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|---|---|---|
| **Name of Sponsor/Company:** Astellas Pharma Global Development, Inc. (APGD) | | |
| **Name of Finished Product:** Xtandi® | | |
| **Name of Active Ingredient:** Enzalutamide | | |

## SYNOPSIS

**Title of Study:** A Multicenter, Single-arm, Open-label, Postmarketing Safety Study to Evaluate the Risk of Seizure Among Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated with Enzalutamide Who Are at Potential Increased Risk of Seizure (UPWARD) (9785-CL-0403)

**Investigators/Coordinating Investigator:** [redacted] MD and [redacted] MD

**Study Center(s):** 73 sites in a total of 20 countries (Argentina, Australia, Belgium, Canada, Chile, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, New Zealand, Republic of Korea, Singapore, Spain, Sweden, Taiwan, the United Kingdom and the United States)

**Publication Based on the Study:** No publications based on the results of this study were available at the time this report was approved.

**Study Period:** The total duration of treatment was 4 months. At the end of the 4-month treatment period, patients who were assessed as deriving benefit from enzalutamide treatment could continue in the extension period. Patients who continued to receive clinical benefit from treatment with enzalutamide and did not meet any discontinuation criteria may have transitioned to an open label roll-over extension study upon approval of the study protocol at the institution where they were receiving treatment.

**Study Initiation Date (Date of First Evaluation):** 25 September 2013

**Study Completion Date (Date of Last Evaluation):** 11 January 2019

**Phase of Development:** 4

**Objectives:** The study objective was to evaluate the seizure rate and monitor the safety of enzalutamide treatment in patients with mCRPC known to have risk factor(s) for seizure.

**Methodology:** This was a multicenter, single-arm, open-label, postmarketing safety study to evaluate the risk of seizure among patients with mCRPC treated with enzalutamide who were at potential increased risk of seizure. Eligible patients were drawn from various sources including hospitals, private practices of urologists and oncologists, and community-based organizations. Patients who met all inclusion and none of the exclusion criteria were enrolled into the study and participated in a 4-month treatment period, during which once daily dosing of enzalutamide (160 mg/day) occurred.

At the end of the 4-month treatment period, patients who were assessed as deriving benefit from enzalutamide treatment were allowed to continue in the extension period whereby patients continued to receive enzalutamide until 1 of the following criteria was met: the patient experienced bone disease progression per Prostate Cancer Working Group 2 (PCWG2) guidelines or soft tissue disease progression per Response Evaluation Criteria in

Solid Tumors (RECIST) v1.1, the patient initiated treatment with another anticancer therapy or, in the opinion of the investigator, continued dosing would have led to undue risk to the patient, the patient met a discontinuation criterion, or the sponsor terminated the study.

Patients who continued to receive clinical benefit from treatment with enzalutamide and did not meet any discontinuation criteria may have transitioned to an open label roll-over extension study upon approval of the study protocol at the institution where they were receiving treatment.

Patients who did not continue in the extension period or who met a discontinuation criterion were discontinued from enzalutamide therapy and completed a follow-up visit 30 days from the last dose of enzalutamide or prior to the initiation of another anticancer therapy, whichever occurred first. For patients who continued on treatment after the 12-month extension period, data collection was limited to dosing information, concomitant medications and all adverse events (AEs) including serious adverse events (SAEs).

In the event of a suspected seizure event, the patient contacted the investigator immediately (within 24 hours) after onset and returned to the site with best efforts in 3 days after the event for evaluation by the local neurologist. Evaluation by a local neurologist included an electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain as soon as possible after a potential seizure event occurrence. A description of the events leading up to the seizure was obtained from the patient and any witnesses. All relevant information, including the completed Suspected Seizure Event Questionnaire, the local neurologist's evaluation and results of the MRI of the brain and EEG, were submitted to the Independent Adjudication Committee (IAC) for evaluation. Results of the assessment of the IAC were provided to the investigator and the patient was allowed to continue in the study if the event was determined to be a first confirmed seizure. If the seizure was determined by the IAC to be a second confirmed seizure event, the patient was withdrawn from the study. If it was determined that the event did not meet criteria for a confirmed seizure, the patient could continue in the study if no other discontinuation criteria had been met.

