

KYPROLIS™ Injection

60 mg/vial, 30 mg/vial

(carfilzomib)

[COMPOSITION]

[60 mg Drug Product] 1 vial contains

Active Ingredient: carfilzomib (in-house) 61.8 mg

Excipients: Sulfolbutylether Beta-cyclodextrin (SBECD), Anhydrous Citric Acid, Sodium Hydroxide

[30 mg Drug Product] 1 vial contains

Active Ingredient: carfilzomib (in-house) 32 mg

Excipients: Sulfolbutylether Beta-cyclodextrin (SBECD), Anhydrous Citric Acid, Sodium Hydroxide

[APPEARANCE]

White to off-white lyophilized cake or powder in a colorless and clear glass vial.

[INDICATION]

The combination therapy with lenalidomide and dexamethasone or with dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

[DOSAGE AND ADMINISTRATION]

THIS DRUG in Combination with Lenalidomide and Dexamethasone

For the combination regimen with lenalidomide and dexamethasone, administer THIS DRUG intravenously as a 10-minute infusion on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 1. Each 28-day period is considered one treatment cycle. The recommended starting dose of THIS DRUG is 20 mg/m² in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 27 mg/m² on Day 8 of Cycle 1. From Cycle 13, omit the Day 8 and 9 doses of THIS DRUG. Discontinue THIS DRUG after Cycle 18. Lenalidomide 25 mg is taken orally on Days 1–21 and dexamethasone 40 mg by mouth or intravenously on Days 1, 8, 15, and 22 of the 28-day cycles.

Table 1. THIS DRUG (10-Minute Infusion) in Combination with Lenalidomide and Dexamethasone

	Cycle 1										
	Week 1			Week 2			Week 3			Week 4	
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Days 23–28
THIS DRUG (mg/m²)	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1–21									-	-
	Cycles 2 to 12										
	Week 1			Week 2			Week 3			Week 4	
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Days 23–28
THIS DRUG (mg/m²)	27	27	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1–21									-	-
	Cycles 13 and later ^a										
	Week 1			Week 2			Week 3			Week 4	
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Days 23–28
THIS DRUG (mg/m²)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1–21									-	-

^a THIS DRUG is administered through Cycle 18, lenalidomide and dexamethasone continue thereafter

Continue treatment until disease progression or unacceptable toxicity occurs. Refer to the lenalidomide and dexamethasone Prescribing Information for other concomitant medications, such as the use of anticoagulant and antacid prophylaxis, that may be required with those agents.

THIS DRUG in Combination with Dexamethasone

For the combination regimen with dexamethasone, administer THIS DRUG intravenously as a 30-minute infusion on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 2. Each 28-day period is considered one treatment cycle. Administer THIS DRUG by 30-minute infusion at a starting dose of 20 mg/m² in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m² on Day 8 of Cycle 1. Dexamethasone 20 mg is taken by mouth or intravenously on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle. Administer dexamethasone 30 minutes to 4 hours before THIS DRUG.

Table 2. THIS DRUG (30-Minute Infusion) in Combination with Dexamethasone

	Cycle 1											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24–28
THIS DRUG (mg/m²)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-
	Cycles 2 and later											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24–28
THIS DRUG (mg/m²)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

Treatment may be continued until disease progression or unacceptable toxicity occurs. Refer to the dexamethasone Prescribing Information for other concomitant medications.

Dose Modifications Based on Toxicities

Modify dosing based on toxicity. Recommended actions and dose modifications for THIS DRUG are presented in Table 3. Dose level reductions are presented in Table 4. See the lenalidomide and dexamethasone Prescribing Information respectively for dosing recommendations.

Table 3. Dose Modifications for Toxicity^a during THIS DRUG Treatment

Hematologic Toxicity	Recommended Action
<ul style="list-style-type: none"> ANC less than $0.5 \times 10^9/L$ 	<ul style="list-style-type: none"> Withhold dose <ul style="list-style-type: none"> If recovered to greater than or equal to $0.5 \times 10^9/L$, continue at the same dose level For subsequent drops to less than $0.5 \times 10^9/L$, follow the same recommendations as above and consider 1 dose level reduction when restarting THIS DRUG^a
<ul style="list-style-type: none"> Febrile neutropenia ANC less than $0.5 \times 10^9/L$ and an oral temperature more than $38.5^\circ C$ or two consecutive readings of more than $38.0^\circ C$ for 2 hours 	<ul style="list-style-type: none"> Withhold dose <ul style="list-style-type: none"> If ANC returns to baseline grade and fever resolves, resume at the same dose level

<ul style="list-style-type: none"> Platelets less than $10 \times 10^9/L$ or evidence of bleeding with thrombocytopenia 	<ul style="list-style-type: none"> Withhold dose <ul style="list-style-type: none"> If recovered to greater than or equal to $10 \times 10^9/L$ and/or bleeding is controlled, continue at the same dose level For subsequent drops to less than $10 \times 10^9/L$, follow the same recommendations as above and consider 1 dose level reduction when restarting THIS DRUG^a
Renal Toxicity	Recommended Action
<ul style="list-style-type: none"> Serum creatinine greater than or equal to $2 \times$ baseline, or Creatinine clearance less than 15 mL/min, or creatinine clearance decreases to less than or equal to 50% of baseline, or need for hemodialysis 	<ul style="list-style-type: none"> Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance) <ul style="list-style-type: none"> If attributable to THIS DRUG, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction^a If not attributable to THIS DRUG, dosing may be resumed at the discretion of the physician For patients on hemodialysis receiving THIS DRUG, the dose is to be administered after the hemodialysis procedure
Other Non-hematologic Toxicity	Recommended Action
<ul style="list-style-type: none"> All other severe or life-threatening^b non-hematological toxicities 	<ul style="list-style-type: none"> Withhold until resolved or returned to baseline Consider restarting the next scheduled treatment at 1 dose level reduction^a

ANC = absolute neutrophil count

^a See Table 4 for dose level reductions

^b CTCAE Grade 3 and 4

Table 4. Dose Level Reductions for THIS DRUG

Regimen	Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
THIS DRUG, Lenalidomide, and Dexamethasone (20/27 mg/m ²)	27 mg/m ²	20 mg/m ²	15 mg/m ^{2a}	—
THIS DRUG and Dexamethasone (20/56 mg/m ²)	56 mg/m ²	45 mg/m ²	36 mg/m ²	27 mg/m ^{2a}

Note: Infusion times remain unchanged during dose reduction(s)

^a If toxicity persists, discontinue THIS DRUG treatment

Dose Modifications for Use in Hepatic Impairment

For patients with mild or moderate hepatic impairment, reduce the dose of THIS DRUG by 25%. It has not been evaluated in patients with severe hepatic impairment.

