יוני 2025

Jevtana

Concentrate and Solvent for Solution for Infusion

חומר פעיל:

Cabazitaxel 60 mg / 1.5 mL

התוויה:

Jevtana is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen.

חברת סאנופי מבקשת להודיע על עדכון העלון לרופא של התכשיר שבנדון.

בסעיף משטר המינון חל העדכון הבא:

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of JEVTANA is based on calculation of the Body Surface Area (BSA), and is 20 mg/m^2 administered as a one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout JEVTANA treatment.

A dose of 25 mg/m^2 can be used in select patients at the discretion of the treating healthcare provider *[see Warnings and Precautions (5.1, 5.2), Adverse Reactions (6.1), and Clinical Studies (14)]*.

Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m^2 [see Contraindications (4) and Warnings and Precautions (5.1, 5.2)].

[…]

העלון ובו מסומנים העדכונים העיקריים מצורף למכתב זה.

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על ידי פנייה לבעל הרישום - סאנופי ישראל בע"מ, Greenwork Park, מתחם העסקים בקיבוץ יקום, בניין E (קומה 1), 6097600, יקום או בטלפון: 09-8633081.

להלן הקישור לאתר משרד הבריאות: https://israeldrugs.health.gov.il/#!/byDrug

בברכה,

חברת סאנופי ישראל בע"מ

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

Neutropenia: Neutropenic deaths have been reported. Monitor for neutropenia with frequent blood cell counts. JEVTANA is contraindicated in patients with neutrophil counts of ≤1,500 cells/mm^3. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m^2 *[see Contraindications (4) and Warnings and Precautions (5.1, 5.2)].*

Severe hypersensitivity: Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and administration of appropriate therapy. Patients should receive premedication.
JEVTANA is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 *[see Dosage and Administration (2.1), Contraindications (4), and Warnings and Precautions (5.3)]*.

[…]

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A dose of 25 mg/m^2 can be used in select patients at the discretion of the treating healthcare provider *[see Warnings and Precautions (5.1, 5.2), Adverse Reactions (6.1), and Clinical Studies (14)]*.

Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m^2 [see Contraindications (4) and Warnings and Precautions (5.1, 5.2)].

Premedicate at least 30 minutes prior to each dose of JEVTANA with the following intravenous medications to reduce the risk and/or severity of hypersensitivity *[see Warnings and Precautions (5.3)]:*

- antihistamine (dexchlorpheniramine 5 mg, or diphenhydramine 25 mg or equivalent antihistamine),
- corticosteroid (dexamethasone 8 mg or equivalent steroid),
- H_2 antagonist (ranitidine 50 mg or equivalent H_2 antagonist).

Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed *[see Warnings and Precautions (5.3)]*.

JEVTANA injection single-dose vial requires **two** dilutions prior to administration *[see Dosage and Administration (2.5)]*.

[…]

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

JEVTANA is contraindicated in patients with neutrophils ≤1,500/mm^3 *[see Contraindications (4)]*. Closely monitor patients with hemoglobin <10 g/dL.

Bone marrow suppression manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported.

TROPIC Trial (JEVTANA 25 mg/m^2)

In ~~a randomized~~ the TROPIC trial ~~(TROPIC) in previously treated patients~~ with ~~metastatic castration-resistant prostate cancer, five~~ G-CSF administered only at the investigator's discretion, 5 patients (1.3%) died from neutropenic infection (sepsis or septic shock). ~~All had grade~~ 4 ~~neutropenia and one had febrile neutropenia~~ of these patients died in the first 30 days of treatment. One additional patient's death was attributed to neutropenia without a documented infection. Twenty-two (6%) patients discontinued JEVTANA treatment due to neutropenia, febrile neutropenia, infection, or sepsis. ~~The most common adverse reaction leading to treatment discontinuation in the JEVTANA group was neutropenia (2%).~~ Grade 3-4 neutropenia occurred ~~has been observed~~ in 82% of patients treated with JEVTANA in the randomized trial. *[see Adverse Reactions (6.1)].*

PROSELICA Trial (comparison of JEVTANA 20 mg/m^2 versus 25 mg/m^2)

In ~~a randomized~~ the PROSELICA trial ~~(PROSELICA)~~ comparing two doses of JEVTANA ~~in previously treated metastatic castration-resistant prostate cancer, 8~~, primary prophylaxis with G-CSF was not allowed, but could be administered after development of neutropenia at investigators discretion. Eight patients (1%) on the 20 mg/m^2 arm and 15 patients (3%) on the 25 mg/m^2 arm died from infection; of these, 4 deaths on the 20 mg/m^2 arm and 8 deaths on the 25 mg/m^2 arm occurred within the first 30 days of treatment. Clinically important neutropenia-related events-occurred and included febrile neutropenia (2.1% on 20 mg/m^2 arm and 9.2% on 25 mg/m^2 arm), neutropenic infection/sepsis (2.1% on 20 mg/m^2 arm and 6.4% on 25 mg/m^2 arm), and neutropenic deaths (0.3% on 20 mg/m^2 arm and 0.7% on 25 mg/m^2 arm).

Fewer patients receiving JEVTANA 20 mg/m^2 were reported to have infectious adverse reactions. Grade 1-4 infections were experienced by 160 patients (28%) on the 20 mg/m^2 arm and 227 patients (38%) on the 25 mg/m^2 arm. Grade 3-4 infections were experienced by 57 patients (10%) on the 20 mg/m^2 arm and 120 patients (20%) on the 25 mg/m^2 arm. Noninferiority for overall survival was demonstrated between these two arms *[see Adverse Reactions (6.1)]*.