The study also had an independent Data Safety Monitoring Board (DSMB) to monitor the safety.

**Number of Patients (Planned, Enrolled and Analyzed):** Approximately 400 patients were planned to be enrolled in the study. A total of 531 male patients were screened, 424 patients were enrolled and 423 patients received study drug (1 patient died before receiving study drug). A total of 423 patients were included in the safety analysis set (SAF), 366 patients were included in the seizure risk evaluation set (SRES) and 358 patients were included in the per protocol SRES.

**Diagnosis and Main Criteria for Inclusion:** The main inclusion criteria were the following:

1. Patient had histologically-confirmed metastatic adenocarcinoma of the prostate.
2. Patient had ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) analogue (agonist or antagonist) or had a prior orchiectomy (i.e., surgical or medical castration).
3. Patient had disease progressive by at least 1 of the following:
    a. PSA progression defined by a minimum of 2 rising PSA levels with an interval of at least 1 week between each draw
    b. Bone disease progression as defined by PCWG2 guidelines (at least 2 new lesions) on bone scan
    c. Soft tissue disease progression as defined by RECIST v1.1

4. For patients who had not had an orchiectomy, there must have been a plan to maintain effective GnRH-analogue therapy for the duration of the study.
5. Patient must have failed at least 1 course of androgen deprivation therapy, i.e., treatment with GnRH analogues.
6. Patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
7. Prior to study entry, patient had been evaluated by a local neurologist who determined the patient had at least 1 risk factor for seizure including:
    a. Past history of seizure due to any cause except a single febrile seizure in childhood. Patients with a history of seizures should not have had a seizure within 12 months of screening and must have had no anticonvulsants for 12 months prior to screening.
    b. History of cerebrovascular accident or transient ischemic attack
    c. History of traumatic brain or head injury with loss of consciousness
    d. Unexplained loss of consciousness within the last 12 months
    e. Presence of a space occupying lesion in the brain including previously treated brain metastasis(es) or primary central nervous system tumor
    f. History of arteriovenous malformations of the brain
    g. History of brain infection (i.e., abscess, meningitis, or encephalitis)
    h. Current use of medication that may lower seizure threshold (refer to Appendix 12.1 in the protocol [Appendix 13.1.1])
    i. Presence of Alzheimer's disease, meningioma or leptomeningeal disease from prostate cancer.

The main exclusion criteria were the following:

1. Patient had severe concurrent disease, infection or comorbidity that, in the judgment of the investigator, made the patient inappropriate for enrollment.
2. Patient was currently being treated with anti-epileptics.
3. Patient had a history of seizure in the past 12 months prior to screening, as assessed by neurology examination and history.
4. Patient with rapidly progressive visceral disease and had not received and was thought able to tolerate cytotoxic chemotherapy. (However, enrollment of a patient who had previously received cytotoxic chemotherapy was permitted).
5. Patient has clinical signs suggestive of high or imminent risks for pathological fracture, spinal cord compression and/or cauda equina syndrome.
6. Patient had uncontrolled hypertension as indicated by a resting systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at screening.

**Test Product, Dose and Mode of Administration, Batch Numbers:** Patients received 160 mg (four 40 mg capsules) of enzalutamide once daily, taken orally with or without food. The batch numbers were CLR9007790-001, CLR9007790-002, CLR9007790-003, CLR9007790-004, CLR9007790-005, CLR9007790-006 and CLR9007790-007.

**Duration of Treatment (or Duration of Study, if applicable):** The duration of treatment for the primary endpoint was 4 months. At the end of the 4-month treatment period, patients who were assessed as deriving benefit from enzalutamide treatment could continue in the extension period. Patients who continued to receive clinical benefit from treatment with enzalutamide and did not meet any discontinuation criteria may have transitioned to an open label roll-over extension study upon approval of the study protocol at the institution where they were receiving treatment.