Dosing in Patients with End Stage Renal Disease

For patients with end stage renal disease who are on dialysis, administer THIS DRUG after the hemodialysis procedure.

Administration Precautions

- **Hydration** - Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome (TLS) or renal toxicity. The recommended hydration includes both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid prior to each dose in Cycle 1). If needed, give an additional 250 mL to 500 mL of intravenous fluids following THIS DRUG administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles. Monitor patients for evidence of volume overload and adjust hydration to individual patient needs, especially in patients with or at risk for cardiac failure.
- **Electrolyte Monitoring** - Monitor serum potassium levels regularly during treatment with THIS DRUG.
- **Premedications** - Premedicate with the recommended dose of dexamethasone. Administer dexamethasone orally or intravenously at least 30 minutes but no more than 4 hours prior to all doses of THIS DRUG during Cycle 1 to reduce the incidence and severity of infusion reactions. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles.
- **Administration** – THIS DRUG can be administered in a 50 mL or 100 mL intravenous bag of **5% Dextrose Injection**. Infuse over 10 or 30 minutes depending on THIS DRUG dose regimen. Administer as an intravenous infusion. Flush the intravenous administration line with normal saline or 5% Dextrose Injection immediately before and after THIS DRUG administration. Do not mix THIS DRUG with or administer as an infusion with other medicinal products.
- **Dose Calculation** - Calculate THIS DRUG dose using the patient's actual body surface area (BSA) at baseline. In patients with a BSA greater than 2.2 m², calculate the dose based upon a BSA of 2.2 m².
- **Thromboprophylaxis** - Thromboprophylaxis is recommended for patients being treated with the combination of THIS DRUG with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.
- **Infection Prophylaxis** - Consider antiviral prophylaxis for patients being treated with THIS DRUG to decrease the risk of herpes zoster reactivation.
- **Patients on Hemodialysis** - Administer THIS DRUG after the hemodialysis procedure.
- Refer to 10. Cautions in Administration of PRECAUTIONS FOR USE about **Reconstitution and Preparation for Intravenous Administration**

[PRECAUTIONS FOR USE]

1. Contraindications

THIS DRUG is contraindicated in patients with known hypersensitivity to carfilzomib or to any component of the product formulation.

2. Adverse Reactions

The following clinically significant adverse reactions are discussed in greater detail in section 3. General Cautions:

- Cardiac Toxicities
- Acute Renal Failure
- Tumor Lysis Syndrome
- Pulmonary Toxicity
- Pulmonary Hypertension
- Dyspnea
- Hypertension
- Venous Thrombosis
- Infusion Reactions
- Hemorrhage
- Thrombocytopenia
- Hepatic Toxicity and Hepatic Failure
- Thrombotic Microangiopathy
- Posterior Reversible Encephalopathy Syndrome
- Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients with Multiple Myeloma

1) Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug, and may not reflect the rates observed in medical practice.

1.1) Safety Experience with THIS DRUG in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma

The safety of THIS DRUG in combination with lenalidomide and dexamethasone (KRd) was evaluated in an open-label randomized study in patients with relapsed multiple myeloma. The median number of cycles initiated was 22 cycles for the KRd arm and 14 cycles for the Rd arm. Details of the study treatment are described in Section 12, 2.1.

Deaths due to adverse reactions within 30 days of the last dose of any therapy in the KRd arm occurred in 45/392 (12%) patients compared with 42/389 (11%) patients who died due to adverse events within 30 days of the last dose of any Rd therapy. The most common cause of deaths occurring in patients (%) in the two arms (KRd *versus* Rd) included infection 12 (3%) *versus* 11 (3%), cardiac 10 (3%) *versus* 9 (2%), and other adverse reactions 23 (6%) *versus* 22 (6%). Serious adverse reactions were reported in 65% of the patients in the KRd arm and 57% of the patients in the Rd arm. The most common serious adverse reactions reported in the KRd arm as compared with the Rd arm were pneumonia (17% *versus* 13%), respiratory tract infection (4% *versus* 2%), pyrexia (4% *versus* 3%), and pulmonary embolism (3% *versus* 2%). Discontinuation due to any adverse reaction occurred in 33% in the KRd arm *versus* 30% in the Rd arm. Adverse reactions leading to discontinuation of THIS DRUG occurred in 12% of patients and the most common reactions included pneumonia (1%), myocardial infarction (0.8%), and upper respiratory tract infection (0.8%).

Common Adverse Reactions ($\geq 10\%$)

The adverse reactions in the first 12 cycles of therapy that occurred at a rate of 10% or greater in the KRd arm are presented in Table 5.

Table 5. Most Common Adverse Reactions ($\geq 10\%$ in the KRd Arm) Occurring in Cycles 1–12 (20/27 mg/m² Regimen in Combination with Lenalidomide and Dexamethasone)

Adverse Reactions by Body System	KRd Arm (N = 392) n (%)		Rd Arm (N = 389) n (%)	
	Any Grade	\geq Grade 3	Any Grade	\geq Grade 3
Blood and Lymphatic System Disorders				
Anemia	138 (35)	53 (14)	127 (33)	47 (12)
Neutropenia	124 (32)	104 (27)	115 (30)	89 (23)
Thrombocytopenia	100 (26)	58 (15)	75 (19)	39 (10)
Gastrointestinal Disorders				
Diarrhea	119 (30)	8 (2)	106 (27)	12 (3)
Constipation	68 (17)	0 (0)	55 (14)	1 (0)
Nausea	63 (16)	1 (0)	43 (11)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	113 (29)	23 (6)	107 (28)	20 (5)
Pyrexia	93 (24)	5 (1)	64 (17)	1 (0)
Edema peripheral	59 (15)	3 (1)	48 (12)	2 (1)
Asthenia	54 (14)	11 (3)	49 (13)	7 (2)
Infections and Infestations				
Upper respiratory tract infection	87 (22)	7 (2)	54 (14)	4 (1)
Bronchitis	55 (14)	5 (1)	40 (10)	2 (1)
Viral upper respiratory tract infection	55 (14)	0 (0)	44 (11)	0 (0)
Pneumonia ^a	54 (14)	35 (9)	43 (11)	27 (7)
Metabolism and Nutrition Disorders				
Hypokalemia	78 (20)	22 (6)	35 (9)	12 (3)
Hypocalcemia	55 (14)	10 (3)	39 (10)	5 (1)
Hyperglycemia	43 (11)	18 (5)	33 (9)	15 (4)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	92 (24)	3 (1)	75 (19)	3 (1)
Back pain	41 (11)	4 (1)	54 (14)	6 (2)
Nervous System Disorders				
Peripheral neuropathies ^b	43 (11)	7 (2)	39 (10)	4 (1)