CARD Trial (JEVTANA 25 mg/m^2 + primary prophylaxis G-CSF)

In the CARD trial where JEVTANA 25 mg/m^2 was administered with primary prophylaxis of G-CSF, 1 patient (0.8%) died from sepsis within the first 30 days of treatment. Grade 1-4 neutropenia-related adverse reactions were experienced in 33 patients (26%). Grade 3-4 neutropenias were experienced by 26 patients (21%). Clinically important neutropenia-related events occurred and included febrile neutropenia (3.2%), neutropenic infection/sepsis (0.8%) and neutropenic deaths (0.8%) *[see Adverse Reactions (6.1)]*.

Based on guidelines for the use of G-CSF and the adverse reactions profile of JEVTANA, primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features (older patients, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia.

~~The effectiveness of~~ Consider primary prophylaxis with G-CSF in all patients receiving JEVTANA ~~has not been studied. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients at increased risk for neutropenia complications~~ 25 mg/m^2.

Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed *[see Dosage and Administration (2.2)]*.

5.2 Increased Toxicities in Elderly Patients

In a randomized trial (TROPIC), 2% of patients (3/131) <65 years of age and 6% (15/240) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose. Patients ≥65 years of age are more likely to experience certain adverse reactions, including neutropenia and febrile neutropenia. The incidence of the following grade 3-4 adverse reactions ~~were~~was higher in patients ≥65 years of age compared to younger patients; neutropenia (87% vs 74%), and febrile neutropenia (8% vs 6%).

In a randomized clinical trial (PROSELICA) comparing two doses of JEVTANA, deaths due to infection within 30 days of starting JEVTANA occurred in 0.7% (4/580) patients on the 20 mg/m^2 arm and 1.3% (8/595) patients on the 25 mg/m^2 arm; all of these patients were >60 years of age.

In PROSELICA, on the 20 mg/m^2 arm, 3% (5/178) of patients <65 years of age and 2% (9/402) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose. On the 25 mg/m^2 arm, 2% (3/175) patients <65 years of age and 5% (20/420) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose *[see Adverse Reactions (6) and Use in Specific Populations (8.5)]*.

In CARD, a death due to infection within 30 days of starting JEVTANA occurred in 0.8% (1/126) patient who was >75 years of age. There were 2.4% (3/126) of patients who died of causes other than disease progression within 30 days of the last JEVTANA dose; all of these patients were >75 years of age.

[…]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

TROPIC Trial (JEVTANA 25mg/m^2 ~~+ prednisone~~ compared to mitoxantrone)

The safety of JEVTANA in combination with prednisone was evaluated in 371 patients with metastatic castration-resistant prostate cancer treated in the randomized TROPIC trial, compared to mitoxantrone plus prednisone.

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) JEVTANA-treated patients and 3 (< 1%) mitoxantrone-treated patients. The most common fatal adverse reactions in JEVTANA-treated patients were infections (n=5) and renal failure (n=4). The majority (4 of 5 patients) of fatal infection-related adverse reactions occurred after a single dose of JEVTANA. Other fatal adverse reactions in JEVTANA-treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.

The most common (≥10%) grade 1-4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.

The most common (≥5%) grade 3-4 adverse reactions in patients who received JEVTANA were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia.

Treatment discontinuations due to adverse ~~drug~~ reactions occurred in 18% of patients who received JEVTANA and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation in the JEVTANA group were neutropenia and renal failure. Dose reductions were reported in 12% of JEVTANA-treated patients and 4% of mitoxantrone-treated patients. Dose delays were reported in 28% of JEVTANA-treated patients and 15% of mitoxantrone-treated patients.

Table 2: ~~Incidence of~~ Adverse Reactions* and Hematologic Abnormalities in ≥ 5% of Patients ~~Receiving JEVTANA in Combination with Prednisone or Mitoxantrone in Combination with Prednisone~~ in TROPIC

	JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=371		Mitoxantrone 12 mg/m^2 every 3 weeks with prednisone 10 mg daily n=371	
Adverse Reactions	Grade 1-4 ~~n (%)~~ %	Grade 3-4 ~~n (%)~~ %	Grade 1-4 ~~n (%)~~ %	Grade 3-4 ~~n (%)~~ %
~~Any Adverse Reaction~~				
Blood and Lymphatic System Disorders				
~~Neutropenia‡~~	~~347 (94%)~~	~~303 (82%)~~	~~325 (87%)~~	~~215 (58%)~~
~~Febrile Neutropenia~~	~~27 (7%)~~	~~27 (7%)~~	~~5 (1%)~~	~~5 (1%)~~
Anemia†	~~361 (~~98~~%)~~	~~39 (~~11~~%)~~	~~302 (~~82~~%)~~	~~18 (~~5~~%)~~
Leukopenia†	~~355 (~~96~~%)~~	~~253 (~~69~~%)~~	~~343 (~~93~~%)~~	~~157 (~~42~~%)~~