**Reference Product, Dose and Mode of Administration, Batch Numbers:** Not applicable.

**Criteria for Evaluation:** Efficacy data were not analyzed during this study; however, disease assessments were performed regularly while the patients were receiving enzalutamide. Pharmacokinetic and pharmacodynamic data were not collected. The primary endpoint in the study was the proportion of evaluable patients with at least 1 confirmed seizure as adjudicated by the IAC during the first 4 months of treatment. Analysis of the primary endpoint was provided in a separate report. An evaluable patient was defined as a patient with a confirmed seizure during the 4-month treatment period of the study or a patient who completed at least 3 months (75%) of the planned treatment. Safety was further assessed by evaluation of the following variables at selected time points throughout the study: AEs, clinical laboratory test results, vital sign measurements and 12-lead ECG results. The current report was generated to report on the additional safety information collected through the last day of evaluation.

**Statistical Methods:** The primary endpoint, the proportion of evaluable patients with at least 1 confirmed seizure as adjudicated by the IAC during the first 4 months of treatment, was estimated using point estimate and its 95% exact confidence interval (CI) using all SRES. As a secondary analysis, the same analysis of the primary endpoint was conducted for a cumulative proportion to include all seizure events, including those occurring beyond the 4 month-treatment period using all SRES. Incidence of seizure events, including only the first seizure event, per patient-time exposure was summarized for SAF. Any subsequent seizure event(s) were listed.

AEs were coded by SOC and preferred term using MedDRA v16.0 and graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE). Summary tabulations by SOC and preferred term were generated for all TEAEs, drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, TEAEs leading to permanent discontinuation of study drug, drug-related TEAEs leading to permanent discontinuation of study drug, deaths, TEAEs that occurred in $\geq$ 5.0% of patients and TEAEs excluding SAEs that occurred in $\geq$ 3.0% of patients. A TEAE was defined as an AE observed after starting administration of the test drug or that begin within 30 days after taking the last dose of the study drug. A drug-related TEAE was defined as any TEAE with at least a possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

Quantitative clinical laboratory variables were summarized using mean, SD, minimum, maximum and median at each visit. Additionally, a within-patient postbaseline change was calculated. Each laboratory result was classified as low (L), normal (N) or high (H) at each visit according to the laboratory supplied reference ranges. The number and percentage of patients below and above reference range were summarized at each visit. Shift analysis tables were provided to present shifts from baseline to worst finding during the treatment period and to present shifts of NCI-CTCAE grade changes.

The number and percentage of patients with potentially clinically significant values for alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase and combinations thereof were summarized. The patient's highest value during the investigational period was used.

Vital signs (systolic blood pressure, diastolic blood pressure and pulse rate) were summarized using mean, SD, minimum, maximum and median by visit. Additionally, a within-patient postbaseline change was calculated.

Physical examination findings were provided in a listing.

ECG variables were summarized using mean, SD, minimum, maximum and median at each treatment visit and time point, including changes from baseline. Number and percent of patients with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator for the 12-lead ECG were tabulated at each treatment visit and time point.

The overall ECG interpretations (normal, abnormal – not clinically significant, abnormal – clinically significant) from the local investigator and the central reader were summarized. A shift table was produced showing the shift from baseline to each visit. Parameters from central ECG readings (QT, QTcB, QTcF, HR, PR, QRS, RR, coded abnormalities and overall conclusion) and their change from baseline were summarized using descriptive statistics. The QTc interval was also summarized by the frequencies of patients with a change from baseline of clinical importance for each treatment visit and time point.

No formal interim analysis was planned for a specific time point. However, the study design included early stopping criteria that could have been applied to the study as a whole or to a specific risk factor group based on the statistical boundary calculated from a Maximized Sequential Probability Ratio Test.