	KRd Arm (N = 392) n (%)		Rd Arm (N = 389) n (%)	
Adverse Reactions by Body System	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3
Psychiatric Disorders				
Insomnia	64 (16)	6 (2)	51 (13)	8 (2)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough ^c	93 (24)	2 (1)	54 (14)	0 (0)
Dyspnea ^d	71 (18)	8 (2)	61 (16)	6 (2)
Skin and Subcutaneous Tissue Disorders				
Rash	45 (12)	5 (1)	54 (14)	5 (1)
Vascular Disorders				
Embolic and thrombotic events ^e	49 (13)	16 (4)	23 (6)	9 (2)
Hypertension ^f	41 (11)	12 (3)	15 (4)	4 (1)

KRd = THIS DRUG, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone

^a Pneumonia includes pneumonia, bronchopneumonia

^b Peripheral neuropathies includes peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy

^c Cough includes cough and productive cough

^d Dyspnea includes dyspnea and dyspnea exertional

^e Embolic and thrombotic events, venous includes deep vein thrombosis, pulmonary embolism, thrombophlebitis superficial, thrombophlebitis, venous thrombosis limb, post thrombotic syndrome, venous thrombosis

^f Hypertension includes hypertension, hypertensive crisis

There were 274 (70%) patients in the KRd arm who received treatment beyond Cycle 12. There were no new clinically relevant adverse reactions that emerged in the later treatment cycles.

Adverse Reactions Occurring at a Frequency of < 10%

- **Blood and lymphatic system disorders:** febrile neutropenia, lymphopenia
- **Cardiac disorders:** cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia, pericardial effusion
- **Ear and labyrinth disorders:** deafness, tinnitus
- **Eye disorders:** cataract, vision blurred
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, gastrointestinal hemorrhage, toothache
- **General disorders and administration site conditions:** chills, infusion site reaction, multi-organ failure, pain
- **Infections and infestations:** clostridium difficile colitis, influenza, lung infection, rhinitis, sepsis, urinary tract infection, viral infection
- **Metabolism and nutrition disorders:** dehydration, hyperkalemia, hyperuricemia, hypoalbuminemia, hyponatremia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders:** muscular weakness, myalgia
- **Nervous system disorders:** hypoesthesia, intracranial hemorrhage, paresthesia
- **Psychiatric disorders:** anxiety, delirium
- **Renal and urinary disorders:** renal failure, renal failure acute, renal impairment

- **Respiratory, thoracic and mediastinal disorders:** dysphonia, epistaxis, oropharyngeal pain, pulmonary embolism, pulmonary edema, pulmonary hemorrhage
- **Skin and subcutaneous tissue disorders:** erythema, hyperhidrosis, pruritus
- **Vascular disorders:** deep vein thrombosis, hemorrhage, hypotension

Grade 3 and higher adverse reactions that occurred during Cycles 1–12 with a substantial difference ($\geq 2\%$) between the two arms were neutropenia, thrombocytopenia, hypokalemia, and hypophosphatemia.

Laboratory Abnormalities

Table 6 describes Grade 3–4 laboratory abnormalities reported at a rate of $\geq 10\%$ in the KRd arm for patients who received combination therapy.

Table 6. Grade 3–4 Laboratory Abnormalities ($\geq 10\%$ in the KRd Arm) in Cycles 1–12 (20/27 mg/m² Regimen in Combination with Lenalidomide and Dexamethasone)

Laboratory Abnormality	KRd (N = 392) n (%)	Rd (N = 389) n (%)
Decreased lymphocytes	182 (46)	119 (31)
Decreased absolute neutrophil count	152 (39)	141 (36)
Decreased phosphorus	122 (31)	106 (27)
Decreased platelets	101 (26)	59 (15)
Decreased total white blood cell count	97 (25)	71 (18)
Decreased hemoglobin	58 (15)	68 (18)
Increased glucose	53 (14)	30 (8)
Decreased potassium	41 (11)	23 (6)

KRd = THIS DRUG, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone

1.2) Safety Experience with THIS DRUG in Combination with Dexamethasone in Patients with Multiple Myeloma

The safety of THIS DRUG in combination with dexamethasone was evaluated in an open-label, randomized trial of patients with relapsed multiple myeloma. The study treatment is described in Section 12, 2.2. Patients received treatment for a median duration of 48 weeks in the THIS DRUG/dexamethasone (Kd) arm and 27 weeks in the bortezomib/dexamethasone (Vd) arm.

Deaths due to adverse reactions within 30 days of last study treatment occurred in 32/463 (7%) patients in the Kd arm and 21/456 (5%) patients in the Vd arm. The causes of death occurring in patients (%) in the two arms (Kd *versus* Vd) included cardiac 4 (1%) *versus* 5 (1%), infections 8 (2%) *versus* 8 (2%), disease progression 7 (2%) *versus* 4 (1%), pulmonary 3 (1%) *versus* 2 (< 1%), renal 1 (< 1%) *versus* 0 (0%), and other adverse events 9 (2%) *versus* 2 (< 1%). Serious adverse reactions were reported in 59% of the patients in the Kd arm and 40% of the patients in the Vd arm. In both treatment arms, pneumonia was the most commonly reported serious adverse reaction (8% *versus* 9%). Discontinuation due to any adverse reaction occurred in 29% in the Kd arm *versus* 26% in the Vd arm. The most common reaction leading to discontinuation was cardiac failure in the Kd arm (n = 8, 2%) and peripheral neuropathy in the Vd arm (n = 22, 5%).