Neutropenia†	94	82	87	58
Thrombocytopenia†	~~176 (48%)~~	~~15 (4%)~~	~~160 (43%)~~	~~6 (2%)~~
~~**Cardiac Disorders**~~				
~~Arrhythmia‡~~ Febrile Neutropenia	~~18 (5%)~~ 7	~~4 (1%)~~ 7	~~6 (2%)~~ 1	1 ~~(<1%)~~
Gastrointestinal Disorders				
Diarrhea	~~173 (47%)~~	~~23 (6%)~~	~~39 (11%)~~	≤1 ~~(<1%)~~
Nausea	~~127 (34%)~~	~~7 (2%)~~	~~85 (23%)~~	≤1 ~~(<1%)~~
Vomiting	~~83 (22%)~~	~~6 (2%)~~	~~38 (10%)~~	0
Constipation	~~76 (20%)~~	~~4 (1%)~~	~~57 (15%)~~	~~2 (<1%)~~
Abdominal Pain~~§‡~~	~~64 (17%)~~	~~7 (2%)~~	~~23 (6%)~~	0
Dyspepsia~~¶§~~	~~36 (10%)~~	0	~~9 (2%)~~	0
General Disorders and Administration Site Conditions				
Fatigue	~~136 (37%)~~	~~18 (5%)~~	~~102 (27%)~~	~~11 (3%)~~
Asthenia	~~76 (20%)~~	~~17 (5%)~~	~~46 (12%)~~	~~9 (2%)~~
Pyrexia	~~45 (12%)~~	~~4 (1%)~~	~~23 (6%)~~	≤1 ~~(<1%)~~
Peripheral Edema	~~34 (9%)~~	~~2 (<1%)~~	~~34 (9%)~~	~~2 (<1%)~~
Mucosal Inflammation	~~22 (6%)~~	≤1 ~~(<1%)~~	~~10 (3%)~~	≤1 ~~(<1%)~~
Pain	~~20 (5%)~~	~~4 (1%)~~	~~18 (5%)~~	~~7 (2%)~~
~~**Infections and Infestations**~~				
Renal and Urinary Tract ~~Infection#~~ **Disorders** ~~29 (8%)~~ ~~6 (2%)~~ ~~12 (3%)~~ ~~4 (1%)~~				
~~**Investigations**~~ Hematuria	17	2	4	<1
~~Weight Decreased~~ Dysuria	~~32 (9%)~~ 7	0	~~28 (8%)~~ 1	~~1 (<1%)~~ 0
~~**Metabolism and Nutrition Disorders**~~				
~~Anorexia~~	~~59 (16%)~~	~~3 (<1%)~~	~~39 (11%)~~	~~3 (<1%)~~
~~Dehydration~~	~~18 (5%)~~	~~8 (2%)~~	~~10 (3%)~~	~~3 (<1%)~~
Musculoskeletal and Connective Tissue Disorders				
Back Pain	~~60 (16%)~~	~~14 (4%)~~	~~45 (12%)~~	~~11 (3%)~~
Arthralgia	~~39 (11%)~~	~~4 (1%)~~	~~31 (8%)~~	~~4 (1%)~~
Muscle Spasms	~~27 (7%)~~	0	~~10 (3%)~~	0
Metabolism and Nutrition Disorders				
Anorexia	16	<1	11	<1
Dehydration	5	2	3	<1

Nervous System Disorders				
Peripheral Neuropathy[þ¶]	~~50 (~~13~~%)~~	~~3 (<~~<1~~%)~~	~~12 (~~3~~%)~~	~~3 (<~~<1~~%)~~
Dysgeusia	~~41 (~~11~~%)~~	0	~~15 (~~4~~%)~~	0
Dizziness	~~30 (~~8~~%)~~	0	~~21 (~~6~~%)~~	~~2 (<~~<1~~%)~~
Headache	~~28 (~~8~~%)~~	0	~~19 (~~5~~%)~~	0
~~**Renal and Urinary Tract Disorders**~~				
~~Hematuria~~	~~62 (17%)~~	~~7 (2%)~~	~~13 (4%)~~	~~1 (<1%)~~
~~Dysuria~~	~~25 (7%)~~	~~0~~	~~5 (1%)~~	~~0~~
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	~~43 (~~12~~%)~~	~~4 (~~1~~%)~~	~~16 (~~4~~%)~~	~~2 (<~~<1~~%)~~
Cough	~~40 (~~11~~%)~~	0	~~22 (~~6~~%)~~	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	~~37 (~~10~~%)~~	0	~~18 (~~5~~%)~~	0
Investigations				
Weight Decreased	9	0	8	<1
Infections and Infestations				
Urinary Tract Infection[#]	8	2	3	1
Cardiac Disorders				
Arrhythmia[þ]	5	1	2	<1
Vascular Disorders				
Hypotension	~~20 (~~5~~%)~~	~~2 (<~~<1 ~~%)~~	~~9 (~~2~~%)~~	~~1 (<~~<1~~%)~~
~~**Median Duration of Treatment**~~	~~6 cycles~~		~~4 cycles~~	

[*]Graded using NCI CTCAE version 3

[†]Based on laboratory values, JEVTANA: n =369, mitoxantrone: n = 370.

[‡] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.

[§] Includes gastroesophageal reflux disease and reflux gastritis.

[¶] Includes peripheral motor neuropathy and peripheral sensory neuropathy.

[#] Includes urinary tract infection enterococcal and urinary tract infection fungal.

[þ‡]Includes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.

~~[§] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.~~

~~[¶] Includes gastroesophageal reflux disease and reflux gastritis.~~

~~[#] Includes urinary tract infection enterococcal and urinary tract infection fungal.~~

~~[þ] Includes peripheral motor neuropathy and peripheral sensory neuropathy.~~

PROSELICA Trial (comparison of two doses of JEVTANA)

In a noninferiority, multicenter, randomized, open-label study (PROSELICA), 1175 patients with metastatic castration-resistant prostate cancer, previously treated with a docetaxel-containing regimen, were treated with either JEVTANA 25 mg/m^2 (n=595) or the 20 mg/m^2 (n=580) dose.