**Summary of Results/Conclusions:**

**Population:** A total of 531 male patients were screened, 424 patients were enrolled and 423 patients received the study drug (1 patient was screened and enrolled but died the following day before receiving the study drug). A total of 322/423 (76.1%) patients completed the primary 4-month treatment period, 287/423 (67.8%) patients continued into the 1-year extension period, and 145/423 (34.3%) patients continued post the 1-year extension period Table 1. The most frequent (≥ 5% patients) reasons for discontinuation from the 4 month treatment period were progressive disease (43/423 [10.2%]) and AE (34/423 [8.0%]). The most frequent (≥ 5% patients) reason for discontinuation from the 1 year extension period was progressive disease (86/423 [20.3%]). The most frequent (≥ 5% patients) reasons for discontinuation post the 1-year extension period was progressive disease (60/423 [14.2%]) and other (49/423 [11.6%]). Overall, as of the last day of evaluation on 11 Jan 2019, 48/423 (11.3%) patients were still receiving enzalutamide and 375/423 (88.7%) patients had discontinued treatment. The 48 patients remaining on enzalutamide treatment were rolled over into Study 9785-CL-0123.

**Efficacy/Pharmacokinetic/Pharmacodynamic Results:** Efficacy, pharmacokinetic and pharmacodynamic parameters were not assessed in this study.

**Safety Results:** TEAEs were most frequently reported (≥ 25% of patients) in the SOCs of general disorders and administration site conditions, musculoskeletal and connective tissue disorders, gastrointestinal disorders, nervous system disorders and metabolism and nutrition disorders. By preferred term, the most frequently reported TEAEs (reported in ≥ 10% of patients) were fatigue (94/423 [22.2%]), asthenia (88/423 [20.8%]), decreased appetite (78/423 [18.4%]), back pain (71/423 [16.8%]), anemia (61/423 [14.4%]), nausea (56/423 [13.2%]), constipation (49/423 [11.6%]), arthralgia (47/423 [11.1%]) and diarrhea (43/423 [10.2%]) Table 2. Fatigue (74/423 [17.5%] patients) and asthenia (44/423 [10.4%]) were the only drug-related TEAEs reported in ≥ 10% of patients.

A total of 58/423 (13.7%) patients died after receiving at least 1 dose of enzalutamide (as of the last day of evaluation, 11 Jan 2019). The most common reason for death was malignant neoplasm progression, which was reported for 23/58 patients; the second most common reason for death was general physical health deterioration, which was reported for 6/58 patients. No deaths were reported that were due to seizures. Six patients died due to SAEs that were considered by the investigator to be possibly related to the study drug (1 patient each died

due to the following possibly related SAEs: cerebral hemorrhage, cerebrovascular accident, malignant neoplasm progression, sudden cardiac death, anuria and general physical health deterioration).

A total of 193/423 patients (45.6%) experienced an SAE. By preferred term, the most frequently reported SAEs (reported in ≥ 2% of patients) were malignant neoplasm progression (34/423 [8.0%]), pneumonia (13/423 [3.1%]), general physical health deterioration (10/423 [2.4%]), confusional state (10/423 [2.4%]), fall (10/423 [2.4%]) and anemia (9/423 [2.1%]) Table 3. Drug related SAEs were reported in 37/423 (8.7%) patients; confusional state was the most frequently reported drug related SAE (5/423 [1.2%] patients).

A total of 90/423 (21.3%) patients permanently discontinued the study drug due to a TEAE. The 3 most common TEAEs leading to discontinuation of the study drug were malignant neoplasm progression (17/423 [4.0%]), general physical health deterioration (7/423 [1.7%]) and spinal cord compression (5/423 [1.2%]). A total of 20/423 (4.7%) patients permanently discontinued the study drug due to a TEAE that was considered by the investigator to be drug related. The 4 most common drug-related TEAEs leading to discontinuation of the study drug were fatigue, general physical health deterioration, decreased appetite and decreased weight, each of which occurred in 2 patients; all other drug-related TEAEs leading to discontinuation of the study drug were single events. Of the 8 patients with IAC confirmed seizure events, 6 patients had seizure events that were considered by the investigator to be at least possibly related to the study drug and 3 patients permanently discontinued enzalutamide treatment due to a seizure event.

