient-treatment years.

defined on the basis of a postrandomisation characteristic and may be influenced by treatment-related factors and survivorship bias, with potential for biased estimates of the treatment risk. Patients with the poorest prognosis and the highest likelihood of having an AE may have either experienced disease progression, died, or discontinued treatment because of toxicity during the first 4 cycles of treatment. Furthermore, ^{177}Lu-PSMA-617 treatment beyond cycle 4 was administered at the investigator's discretion for patients without disease progression who were deemed to be tolerating therapy. The most common reason for discontinuation of the study treatment in the ^{177}Lu-PSMA-617 arm overall was disease progression. The proportion of patients who discontinued ^{177}Lu-PSMA-617 owing to AEs was quite low and remained approximately consistent between dosing cycles.

We analysed the incidence of TEAEs and TRAEs within each ^{177}Lu-PSMA-617 treatment cycle to evaluate whether there were additional safety risks for patients who continued onto 5 or 6 cycles of treatment. There was no signal of an increase in the incidence of TEAEs or a transition to higher-grade events in later cycles of treatment. As cycles of onset were not for mutually exclusive patient groups, the results suggest that event recurrence may decrease over time. However, it is important to note that new and recurring events were not captured separately, and that the data do not capture multiple occurrences of an AE in a single patient within a dosing cycle. It is therefore not possible to draw firm conclusions about event recurrence. Cumulative time-to-first-event curves show that the greatest first-event incidence occurred early in treatment, suggesting that events in later cycles may have been recurrences. Overall, it does not appear that an increase in the number of treatment cycles results in accumulating toxicity risk.

The previously published VISION data showed that the incidence for any-grade or grade $\geq$3 TEAEs during treatment was higher in the ^{177}Lu-PSMA-617 arm than in the control arm [6]. However, differences in TEAE incidence may have been affected by ascertainment bias. A longer safety observation period increases the likelihood of detecting TEAEs, including those unrelated to treatment. Here, we report an exposure-adjusted analysis that accounts for the impact of this longer follow-up and exposure to treatment in the ^{177}Lu-PSMA-617 arm than in the control arm. Three distinct TEAE patterns were observed. First, the incidence for dry eyes, dry mouth, and myelosuppression remained higher in the ^{177}Lu-PSMA-617 arm than in the control arm after accounting for treatment exposure, which demonstrates that these TEAEs are associated with ^{177}Lu-PSMA-617 treatment. Second, although the unadjusted incidence for any-grade fatigue and gastrointestinal events was two to three times higher in the ^{177}Lu-PSMA-617 arm than in the control arm [6], the differences decreased after adjustment for exposure duration. Incidence for diarrhoea and vomiting remained higher in the ^{177}Lu-PSMA-617 arm than in the control arm, although it must be considered that patients with mCRPC commonly experience constipation, fatigue, and nausea because of disease progression and the secondary effects of various medications. Third, exposure-adjusted incidence for musculoskeletal, renal, and liver events and dyspnoea was higher in the control arm than in the ^{177}Lu-PSMA-617 arm. This represents a change from the trend for the unadjusted incidence [6], and suggests that these AEs have a stronger association with disease progression, complications, and follow-up duration than with ^{177}Lu-PSMA-617 treatment itself.

Given the overall poor prognosis for these heavily pretreated patients with mCRPC, the long-term safety of ^{177}Lu-PSMA-617 is difficult to ascertain. It should also be borne in mind that some TEAEs may be signs and symptoms of disease progression; the study protocol did not require investigators to attribute events to possible disease progression. TRAEs were those deemed by the investigator as being related to treatment. Another point to note is that these analyses do not account for patients who had ^{177}Lu-PSMA-617 dose reductions during treatment cycles. Overall, 5.7% of patients had a ^{177}Lu-PSMA-617 dose reduction at least once because of TEAEs [6]. It may also be important to investigate correlations between toxicity and PSMA uptake in lesions and off-target sites via dosimetry, and with other parameters that might predict late toxicity.

5. Conclusions

Overall, these safety analyses support a favourable benefit-risk profile of up to 6 cycles of ^{177}Lu-PSMA-617 plus SoC in heavily pretreated patients with PSMA-positive mCRPC. The results provide important information for health care providers supporting the use of a further 2 cycles of ^{177}Lu-PSMA-617 in patients who are clinically benefiting and tolerating the therapy after 4 cycles. The analyses also emphasise that differences in treatment exposure and safety observation time between treatment groups are an important consideration when evaluating safety data in clinical studies. Ongoing phase 3 trials are investigating whether radioligand therapy with ^{177}Lu-PSMA-617 has a good safety profile and therapeutic benefit earlier in the treatment sequence for mCRPC.

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