Deaths within 30 days of last study drug dose were reported in 22 (3.8%) patients in the 20 mg/m^2 and 32 (5.4%) patients in the 25 mg/m^2 arm. The most common fatal adverse reactions in JEVTANA-treated patients were related to infections, and these occurred more commonly on the 25 mg/m^2 arm (n=15) than on the 20 mg/m^2 arm (n=8). Other fatal adverse reactions in JEVTANA-treated patients included cerebral hemorrhage, respiratory failure, paralytic ileus, diarrhea, acute pulmonary edema, disseminated intravascular coagulation, renal failure, sudden death, cardiac arrest, ischemic stroke, diverticular perforation, and cardiorenal syndrome.

Grade 1-4 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m^2 versus 20 mg/m^2 arms were leukopenia, neutropenia, thrombocytopenia, febrile neutropenia, decreased appetite, nausea, diarrhea, asthenia, and hematuria.

Grade 3-4 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m^2 versus 20 mg/m^2 arms were leukopenia, neutropenia, and febrile neutropenia.

Treatment discontinuations due to adverse ~~drug~~ reactions occurred in 17% of patients in the 20 mg/m^2 group and 20% of patients in the 25 mg/m^2 group. The most common adverse reactions leading to treatment discontinuation were fatigue and hematuria. The patients in the 20 mg/m^2 group received a median of 6 cycles (median duration of 18 weeks), while patients in the 25 mg/m^2 group received a median of 7 cycles (median duration of 21 weeks). In the 25 mg/m^2 group, 128 patients (22%) had a dose reduced from 25 to 20 mg/m^2, 19 patients (3%) had a dose reduced from 20 to 15 mg/m^2 and 1 patient (0.2%) had a dose reduced from 15 to 12 mg/m^2. In the 20 mg/m^2 group, 58 patients (10%) had a dose reduced from 20 to 15 mg/m^2, and 9 patients (2%) had a dose reduced from 15 to 12 mg/m^2.

Table 3: ~~Incidence of~~ Adverse Reactions* and Hematologic Abnormalities in ≥5% of Patients ~~Receiving JEVTANA 20 mg/m^2 or 25 mg/m^2 in Combination with Prednisone~~ in PROSELICA

Adverse Reactions ~~Primary System Organ Class~~ ~~Preferred Term~~	JEVTANA 20 mg/m^2 every 3 weeks with prednisone 10 mg daily n=580		JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=595	
	Grade 1-4 ~~n (%)~~%	Grade 3-4 ~~n (%)~~%	Grade 1-4 ~~n (%)~~%	Grade 3-4 ~~n (%)~~%
Blood and Lymphatic System Disorders				
Anemia†	99.8	10	99.7	14
Leukopenia†	80	29	95	60
Neutropenia†	67	42	89	73
Thrombocytopenia†	35	3	43	4
Febrile Neutropenia	~~12 (~~2~~%)~~	~~12 (~~2~~%)~~	~~55 (~~9~~%)~~	~~55 (~~9~~%)~~
~~Neutropenia‡~~	~~18 (3%)~~	~~14 (2%)~~	~~65 (11%)~~	~~57 (10%)~~
Gastrointestinal Disorders				
Diarrhea	31	1	40	4
Nausea	25	0.7	32	1

Adverse Reactions ~~Primary System Organ Class~~ ~~Preferred Term~~	JEVTANA 20 mg/m^2 every 3 weeks with prednisone 10 mg daily n=580		JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=595	
	Grade 1-4 ~~n (%)~~%	Grade 3-4 ~~n (%)~~%	Grade 1-4 ~~n (%)~~%	Grade 3-4 ~~n (%)~~%
Constipation	18	0.3	18	0.7
Vomiting	15	1.2	18	1
Abdominal pain	6	0.5	9	1
Stomatitis	5	0	5	0.3
General Disorders and Administration Site Conditions				
Fatigue	25	3	27	4
Asthenia	15	2	20	2
Edema peripheral	7	0.2	9	0.2
Pyrexia	5	0.2	6	0.2
Renal and Urinary Disorders				
Hematuria	14	2	21	4
Dysuria	5	0.3	4	0
~~**Infections and Infestations**~~				
~~Urinary tract infection‡~~	~~43 (7%)~~	~~12 (2%)~~	~~66 (11%)~~	~~14 (2%)~~
~~Neutropenic infection§~~	~~15 (3%)~~	~~13 (2%)~~	~~42 (7%)~~	~~36 (6%)~~
Metabolism and Nutrition Disorders				
Decreased appetite	~~76 (~~13~~%)~~	~~4 (~~0.7~~%)~~	~~110 (~~19~~%)~~	~~7 (~~1~~%)~~
Musculoskeletal and Connective Tissue Disorders				
Back pain	11	0.9	14	1
Bone pain	8	2	8	2
Arthralgia	8	0.5	7	0.8
Pain in extremity	5	0.2	7	0.5
Nervous System Disorders				
Dysgeusia	~~41 (~~7~~%)~~	0	~~63 (~~11~~%)~~	0
Peripheral sensory neuropathy	~~38 (~~7~~%)~~	0	~~63 (~~11~~%)~~	~~4 (~~0.7~~%)~~
Dizziness	~~24 (~~4~~%)~~	0	~~32 (~~5~~%)~~	0
Headache	~~29 (~~5~~%)~~	~~1 (~~0.2~~%)~~	~~24 (~~4~~%)~~	~~1 (~~0.2~~%)~~
Infections and Infestations				
Urinary tract infection‡	7	2	11	2
Neutropenic infection§	3	2	7	6
Respiratory, Thoracic and Mediastinal Disorders				