Overall, the incidences of TEAEs, SAEs and TEAEs leading to discontinuation of the study drug were consistent with those previously seen in clinical studies of enzalutamide in which patients with risk factors for seizure were excluded (e.g., CRPC2 and MDV3100-03).

Seventeen patients were noted to have had potentially clinically significant elevations in LFT results; no patients experienced LFT elevations consistent with Hy's law criteria. The majority of the increased LFT values were sporadic and subsequently resolved or were also elevated at the screening visit.

Safety assessments of vital signs and ECGs were clinically unremarkable.

The primary endpoint in this study was the proportion of evaluable patients with at least 1 confirmed seizure, as adjudicated by the IAC, during the first 4 months of treatment; the primary analysis of this endpoint was reported previously. A secondary analysis of the primary endpoint was conducted to determine a cumulative proportion of seizure events, including those occurring beyond the 4 month-treatment period. During the entire study period, the IAC assessed a total of 31 suspected seizure events that occurred in a total of 26 patients during the entire study period. A total of 8 patients in the SRES (n = 366) had at least 1 IAC confirmed seizure (3 patients had 2 IAC-confirmed seizures) during the entire study period, yielding an event rate of 2.2% (95% CI: 0.9, 4.3). Based on a total exposure time of 530.22 patient-years and a total of 8 patients with an IAC confirmed seizure, the exposure adjusted rate of seizure events was determined to be 1.5% per 100 patient-years. The expected seizure rate in men with CRPC with seizure risk factors without enzalutamide is 2.8 per 100 patient-years.

**CONCLUSIONS:** In summary, the seizure event rate in patients with mCRPC who were treated with enzalutamide and who were potentially at an increased risk of seizure was 2.2%, which was similar to findings from other clinical studies with enzalutamide and similar to the risk of seizure in the general population of patients with mCRPC. Enzalutamide was well tolerated in the patient population and no new safety signals were observed.

**Date of Report:** 24 Jul 2019

**Table 1 Treatment Disposition (SAF)**

| **Period**<br>**Parameter**<br>Category, n (%) | **Total**<br>**(n = 423)** |
|---|---|
| **Overall** | |
| **Treatment discontinuation** | |
| Yes | 375 (88.7) |
| No | 48 (11.3) |
| **Primary reason for discontinuation†** | |
| Adverse event | 53 (12.5) |
| Death | 26 (6.1) |
| Lost to follow-up | 2 (0.5) |
| Progressive disease | 189 (44.7) |
| Protocol violation | 0 |
| Withdrawal by patient | 41 (9.7) |
| Physician decision | 14 (3.3) |
| Other | 50 (11.8) |
| **Primary 4-Month Period** | |
| **Treatment discontinuation between 0 and 4 months** | |
| Yes | 101 (23.9) |
| No | 322 (76.1) |
| **Primary reason for discontinuation†** | |
| Adverse event | 34 (8.0) |
| Death | 3 (0.7) |
| Lost to follow-up | 0 |
| Progressive disease | 43 (10.2) |
| Protocol violation | 0 |
| Withdrawal by patient | 17 (4.0) |
| Physician decision | 4 (0.9) |
| Other | 0 |
| **1-Year Extension** | |
| **Continued to 1-year extension** | |
| Yes | 287 (67.8) |
| No | 35 (8.3) |
| **Treatment discontinuation between 4 and 12 months** | |
| Yes | 130 (30.7) |
| No | 157 (37.1) |
| **Primary reason for discontinuation†** | |
| Adverse event | 14 (3.3) |
| Death | 10 (2.4) |
| Lost to follow-up | 2 (0.5) |
| Progressive disease | 86 (20.3) |
| Protocol violation | 0 |
| Withdrawal by patient | 11 (2.6) |
| Physician decision | 6 (1.4) |
| Other | 1 (0.2) |