Common Adverse Reactions ($\geq 10\%$)

Adverse reactions in the first 6 months of therapy that occurred at a rate of 10% or greater in the Kd arm are presented in Table 7.

Table 7. Most Common Adverse Reactions ($\geq 10\%$ in the Kd Arm) Occurring in Months 1–6 (20/56 mg/m² Regimen in Combination with Dexamethasone)

Adverse Reactions by Body System	Kd (N = 463) n (%)		Vd (N = 456) n (%)	
	Any Grade	\geq Grade 3	Any Grade	\geq Grade 3
Blood and Lymphatic System Disorders				
Anemia	161 (35)	57 (12)	112 (25)	43 (9)
Thrombocytopenia ^a	125 (27)	45 (10)	112 (25)	64 (14)
Gastrointestinal Disorders				
Diarrhea	117 (25)	14 (3)	149 (33)	27 (6)
Nausea	70 (15)	4 (1)	68 (15)	3 (1)
Constipation	60 (13)	1 (0)	113 (25)	6 (1)
Vomiting	45 (10)	5 (1)	33 (7)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	116 (25)	14 (3)	126 (28)	25 (6)
Pyrexia	102 (22)	9 (2)	52 (11)	3 (1)
Asthenia	73 (16)	9 (2)	65 (14)	13 (3)
Peripheral edema	62 (13)	3 (1)	62 (14)	3 (1)
Infections and Infestations				
Upper respiratory tract infection	67 (15)	4 (1)	55 (12)	3 (1)
Bronchitis	54 (12)	5 (1)	25 (6)	2 (0)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	70 (15)	1 (0)	23 (5)	3 (1)
Back pain	64 (14)	7 (2)	61 (13)	10 (2)
Nervous System Disorders				
Headache	67 (15)	4 (1)	39 (9)	2 (0)
Peripheral neuropathies ^{b,c}	56 (12)	7 (2)	170 (37)	23 (5)
Psychiatric Disorders				
Insomnia	105 (23)	5 (1)	116 (25)	10 (2)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea ^d	128 (28)	23 (5)	69 (15)	8 (2)
Cough ^e	97 (21)	0 (0)	61 (13)	2 (0)
Vascular Disorders				
Hypertension ^f	83 (18)	30 (7)	33 (7)	12 (3)

Kd = THIS DRUG and dexamethasone; Vd = bortezomib and dexamethasone

^a Thrombocytopenia includes platelet count decreased and thrombocytopenia

^b Peripheral neuropathies includes peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy

^c See Clinical Studies (Section 12, 2.2)

^d Dyspnea includes dyspnea and dyspnea exertional

^e Cough includes cough and productive cough

^f Hypertension includes hypertension, hypertensive crisis, and hypertensive emergency

The event rate of \geq Grade 2 peripheral neuropathy in the Kd arm was 7% (95% CI: 5, 9) *versus* 35% (95% CI: 31, 39) in the Vd arm.

Adverse Reactions Occurring at a Frequency of < 10%

- **Blood and lymphatic system disorders:** febrile neutropenia, leukopenia, lymphopenia, neutropenia, thrombotic microangiopathy, thrombotic thrombocytopenic purpura
- **Cardiac disorders:** atrial fibrillation, cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia, palpitations, tachycardia
- **Ear and labyrinth disorders:** tinnitus
- **Eye disorders:** cataract, vision blurred
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, gastrointestinal hemorrhage, toothache
- **General disorders and administration site conditions:** chest pain, chills, influenza like illness, infusion site reactions (including inflammation, pain, and erythema), malaise, pain
- **Hepatobiliary disorders:** cholestasis, hepatic failure, hyperbilirubinemia
- **Immune system disorders:** drug hypersensitivity
- **Infections and infestations:** bronchopneumonia, gastroenteritis, influenza, lung infection, nasopharyngitis, pneumonia, rhinitis, sepsis, urinary tract infection, viral infection
- **Metabolism and nutrition disorders:** decreased appetite, dehydration, hypercalcemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders:** muscular weakness, musculoskeletal chest pain, musculoskeletal pain, myalgia
- **Nervous system disorders:** cerebrovascular accident, dizziness, hypoesthesia, paresthesia, posterior reversible encephalopathy syndrome
- **Psychiatric disorders:** anxiety
- **Renal and urinary disorders:** renal failure, renal failure acute, renal impairment
- **Respiratory, thoracic and mediastinal disorders:** acute respiratory distress syndrome, dysphonia, epistaxis, interstitial lung disease, oropharyngeal pain, pneumonitis pulmonary embolism, pulmonary edema, pulmonary hypertension, wheezing
- **Skin and subcutaneous tissue disorders:** erythema, hyperhidrosis, pruritus, rash
- **Vascular disorders:** deep vein thrombosis, flushing, hypotension

Laboratory Abnormalities

Table 8 describes Grade 3–4 laboratory abnormalities reported at a rate of \geq 10% in the Kd arm.

**Table 8. Grade 3–4 Laboratory Abnormalities (\geq 10%)
in Months 1–6 (20/56 mg/m² Regimen in Combination with Dexamethasone)**

Laboratory Abnormality	Kd (N = 463) n (%)	Vd (N = 456) n (%)
Decreased lymphocytes	249 (54)	180 (40)
Increased uric acid	244 (53)	198 (43)
Decreased hemoglobin	79 (17)	68 (15)
Decreased platelets	85 (18)	77 (17)

Laboratory Abnormality	Kd (N = 463) n (%)	Vd (N = 456) n (%)
Decreased phosphorus	74 (16)	61 (13)
Decreased creatinine clearance ^a	65 (14)	49 (11)
Increased potassium	55 (12)	21 (5)

Kd = THIS DRUG and dexamethasone; Vd = bortezomib and dexamethasone

^a Calculated using the Cockcroft-Gault formula

2) Post-marketing Experience

The following additional adverse reactions were reported in the post-marketing experience with THIS DRUG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: cardiomyopathy, hepatitis B virus (HBV) reactivation, hemolytic uremic syndrome (HUS), gastrointestinal perforation, pericarditis, herpes zoster, confusional state, cytomegalovirus infection including chorioretinitis, pneumonitis, enterocolitis, and viremia.