Adverse Reactions ~~Primary System Organ Class~~ ~~Preferred Term~~	JEVTANA 20 mg/m^2 every 3 weeks with prednisone 10 mg daily n=580		JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=595	
	Grade 1-4 ~~n (%)~~%	Grade 3-4 ~~n (%)~~%	Grade 1-4 ~~n (%)~~%	Grade 3-4 ~~n (%)~~%
Dyspnea	~~30 (~~5~~%)~~	~~5 (~~0.9~~%)~~	~~46 (~~8~~%)~~	~~4 (~~0.7~~%)~~
Cough	~~34 (~~6~~%)~~	0	~~35 (~~6~~%)~~	0
~~**Gastrointestinal Disorders**~~				
~~Diarrhea~~	~~178 (31%)~~	~~8 (1%)~~	~~237 (40%)~~	~~24 (4%)~~
~~Nausea~~	~~142 (25%)~~	~~4 (0.7%)~~	~~191 (32%)~~	~~7 (1%)~~
~~Vomiting~~	~~84 (15%)~~	~~7 (1.2%)~~	~~108 (18 %)~~	~~8 (1%)~~
~~Constipation~~	~~102 (18%)~~	~~2 (0.3%)~~	~~107 (18%)~~	~~4 (0.7%)~~
~~Abdominal pain~~	~~34 (6%)~~	~~3 (0.5%)~~	~~52 (9%)~~	~~7 (1%)~~
~~Stomatitis~~	~~27 (5%)~~	~~0~~	~~30 (5%)~~	~~2 (0.3%)~~
Investigations				
Weight decreased	4	0.2	7	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	~~15 (~~3~~%)~~	0	~~36 (~~6.1~~%)~~	0
~~**Musculoskeletal and Connective Tissue Disorders**~~				
~~Back pain~~	~~64 (11%)~~	~~5 (0.9%)~~	~~83 (14%)~~	~~7 (1%)~~
~~Bone pain~~	~~46 (8%)~~	~~10 (2%)~~	~~50 (8%)~~	~~13 (2 %)~~
~~Arthralgia~~	~~49 (8%)~~	~~3 (0.5%)~~	~~41 (7%)~~	~~5 (0.8%)~~
~~Pain in extremity~~	~~30 (5%)~~	~~1 (0.2%)~~	~~41 (7%)~~	~~3 (0.5%)~~
~~**Renal and Urinary Disorders**~~				
~~Hematuria~~	~~82 (14%)~~	~~11 (2%)~~	~~124 (21%)~~	~~25 (4%)~~
~~Dysuria~~	~~31 (5%)~~	~~2 (0.3%)~~	~~24 (4%)~~	~~0~~
~~**General Disorders and Administration Site Conditions**~~				
~~Fatigue~~	~~143 (25%)~~	~~15 (3%)~~	~~161 (27%)~~	~~22 (4%)~~
~~Asthenia~~	~~89 (15%)~~	~~11 (2%)~~	~~117 (20%)~~	~~12 (2%)~~
~~Edema peripheral~~	~~39 (7%)~~	~~1 (0.2%)~~	~~53 (9%)~~	~~1 (0.2%)~~
~~Pyrexia~~	~~27 (5%)~~	~~1 (0.2%)~~	~~38 (6 %)~~	~~1 (0.2%)~~
~~**Investigations**~~				
~~Weight decreased~~	~~24 (4%)~~	~~1 (0.2%)~~	~~44 (7%)~~	~~0~~
Injury, Poisoning and Procedural Complications				
Wrong technique in drug usage process	~~2 (~~0.3~~%)~~	0	~~32 (~~5~~%)~~	0

* Grade from NCI CTCAE version 4.03.

† Based on ~~adverse event reporting.~~ laboratory values, JEVTANA 20 mg/m2: n=577, JEVTANA 25 mg/m2: n=590.
‡ Includes urinary tract infection staphylococcal, urinary tract infection bacterial, urinary tract infection fungal, and urosepsis.
§ Includes neutropenic sepsis.

CARD Trial (JEVTANA 25 mg/m^2 + primary prophylaxis with G-CSF)

The safety of JEVTANA 25 mg/m^2 in combination with prednisone/prednisolone and primary prophylaxis G-CSF was evaluated in a randomized, open-label study (CARD) in patients with metastatic castration-resistant prostate cancer who progressed after receiving prior docetaxel-containing regimens and abiraterone acetate or enzalutamide *[see Clinical Studies 14.3]*. This study compared JEVTANA 25 mg/m^2 in combination with prednisone/prednisolone and primary prophylaxis with G-CSF to either abiraterone acetate 1000 mg once daily plus prednisone/prednisolone 5 mg twice daily or enzalutamide 160 mg once daily. Among patients receiving JEVTANA, 35% remained on treatment at 6 months and 4.7% remained on treatment at 12 months.

Serious adverse reactions occurred in 39% of patients receiving JEVTANA. Serious adverse reactions in ≥3% of patients included neutropenia (6%), infections (4.8%), and diarrhea, fatigue, pneumonia, and spinal cord compression (3.2% each). Deaths due to causes other than disease progression were reported in 2.4% of JEVTANA treated patients. Fatal adverse reactions in JEVTANA-treated patients were septic shock, urinary tract infection (UTI), and aspiration (0.8% each).

Treatment discontinuations due to adverse drug reactions occurred in 20% of patients who received JEVTANA and 8% of patients who received abiraterone acetate plus prednisone/prednisolone or enzalutamide. The adverse reactions leading to treatment discontinuation in >1% of patients in JEVTANA arm were nervous system disorders, infections/infestations, and gastrointestinal disorders.