*Table continued on next page*

| **Period**<br>**Parameter**<br>Category, n (%) | **Total**<br>**(n = 423)** |
|---|---|
| **Post 1-Year Extension** | |
| **Continued to post 1-year extension** | |
| Yes | 145 (34.3) |
| No | 12 (2.8) |
| **Treatment discontinuation during the post 1-year extension period** | |
| Yes | 144 (34.0) |
| No | 1 (0.2) |
| **Primary reason for discontinuation†** | |
| Adverse event | 5 (1.2) |
| Death | 13 (3.1) |
| Lost to follow-up | 0 |
| Progressive disease | 60 (14.2) |
| Protocol violation | 0 |
| Withdrawal by patient | 13 (3.1) |
| Physician decision | 4 (0.9) |
| Other | 49 (11.6) |

All enrolled patients who took at least 1 dose of study drug and for whom any data was reported after first dose of study drug (SAF).

SAF: safety analysis set.

† For every patient, only the primary reason for discontinuation was collected.

Source: End-of-Text Table 12.1.1.3

**Table 2 TEAEs Experienced by ≥ 5.0% of Patients (SAF)**

| SOC (MedDRA v16.0)<br>Preferred Term | Total<br>(n = 423)<br>n (%) |
|---|---|
| **General Disorders and Administration Site Conditions** | |
| Fatigue | 94 (22.2) |
| Asthenia | 88 (20.8) |
| Oedema peripheral | 33 (7.8) |
| Pain | 25 (5.9) |
| **Musculoskeletal and Connective Tissue Disorders** | |
| Back pain | 71 (16.8) |
| Arthralgia | 47 (11.1) |
| Pain in extremity | 30 (7.1) |
| Bone pain | 26 (6.1) |
| Musculoskeletal pain | 22 (5.2) |
| **Gastrointestinal Disorders** | |
| Nausea | 56 (13.2) |
| Constipation | 49 (11.6) |
| Diarrhoea | 43 (10.2) |
| Vomiting | 28 (6.6) |
| Abdominal pain | 24 (5.7) |
| **Nervous System Disorders** | |
| Headache | 25 (5.9) |
| **Metabolism and Nutrition Disorders** | |
| Decreased appetite | 78 (18.4) |
| **Renal and Urinary Disorders** | |
| Haematuria | 23 (5.4) |
| **Respiratory, Thoracic and Mediastinal Disorders** | |
| Dyspnoea | 36 (8.5) |
| **Psychiatric Disorders** | |
| Insomnia | 27 (6.4) |
| **Blood and Lymphatic System Disorders** | |
| Anaemia | 61 (14.4) |
| **Injury, Poisoning and Procedural Complications** | |
| Fall | 32 (7.6) |
| **Investigations** | |
| Weight decreased | 26 (6.1) |
| **Vascular Disorders** | |
| Hypertension | 32 (7.6) |
| Hot flush | 24 (5.7) |
| **Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)** | |
| Malignant neoplasm progression | 34 (8.0) |

All enrolled patients who took at least 1 dose of study drug and for whom any data was reported after first dose of study drug (SAF).