3. General Cautions

1) Cardiac Toxicities

New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of THIS DRUG. Some events occurred in patients with normal baseline ventricular function. In clinical studies with THIS DRUG, these events occurred throughout the course of THIS DRUG therapy. Death due to cardiac arrest has occurred within one day of THIS DRUG administration. In a randomized, open-label, multicenter trial evaluating THIS DRUG in combination with lenalidomide and dexamethasone (KRd) *versus* lenalidomide/dexamethasone (Rd), the incidence of cardiac failure events was 7% in the KRd arm *versus* 4% in the Rd arm. In a randomized, open-label, multicenter trial of THIS DRUG plus dexamethasone (Kd) *versus* bortezomib plus dexamethasone (Vd), the incidence of cardiac failure events was 11% in the Kd arm *versus* 3% in the Vd arm.

Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold THIS DRUG for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart THIS DRUG at 1 dose level reduction based on a benefit/risk assessment.

While adequate hydration is required prior to each dose in Cycle 1, all patients should also be monitored for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.

In patients ≥ 75 years of age, the risk of cardiac failure is increased compared to patients < 75 years of age. In addition, the risk of cardiac failure is also increased in Asian patients. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications and should have a comprehensive medical

assessment (including blood pressure control and fluid management) prior to starting treatment with THIS DRUG and remain under close follow-up.

2) Acute Renal Failure

Cases of acute renal failure have occurred in patients receiving THIS DRUG. Some of these events have been fatal. Renal insufficiency adverse events (including renal failure) have occurred in approximately 11% of patients treated with THIS DRUG. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received THIS DRUG monotherapy. The risk of fatal renal failure was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft and Gault equation). Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

3) Tumor Lysis Syndrome

Cases of tumor lysis syndrome (TLS), including fatal outcomes, have been reported in patients who received THIS DRUG. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of THIS DRUG in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, including interruption of THIS DRUG until TLS is resolved.

4) Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in approximately 1% of patients receiving THIS DRUG. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue THIS DRUG.

5) Pulmonary Hypertension

Pulmonary arterial hypertension was reported in approximately 1% of patients treated with THIS DRUG and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold THIS DRUG for pulmonary hypertension until resolved or returned to baseline, and consider whether to restart THIS DRUG based on a benefit/risk assessment.

6) Dyspnea

Dyspnea was reported in 31% of patients treated with THIS DRUG and was Grade 3 or greater in 5% of patients. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop THIS DRUG for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart THIS DRUG based on a benefit/risk assessment.

7) Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with THIS DRUG. In a randomized, open-label, multicenter trial evaluating KRd *versus* Rd, the incidence of hypertension events was 17% in the KRd arm *versus* 9% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of hypertension events was 34% in the Kd arm *versus* 11% in the Vd arm. Some of these events have been fatal. It is recommended to control

hypertension prior to starting THIS DRUG. Monitor blood pressure regularly in all patients while on THIS DRUG. If hypertension cannot be adequately controlled, withhold THIS DRUG and evaluate. Consider whether to restart THIS DRUG based on a benefit/risk assessment.

8) Venous Thrombosis

Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with THIS DRUG. In a randomized, open-label, multicenter trial evaluating KRd *versus* Rd (with thromboprophylaxis used in both arms), the incidence of venous thromboembolic events in the first 12 cycles was 13% in the KRd arm *versus* 6% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of venous thromboembolic events in months 1-6 was 9% in the Kd arm *versus* 2% in the Vd arm.

Thromboprophylaxis is recommended for patients being treated with the combination of THIS DRUG with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with THIS DRUG in combination with dexamethasone or lenalidomide plus dexamethasone.

9) Infusion Reactions

Infusion reactions, including life-threatening reactions, have occurred in patients receiving THIS DRUG. Signs and symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, laryngeal edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of THIS DRUG. Administer dexamethasone prior to THIS DRUG to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms and to contact a physician immediately if symptoms of an infusion reaction occur.

10) Hemorrhage

Fatal or serious cases of hemorrhage have been reported in patients treated with THIS DRUG. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. The bleeding can be spontaneous, and intracranial hemorrhage has occurred without trauma. Hemorrhage has been reported in patients having either low or normal platelet counts. Hemorrhage has also been reported in patients who were not on antiplatelet therapy or anticoagulation. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.

11) Thrombocytopenia

THIS DRUG causes thrombocytopenia with platelet nadirs observed on Day 8 or Day 15 of each 28-day cycle, with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in approximately 34% of patients in clinical trials with THIS DRUG. Monitor platelet counts frequently during treatment with THIS DRUG. Reduce or withhold dose as appropriate. Hemorrhage may occur.

12) Hepatic Toxicity and Hepatic Failure

Cases of hepatic failure, including fatal cases, have been reported (< 1%) during treatment with THIS DRUG. THIS DRUG can cause increased serum transaminases. Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold dose as appropriate.

13) Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received THIS DRUG. Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop THIS DRUG and evaluate. If the diagnosis of TTP/HUS is excluded, THIS DRUG may be restarted. The safety of reinitiating THIS DRUG therapy in patients previously experiencing TTP/HUS is not known.

14) Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving THIS DRUG. PRES, formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS), is a neurological disorder which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging (MRI). Discontinue THIS DRUG if PRES is suspected and evaluate. The safety of reinitiating THIS DRUG therapy in patients previously experiencing PRES is not known.

15) Hepatitis B Virus (HBV) Reactivation

Cases of Hepatitis B Virus (HBV) reactivation have been reported in patients receiving THIS DRUG. Patients should be tested for HBV infection before initiating treatment. For patients who are carriers of HBV, prophylaxis with antivirals should be considered. Carriers of HBV who require treatment with THIS DRUG should be closely monitored for signs and symptoms of active HBV infection throughout and following the end of treatment. Consider consulting a specialist for patients who test positive for HBV infection prior to or during treatment.

The safety of resuming THIS DRUG after HBV reactivation is adequately controlled is not known. Therefore, prescribers should weigh the risks and benefits when considering resumption of therapy in this situation.

16) Progressive Multifocal Leukoencephalopathy

Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients treated with THIS DRUG who have had prior or concurrent immunosuppressive therapy. The causal relationship with THIS DRUG is unknown.

Patients should be monitored for any new or worsening neurologic, cognitive or behavioral signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders.

If PML is suspected, patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue THIS DRUG if PML diagnosis is confirmed.

17) Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients with Multiple Myeloma

In a clinical trial, 955 transplant-ineligible patients with newly diagnosed multiple myeloma randomized to THIS DRUG (20/36 mg/m² by 30-minute infusion twice weekly for four of each six-week cycle), melphalan and prednisone (KMP) or bortezomib, melphalan and prednisone (VMP), and administered during 9 treatment cycles composed of each 6 weeks period. A higher incidence of fatal adverse reactions (7% *versus* 4%) and serious adverse reactions (50% *versus* 42%) were observed in the KMP arm compared to patients in the VMP arm, respectively. Patients in the KMP arm were observed to have a higher incidence of any grade adverse reactions involving cardiac failure (11% *versus* 4%), hypertension (25% *versus* 8%), acute renal failure (14% *versus* 6%), and dyspnea (18% *versus* 9%). This study did not meet its primary outcome measure of superiority in progression-free survival for the KMP arm. THIS DRUG in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

18) Embryo-Fetal Toxicity

THIS DRUG can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using THIS DRUG.

Advise females of reproductive potential to avoid becoming pregnant while being treated with THIS DRUG. Advise males of reproductive potential to avoid fathering a child while being treated with THIS DRUG. Advise women who use THIS DRUG during pregnancy or become pregnant during treatment with THIS DRUG of the potential hazard to the fetus.

4. Hepatic Impairment

Reduce the dose of THIS DRUG by 25% in patients with mild or moderate hepatic impairment. It has not been evaluated in patients with severe hepatic function.

The pharmacokinetics and safety of THIS DRUG were evaluated in patients with advanced malignancies who had either normal hepatic function, or mild (bilirubin > 1 to 1.5×ULN or AST > ULN), moderate (bilirubin > 1.5 to 3×ULN), or severe (bilirubin > 3×ULN) hepatic impairment. The AUC of carfilzomib increased by approximately 50% in patients with mild and moderate hepatic impairment compared to patients with normal hepatic function. PK data were not collected in patients with severe hepatic impairment. The incidence of serious adverse events was higher in patients with mild, moderate, and severe hepatic impairment combined (22/35 or 63%) than in patients with normal hepatic function (3/11 or 27%).

Monitor liver enzymes regularly, regardless of baseline values, and modify dose based on toxicity.

5. Renal Impairment

No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic hemodialysis. The pharmacokinetics and safety of THIS DRUG were evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic hemodialysis. In addition, a pharmacokinetic study was conducted in patients with normal renal function and end stage renal disease (ESRD).

In these studies, the pharmacokinetics of THIS DRUG was not influenced by the degree of baseline renal impairment, including the patients on hemodialysis. Since dialysis clearance of THIS DRUG concentrations has not been studied, the drug should be administered after the hemodialysis procedure.

6. Use in Pregnancy and Nursing Mothers

1) Pregnancy

Risk Summary

THIS DRUG can cause fetal harm based on findings from animal studies and the drug's mechanism of action. There are no adequate and well-controlled studies in pregnant women using THIS DRUG.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with THIS DRUG. Males of reproductive potential should be advised to avoid fathering a child while being treated with THIS DRUG. Consider the benefits and risks of THIS DRUG and possible risks to the fetus when prescribing THIS DRUG to a pregnant woman. If THIS DRUG is used during pregnancy, or if the patient becomes pregnant while taking THIS DRUG, apprise the patient of the potential hazard to the fetus.

Animal Data

THIS DRUG administered intravenously to pregnant rats and rabbits during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats and 0.8 mg/kg/day in rabbits. THIS DRUG was not teratogenic at any dose tested. In rabbits, there was an increase in pre-implantation loss at ≥ 0.4 mg/kg/day and an increase in early resorptions and post-implantation loss and a decrease in fetal weight at the maternally toxic dose of 0.8 mg/kg/day. The doses of 0.4 and 0.8 mg/kg/day in rabbits are approximately 20% and 40%, respectively, of the recommended dose in humans of 27 mg/m² based on BSA.

2) Lactation

Risk Summary

There is no information regarding the presence of THIS DRUG in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for THIS DRUG and any potential adverse effects on the breastfed infant from THIS DRUG or from the underlying maternal condition.

3) Females and Males of Reproductive Potential

Contraception

THIS DRUG can cause fetal harm. Advise female patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with THIS DRUG and for at least 30 days following completion of therapy. Advise male patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with THIS DRUG and for at least 90 days following completion of therapy.

7. Pediatric Use

The safety and effectiveness of THIS DRUG in pediatric patients have not been established.

8. Geriatric Use

Of 598 patients in clinical studies of THIS DRUG monotherapy dosed at 20/27 mg/m² by up to 10-minute infusion, 49% were 65 and over, while 16% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 55% in patients 65 to 74 years of age, and 56% in patients ≥ 75 years of age. In a single-arm, multicenter clinical trial of THIS DRUG monotherapy dosed at 20/27 mg/m² [Study PX-171-003 (n = 266)], no overall differences in effectiveness were observed between older and younger patients.

Of 392 patients treated with THIS DRUG in combination with lenalidomide and dexamethasone, 47% were 65 and over and 11% were 75 years and over. The incidence of serious adverse events was 57% in patients < 65 years of age, 73% in patients 65 to 74 years of age, and 81% in patients ≥ 75 years of age. No overall differences in effectiveness were observed between older and younger patients.

Of 463 patients treated with THIS DRUG dosed at 20/56 mg/m² by 30-minute infusion in combination with dexamethasone, 52% were 65 and over and 17% were 75 and over. The incidence of serious adverse events was 54% in patients < 65 years of age, 60% in patients 65 to 74 years of age, and 70% in patients ≥ 75 years of age. No overall differences in effectiveness were observed between older and younger patients.

9. Overdosage

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of THIS DRUG administered in error.

There is no known specific antidote for THIS DRUG overdosage. In the event of overdose, the patient should be monitored, specifically for the side effects and/or adverse reactions listed in Adverse Reactions.

10. Cautions in Administration

Reconstitution and Preparation for Intravenous Administration

THIS DRUG vials contain no preservatives and are intended for single use only. Unopened vials of THIS DRUG are stable until the date indicated on the package when stored in the original package at 2°C to 8°C. The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL.