Dose interruptions (alone or in combination with dose reduction) due to an adverse reaction occurred in 31% of patients receiving JEVTANA. Dose reductions were reported in 18% of JEVTANA-treated patients. The most frequent adverse reactions leading to dose interruption of JEVTANA were fatigue (7%) and hypersensitivity reaction (3.2%); the most frequent adverse reaction leading to reduction of JEVTANA were neutropenia and peripheral neuropathy (3.9% each).

Table 4 summarizes the adverse reactions and laboratory hematologic abnormalities in patients in CARD.

The most common (≥10%) adverse reactions were fatigue, diarrhea, musculoskeletal pain, nausea, infections, peripheral neuropathy, hematuria, constipation, abdominal pain, decreased appetite, vomiting, dysgeusia, edema peripheral and lower urinary tract symptoms.

The most common (≥10%) hematologic abnormalities were anemia, lymphopenia, neutropenia and thrombocytopenia.

Table 4: ~~Incidence of~~ Adverse Reactions* and Hematologic ~~Laboratory~~ Abnormalities in ≥5% of Patients ~~Receiving JEVTANA 20 mg/m^2 or 25 mg/m^2 in Combination with Prednisone in Study PROSELICA~~ in CARD Trial

~~Laboratory Abnormality~~	~~JEVTANA 20 mg/m^2 every 3 weeks with prednisone 10 mg daily n=577~~		~~JEVTANA 25 mg/m^2 every 3 weeks with prednisone 10 mg daily n=590~~	
	~~Grade 1-4 n (%)~~	~~Grade 3-4 n (%)~~	~~Grade 1-4 n (%)~~	~~Grade 3-4 n (%)~~
~~Neutropenia~~	~~384 (67%)~~	~~241 (42%)~~	~~522 (89%)~~	~~432 (73%)~~
~~Anemia~~	~~576 (99.8%)~~	~~57 (10%)~~	~~588 (99.7%)~~	~~81 (14%)~~
~~Leukopenia~~	~~461 (80%)~~	~~167 (29%)~~	~~560 (95%)~~	~~351 (60%)~~
~~Thrombocytopenia~~	~~202 (35%)~~	~~15 (3%)~~	~~251 (43%)~~	~~25 (4%)~~

Adverse Reactions	JEVTANA 25 mg/m^2 + prednisone/prednisolone + G-CSF (N=126)		Abiraterone + prednisone/prednisolone or Enzalutamide (N=124)	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Blood and lymphatic system disorders				
Anemia†	99	8	95	4.8
Lymphopenia†	72	27	55	17
Neutropenia†	66	45	7	3.2
Thrombocytopenia†	41	3.2	16	1.6
General disorders and administration site conditions				
Fatigue‡	53	4	36	2.4
Edema peripheral§	11	0.8	10	1.6
Pyrexia	6	0	7	0
Pain	6	0	6	0.8
Gastrointestinal disorders				
Diarrhea¶	40	4.8	6	0
Nausea	23	0	23	0.8
Constipation	15	0	11	0
Abdominal pain#	14	1.6	6	0.8
Vomiting	13	0	12	1.6
Stomatitis	8	0	1.6	0
Dyspepsia	4.8	0	2.4	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain⊦	27	1.6	40	6
Pain in extremity	4.8	0	11	2.4
Bone fracture§	3.2	1.6	8	2.4

Adverse Reactions	JEVTANA 25 mg/m^2 + prednisone/prednisolone + G-CSF (N=126)		Abiraterone + prednisone/prednisolone or Enzalutamide (N=124)	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Infections and infestations				
Infections[à]	19	4	14	6
Nervous system disorders				
Peripheral neuropathy[è]	18	1.6	4.8	0
Dysgeusia	11	0	4	0
Polyneuropathy	6	1.6	0	0
Dizziness	0.8	0	4.8	0
Renal and urinary disorders				
Hematuria[ð]	16	0.8	6	1.6
Lower urinary tract symptoms[ø]	10	0	9	0
Acute kidney injury[ý]	5	2.4	10	4
Metabolism and nutrition disorders				
Decreased appetite	14	0.8	15	2.4
Hypokalemia	3.2	0	6	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Cancer pain	8	1.6	9	2.4
Cardiac disorders[£]	6	0.8	6	3.2
Respiratory, thoracic and mediastinal disorders				
Pneumonia[¥]	6	1.6	3.2	0.8
Dyspnea	6	0	2.4	0
Skin and subcutaneous tissue disorders				
Alopecia	6	0	0	0
Injury, poisoning and procedural complications				
Fall	4.8	0	0	0
Vascular disorders				
Hypertension[Œ]	4	2.4	8	2.4
Investigations				
Weight decreased	4	0	6	0
Psychiatric disorders				
Insomnia	3.2	0	4.8	0

* Grade from NCI CTC version 4.0.

† Based on laboratory values - % calculated using the number of patients with at least one event(n) over the number of patients assessed for each parameter during the on-treatment period.

‡ includes asthenia, fatigue, lethargy, malaise.

§ includes lymphoedema, edema peripheral, peripheral swelling.

¶ includes colitis, diarrhea, diarrhea hemorrhagic, gastroenteritis.

includes abdominal pain, abdominal pain lower, abdominal pain upper, flank pain, gastrointestinal pain.

Þ includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, noncardiac chest pain.