SAF: safety analysis set; TEAE: treatment-emergent adverse event

Source: End-of-Text Table 12.6.1.18

**Table 3 Serious TEAEs Experienced by ≥ 0.5% of Patients (SAF)**

| SOC (MedDRA v16.0)<br>Preferred Term | Total (n = 423)<br>n (%) |
|---|---|
| **Nervous System Disorders** | |
| Convulsion | 8 (1.9) |
| Spinal cord compression | 7 (1.7) |
| Syncope | 5 (1.2) |
| Transient ischaemic attack | 4 (0.9) |
| Cerebral haemorrhage | 2 (0.5) |
| Cerebrovascular accident | 2 (0.5) |
| Lethargy | 2 (0.5) |
| Loss of consciousness | 2 (0.5) |
| Transient global amnesia | 2 (0.5) |
| **General Disorders and Administration Site Conditions** | |
| General physical health deterioration | 10 (2.4) |
| Pyrexia | 8 (1.9) |
| Pain | 5 (1.2) |
| Asthenia | 3 (0.7) |
| Fatigue | 3 (0.7) |
| **Infections and Infestations** | |
| Pneumonia | 13 (3.1) |
| Sepsis | 4 (0.9) |
| Urinary tract infection | 4 (0.9) |
| Pyelonephritis acute | 3 (0.7) |
| Urinary tract infection bacterial | 3 (0.7) |
| Bronchopneumonia | 2 (0.5) |
| Cellulitis | 2 (0.5) |
| Escherichia urinary tract infection | 2 (0.5) |
| Pyelonephritis | 2 (0.5) |
| Urinary tract infection staphylococcal | 2 (0.5) |
| Urosepsis | 2 (0.5) |
| **Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)** | |
| Malignant neoplasm progression | 34 (8.0) |
| Metastases to liver | 2 (0.5) |
| **Musculoskeletal and Connective Tissue Disorders** | |
| Bone pain | 8 (1.9) |
| Back pain | 6 (1.4) |
| Muscular weakness | 3 (0.7) |
| Pain in extremity | 3 (0.7) |
| Pathological fracture | 3 (0.7) |
| Flank pain | 2 (0.5) |
| **Renal and Urinary Disorders** | |
| Haematuria | 8 (1.9) |
| Urinary retention | 5 (1.2) |
| Dysuria | 4 (0.9) |
| Renal failure | 4 (0.9) |
| Renal failure acute | 4 (0.9) |
| Hydronephrosis | 2 (0.5) |
| Urethral stenosis | 2 (0.5) |

*Table continued on next page*

| SOC (MedDRA v16.0)<br>Preferred Term | Total<br>(n = 423)<br>n (%) |
|---|---|
| **Gastrointestinal Disorders** | |
| Vomiting | 7 (1.7) |
| Abdominal pain | 6 (1.4) |
| Nausea | 4 (0.9) |
| Constipation | 3 (0.7) |
| Intestinal obstruction | 2 (0.5) |
| **Injury, Poisoning and Procedural Complications** | |
| Fall | 10 (2.4) |
| Femur fracture | 4 (0.9) |
| Femoral neck fracture | 2 (0.5) |
| Subdural haematoma | 2 (0.5) |
| Subdural haemorrhage | 2 (0.5) |
| **Metabolism and Nutrition Disorders** | |
| Dehydration | 5 (1.2) |
| Hyponatraemia | 4 (0.9) |
| Hypoglycaemia | 2 (0.5) |
| **Respiratory, Thoracic and Mediastinal Disorders** | |
| Dyspnoea | 5 (1.2) |
| Pulmonary embolism | 4 (0.9) |
| Pleural effusion | 3 (0.7) |
| **Blood and Lymphatic System Disorders** | |
| Anaemia | 9 (2.1) |
| Febrile neutropenia | 3 (0.7) |
| **Cardiac Disorders** | |
| Myocardial infarction | 5 (1.2) |
| Atrial fibrillation | 4 (0.9) |
| Cardiac failure | 4 (0.9) |
| Cardiac failure congestive | 3 (0.7) |
| Acute myocardial infarction | 2 (0.5) |
| Angina pectoris | 2 (0.5) |
| **Psychiatric Disorders** | |
| Confusional state | 10 (2.4) |
| Delirium | 2 (0.5) |
| **Investigations** | |
| Prostatic specific antigen increased | 2 (0.5) |
| **Vascular Disorders** | |
| Deep vein thrombosis | 2 (0.5) |
| Hypertension | 2 (0.5) |

All enrolled patients who took at least 1 dose of study drug and for whom any data was reported after first dose of study drug (SAF).

Includes adverse events either identified as serious by the investigator, or upgraded by the sponsor based on review of the sponsor's list of always serious terms.

SAF: safety analysis set; TEAE: treatment-emergent adverse event

Source: End-of-Text Table 12.6.1.6