Read the complete preparation instructions prior to reconstitution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstitution/Preparation Steps:

- ① Remove vial from refrigerator just prior to use.
- ② Calculate the dose (mg/m²) and number of vials of THIS DRUG required using the patient's BSA at baseline. Patients with a BSA greater than 2.2 m² should receive a dose based upon a BSA of 2.2 m². Dose adjustments do not need to be made for weight changes of less than or equal to 20%.
- ③ Aseptically reconstitute each THIS DRUG vial only with Sterile Water for Injection using the volumes described in Table 9. Use a 21-gauge or larger needle (0.8 mm or smaller external

diameter needle) to reconstitute each vial by slowly injecting through the stopper and directing the Sterile Water for Injection onto the INSIDE WALL OF THE VIAL to minimize foaming.



Table 9. Reconstitution Volumes

Strength	Amount of Sterile Water for Injection required for reconstitution
30 mg vial	15 mL
60 mg vial	29 mL

- ④ Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear.
- ⑤ Visually inspect for particulate matter and discoloration prior to administration. The reconstituted product should be a clear, colorless solution and should not be administered if any discoloration or particulate matter is observed.
- ⑥ Discard any unused portion left in the vial. DO NOT pool unused portions from the vials. DO NOT administer more than one dose from a vial.
- ⑦ THIS DRUG can be administered directly by intravenous infusion or optionally, administered in a 50 mL to 100 mL intravenous bag containing **5% Dextrose Injection**. Do not administer as an intravenous push or bolus.
- ⑧ When administering in an intravenous bag, use a 21-gauge or larger gauge needle (0.8 mm or smaller external diameter needle) to withdraw the calculated dose from the vial and **dilute into 50 mL or 100 mL intravenous bag containing only 5% Dextrose Injection** (based on the calculated total dose and infusion time).

The stabilities of reconstituted drug under various temperature and container conditions are shown in Table 10.

Table 10. Stability of Reconstituted THIS DRUG

Storage Conditions of Reconstituted THIS DRUG	Stability^a per Container		
	Vial	Syringe	Intravenous Bag (D5W^b)
Refrigerated (2°C to 8°C)	24 hours	24 hours	24 hours
Room Temperature (15°C to 30°C)	4 hours	4 hours	4 hours

^a Total time from reconstitution to administration should not exceed 24 hours

^b 5% Dextrose Injection, USP

11. Cautions for Storage and Handling

Unopened vials should be stored refrigerated (2°C to 8°C). Retain in original package to protect from light.

12. Information for Health Care Professionals

1) Pharmacokinetics

The mean (CV%) C_{\max} and AUC following a 2- to 10-minute intravenous infusion of 27 mg/m² of THIS DRUG were 4232 ng/mL (49%) and 379 ng•hr/mL (25%), respectively. Following repeated doses of THIS DRUG at 15 and 20 mg/m², systemic exposure (AUC) and half-life were similar on Days 1 and 15 or 16 of Cycle 1, suggesting there was no systemic THIS DRUG accumulation.

Following a 30-minute infusion of the 56 mg/m² dose, the mean (CV%) AUC of 948 ng•hr/mL (34%) was approximately twice that observed following a 2- to 10-minute infusion at the 27 mg/m² dose with a mean (CV%) of 379 ng•hr/mL (25%). The mean (CV%) C_{\max} of 2079 ng/mL (44%) following a 30-minute infusion of the 56 mg/m² dose was lower compared to that of 27 mg/m² over the 2- to 10-minute infusion with a mean (CV%) of 4232 ng/mL (49%).

At doses between 20 and 56 mg/m², there was a dose-dependent increase in exposure at either infusion duration.

Distribution: The mean steady-state volume of distribution of a 20 mg/m² dose of THIS DRUG was 28 L. When tested *in vitro*, the binding of THIS DRUG to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar.

Metabolism: THIS DRUG was rapidly and extensively metabolized. The predominant metabolites measured in human plasma and urine, and generated *in vitro* by human hepatocytes, were peptide fragments and the diol of THIS DRUG, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450-mediated mechanisms played a minor role in overall THIS DRUG metabolism. The metabolites have no known biologic activity.

Elimination: Following intravenous administration of doses ≥ 15 mg/m², THIS DRUG was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 ~ 263 L/hour, and exceeded hepatic blood flow, suggesting that THIS DRUG was largely cleared extrahepatically. In 24 hours, approximately 25% of the administered dose of THIS DRUG was excreted in urine as metabolites. Urinary and fecal excretion of the parent compound was negligible (0.3% of total dose).

Specific Populations

Age, Gender, and Race: Clinically significant differences were not observed in the pharmacokinetics of THIS DRUG based on age (35–88 years), gender, and race.

Hepatic Impairment: The pharmacokinetics of carfilzomib was studied in patients with relapsed or progressive advanced malignancies with mild (bilirubin > 1 to $1.5 \times \text{ULN}$ or AST $> \text{ULN}$) or moderate (bilirubin > 1.5 to $3 \times \text{ULN}$) chronic hepatic impairment relative to those with normal hepatic function.

Compared to patients with normal hepatic function, patients with mild and moderate hepatic impairment had approximately 50% higher carfilzomib AUC. The pharmacokinetics of carfilzomib has not been evaluated in patients with severe hepatic impairment (bilirubin $> 3 \times \text{ULN}$ and any AST).

Renal Impairment: The pharmacokinetics of carfilzomib was studied in relapsed multiple myeloma patients with normal renal function; mild, moderate or severe renal impairment; and patients with ESRD requiring hemodialysis. Exposures of carfilzomib (AUC and C_{max}) in patients with mild, moderate, and severe renal impairment were similar to those with normal renal function. Relative to patients with normal renal function, ESRD patients on hemodialysis showed 33% higher carfilzomib AUC. No starting dose adjustment is required in patients with baseline renal impairment. Since dialysis clearance of THIS DRUG concentrations has not been studied, the drug should be administered after the hemodialysis procedure.

Drug interactions

THIS DRUG is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of THIS DRUG is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. THIS DRUG is not expected to influence exposure of other drugs.

Cytochrome P450: In an *in vitro* study using human liver microsomes, THIS DRUG showed modest direct ($K_i = 1.7$ micromolar) and time-dependent inhibition ($K_i = 11$ micromolar) of human cytochrome CYP3A4/5. *In vitro* studies indicated that THIS DRUG did not induce human CYP1A2 and CYP3A4 in cultured fresh human hepatocytes. Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of THIS DRUG. A clinical trial of 17 patients using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant THIS DRUG administration. THIS DRUG is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates.