ß includes femoral neck fracture, pathological fracture, rib fracture, spinal compression fracture, sternal fracture, thoracic vertebral fracture.
à includes bacteremia, bacteriuria, cellulitis, device related sepsis, Enterobacter sepsis, erysipelas, furuncle, influenza, influenza like illness, localized infection, oral fungal infection, perineal cellulitis, pulmonary sepsis, pyelocaliectasis, pyelonephritis, pyelonephritis acute, respiratory tract infection, respiratory tract infection viral, sepsis, septic shock, subcutaneous abscess, upper respiratory tract infection, ureteritis, urinary tract infection, urinary tract infection bacterial, urosepsis, viral infection.
è includes neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy.
ð includes hematuria, cystitis hemorrhagic.
ø include lower urinary tract symptoms, micturition urgency, nocturia, pollakiuria, urinary incontinence, urinary retention, dysuria.
ý includes acute kidney injury, blood creatinine increased, renal failure, renal impairment.
£ includes aortic valve incompetence, aortic valve stenosis, atrial fibrillation, atrial flutter, atrioventricular block complete, atrioventricular block second degree, bradycardia, sinus bradycardia, tachycardia, cardiac failure, acute coronary syndrome, angina pectoris.
¥ includes lower respiratory tract infection, lung infection, lung infiltration, pneumonia.
Œ includes hypertension, hypertensive crisis.

Clinically relevant ≥ Grade 3 adverse reactions in <5% of patients who received JEVTANA in combination with prednisone and primary prophylaxis G-CSF: febrile neutropenia (3.2%), pulmonary embolism (1.6%), and neutropenic infection (0.8%).

Hematuria~~:~~

In study TROPIC, adverse reactions of hematuria, including those requiring medical intervention, were more common in JEVTANA-treated patients. The incidence of grade ≥2 hematuria was 6% in JEVTANA-treated patients and 2% in mitoxantrone-treated patients. Other factors associated with hematuria were ~~well~~ well-balanced between arms and do not account for the increased rate of hematuria on the JEVTANA arm.

In study PROSELICA, hematuria of all grades was observed in 18% of patients overall.

In CARD, hematuria of all grades was observed in 16% of patients receiving JEVTANA.

Hepatic Laboratory Abnormalities~~:~~

The incidences of grade 3-4 increased AST, increased ALT, and increased bilirubin were each ≤1%.

[…]

8.5 Geriatric Use

In the TROPIC study, of the 371 patients with prostate cancer treated with JEVTANA every three weeks plus prednisone, 240 patients (64.7%) were 65 years of age and over, while 70 patients (18.9%) were 75 years of age and over. No overall differences in effectiveness were observed between patients ≥65 years of age and younger patients. Elderly patients (≥65 years of age) may be more likely to experience certain adverse reactions. The incidence of death due to causes other than disease progression within 30 days of the last cabazitaxel dose were higher in

patients who were 65 years of age or greater compared to younger patients *[see Warnings and Precautions (5.2)]*. The incidence of grade 3-4 neutropenia and febrile neutropenia were higher in patients who were 65 years of age or greater compared to younger patients. The following grade 1-4 adverse reactions were reported at rates ≥ 5% higher in patients 65 years of age or older compared to younger patients: fatigue (40% vs 30%), neutropenia (97% vs 89%), asthenia (24% vs 15%), pyrexia (15% vs 8%), dizziness (10% vs 5%), urinary tract infection (10% vs 3%), and dehydration (7% vs 2%), respectively.

In the PROSELICA study, the grade 1-4 adverse reactions reported at rates of at least 5% higher in patients 65 years of age or older compared to younger patients were diarrhea (43% vs 33%), fatigue (30% vs 19%), asthenia (22% vs 13%), constipation (20% vs 13%), clinical neutropenia (13% vs 6%), febrile neutropenia (11% vs 5%), and dyspnea (10% vs 3%).

In the CARD study, the grade 1-4 adverse reactions reported at rates of at least 5% higher in patients 65 years of age or older compared to younger patients were decreased appetite (16% vs 7%), hypertension (5% vs 0), constipation (18% vs 7%), paresthesia (6% vs 0), stomatitis (10% vs 3%), musculoskeletal pain (5% vs 0), fatigue (31% vs 23%), asthenia (30% vs 19%), and edema peripheral (11% vs 0).

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of cabazitaxel between patients <65 years (n=100) and older (n=70).

[…]

14.3 CARD Trial (JEVTANA 25 mg/m^2 + prednisone/prednisolone + primary prophylaxis with G-CSF compared to abiraterone acetate + prednisone/prednisolone or enzalutamide)

The efficacy and safety of JEVTANA were evaluated in a multinational, randomized, active-controlled, open-label study (CARD: NCT02485691) in patients with metastatic castration resistant prostate cancer (mCRPC) previously treated with a docetaxel containing regimen and had progressed within 12 months of initiating either abiraterone or enzalutamide. A total of 255 patients were randomized to receive either JEVTANA 25 mg/m^2 every 3 week plus prednisone/prednisolone 10 mg daily (n=129), abiraterone 1000 mg once daily plus prednisone/prednisolone 5 mg twice daily or enzalutamide 160 mg once daily depending on prior therapy received (n=126). Primary prophylactic G-CSF was administered at each cycle for patients in the JEVTANA arm. This study included patients over 18 years of age with ECOG performance status 0-2. Patients had to have neutrophils >1,500 cells/mm^3, platelets >100,000 cells/mm^3, hemoglobin >10 g/dL, creatinine <1.5 × upper limit of normal (ULN), total bilirubin <1 × ULN, AST <1.5 × ULN, and ALT <1.5 × ULN. Patients with a history of congestive heart failure, or myocardial infarction within the last 6 months, or patients with uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension were not included in the study. Randomization was stratified by ECOG performance status (0 or 1 vs 2), time from abiraterone acetate or enzalutamide to disease progression, and receipt of abiraterone acetate or enzalutamide before or after docetaxel containing regimen.

The major efficacy outcome measure was radiographic progression free-survival (rPFS) as defined by Prostate Cancer Working Group-2 (PCWG2) assessed by study investigators. Other efficacy outcome measures included overall survival and objective response rate.

Demographics and baseline disease characteristics were balanced between treatment arms. The overall median age was 70 years (range 45 to 88), 95% of patients had an ECOG PS of 0 to 1 and median Gleason score was 8. A majority of the patients (61%) had their prior treatment with abiraterone acetate or enzalutamide after docetaxel. There were 36% of patients on the cabazitaxel arm with visceral disease (liver 8%, lung 8%, other 20%) and 57% with bone-only disease. Race and ethnicity data were not collected. Approximately 92% of the patients on the cabazitaxel arm received primary prophylaxis with G-CSF therapy during the first 3 cycles and, overall, 90% of the patients on the cabazitaxel arm received primary prophylaxis with G-CSF therapy at each cycle.

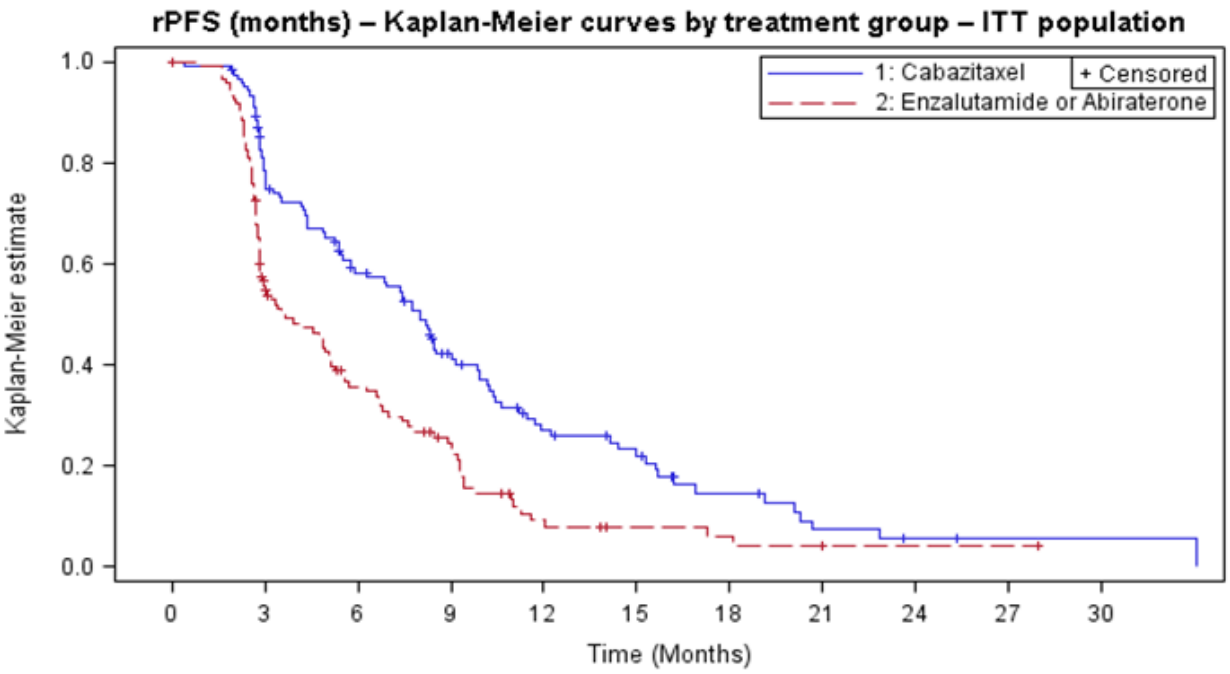
Efficacy results from the CARD trial are summarized in Table 7 and Figure 3.

Table 7: Efficacy of JEVTANA in CARD Trial in the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer (intent-to–treat analysis)

	JEVTANA + prednisone/prednisolone + G-CSF n=129	**Abiraterone + prednisone/prednisolone or Enzalutamide n=126**
Radiographic Progression Free Survival (rPFS)		
Number of events (%)*	95 (73.6%)	101 (80.2%)
Median rPFS (months) (95% CI)	8.0 (5.7 to 9.2)	3.7 (2.8 to 5.1)
Hazard Ratio (95% CI)	0.54 (0.40 to 0.73)	
p-value†	<0.0001	
Overall Survival (OS)‡		
Median OS [95% CI] (months)	13.6 [11.5; 17.5]	11.0 [9.2; 12.9]
Hazard Ratio (95% CI)	0.64 [0.46; 0.89]	
p-value	0.0078	

* Investigator assessed.
† Stratified log-rank test, significance threshold = 0.05.
‡ Overall survival was statistically significant.

Figure 3: Kaplan-Meier of Radiographic PFS (ITT Population)



Number at Risk

1	129	91	64	41	23	17	9	4	2	1	1
2	126	61	36	22	7	4	3	1	1	1	0

In terms of therapy sequence prior to randomization, rPFS was consistent across the subgroups of patients who received abiraterone acetate/enzalutamide prior to docetaxel (HR=0.61, 95% CI: 0.39, 0.96) and those who received abiraterone acetate/enzalutamide after docetaxel (HR=0.48, 95% CI: 0.32, 0.70).

Objective tumor response rate assessed by study investigators was 36.5% (95% CI: 26.6 to 48.4) for JEVTANA arm versus 11.5% (95% CI: 2.9 to 20.2) for abiraterone acetate plus prednisone/prednisolone or enzalutamide arm, p=0.004.

[…]

17 MARKETING AUTHORISATION HOLDER AND IMPORTER

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JEVT-IV-60MG-SPC-~~26~~27.0