P-gp: THIS DRUG is a P-glycoprotein (P-gp) substrate. *In vitro*, THIS DRUG inhibited the efflux transport of P-gp substrate digoxin by 25% in a Caco-2 monolayer system. However, given that THIS DRUG is administered intravenously and is extensively metabolized, the pharmacokinetics of THIS DRUG is unlikely to be affected by P-gp inhibitors or inducers.

2) Clinical Studies

2.1) In Combination with Lenalidomide and Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (Study 1)

Study 1 was a randomized, open-label, multicenter superiority trial which evaluated the combination of THIS DRUG with lenalidomide and dexamethasone (KRd) *versus* lenalidomide and dexamethasone alone (Rd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 lines of therapy (A line of therapy is a planned course of treatment [including sequential induction, transplantation, consolidation, and/or maintenance] without an interruption for lack of efficacy, such as for relapse or progressive disease). Patients who had the following were excluded from the trial: refractory to bortezomib in the most recent regimen, refractory to lenalidomide and dexamethasone in the most recent regimen, not responding to any prior regimen, creatinine clearance < 50 mL/min, ALT/AST $> 3.5 \times$ ULN and bilirubin $> 2 \times$ ULN, New York Heart Association Class III to IV congestive heart failure, or myocardial infarction within the last 4 months. In the KRd arm, THIS DRUG was evaluated at a starting dose of 20 mg/m², which was increased to 27 mg/m² on Cycle 1, Day 8 onward. THIS DRUG was administered as a 10-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle for Cycle 1 through 12. THIS DRUG was dosed on Days 1, 2, 15, and 16 of each

28-day cycle from Cycle 13 through 18. Dexamethasone 40 mg was administered orally or intravenously on Days 1, 8, 15 and 22 of each cycle. Lenalidomide was given 25 mg orally on Days 1 to 21 of each 28-day cycle. The Rd treatment arm had the same regimen for lenalidomide and dexamethasone as the KRd treatment arm. THIS DRUG was administered for a maximum of 18 cycles unless discontinued early for disease progression or unacceptable toxicity. Lenalidomide and dexamethasone administration could continue until progression or unacceptable toxicity. Concurrent use of thromboprophylaxis and a proton pump inhibitor were required for both arms, and antiviral prophylaxis was required for the KRd arm.

The 792 patients in Study 1 were randomized 1:1 to the KRd or Rd arm. The demographics and baseline characteristics were well-balanced between the two arms (see Table 11). Only 53% of the patients had testing for genetic mutations; a high-risk genetic mutation was identified for 12% of patients in the KRd arm and in 13% in the Rd arm.

**Table 11. Demographics and Baseline Characteristics in Study 1
(Combination Therapy for Relapsed or Refractory Multiple Myeloma)**

Characteristics	KRd Combination Therapy	
	KRd Arm (N = 396)	Rd Arm (N = 396)
Age, Median, Years (min, max)	64 (38, 87)	65 (31, 91)
Age ≥ 75 Years, n (%)	43 (11)	53 (13)
Males, n (%)	215 (54)	232 (59)
Race, n (%)		
White	377 (95)	377 (95)
Black	12 (3)	11 (3)
Other or Not Reported	7 (2)	8 (2)
Number of Prior Regimens, n (%)		
1	184 (46)	157 (40)
2	120 (30)	139 (35)
3 ^a	92 (23)	100 (25)
Prior Transplantation, n (%)	217 (55)	229 (58)
ECOG Performance Status, n (%)		
0	165 (42)	175 (44)
1	191 (48)	186 (47)
2	40 (10)	35 (9)
ISS Stage at Study Baseline, n (%)		
I	167 (42)	154 (39)
II	148 (37)	153 (39)
III	73 (18)	82 (21)
Unknown	8 (2)	7 (2)
CrCL, mL/min, Median (min, max)	79 (39, 212)	79 (30, 208)
30 to < 50, n (%)	19 (5)	32 (8)
50 to < 80, n (%)	185 (47)	170 (43)
Refractory to Last Therapy, n (%)	110 (28)	119 (30)

Characteristics	KRd Combination Therapy	
	KRd Arm (N = 396)	Rd Arm (N = 396)
Refractory at Any Time to, n (%):		
Bortezomib	60 (15)	58 (15)
Lenalidomide	29 (7)	28 (7)
Bortezomib + immunomodulatory agent	24 (6)	27 (7)

ECOG = Eastern Cooperative Oncology Group; CrCL = creatinine clearance;

IgG = immunoglobulin G; ISS = International Staging System; KRd = THIS DRUG, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone

^a Including 2 patients with 4 prior regimens

Patients in the KRd arm demonstrated improved progression-free survival (PFS) compared with those in the Rd arm (HR = 0.69, with 2-sided P-value = 0.0001) as determined using standard International Myeloma Working Group (IMWG)/European Blood and Marrow Transplantation (EBMT) response criteria by an Independent Review Committee (IRC).

The median PFS was 26.3 months in the KRd arm *versus* 17.6 months in the Rd arm (see Table 11 and Figure 1).

A pre-planned overall survival (OS) analysis was performed after 246 deaths in the KRd arm and 267 deaths in the Rd arm. The median follow-up was approximately 67 months. A statistically significant advantage in OS was observed in patients in the KRd arm compared to patients in the Rd arm (see Table 12 and Figure 2).

**Table 12. Efficacy Outcomes in Study 1
(Combination Therapy for Relapsed or Refractory Multiple Myeloma)^a**

	Combination Therapy	
	KRd Arm (N = 396)	Rd Arm (N = 396)
PFS ^b		
Median ^c , Months (95% CI)	26.3 (23.3, 30.5)	17.6 (15.0, 20.6)
HR (95% CI) ^d	0.69 (0.57, 0.83)	
P-value (2-sided) ^e	0.0001	
Overall Survival		
Median ^c , Months (95% CI)	48.3 (42.4, 52.8)	40.4 (33.6, 44.4)
HR (95% CI) ^d	0.79 (0.67, 0.95)	
P-value (2-sided) ^e	0.0091	
Overall Response ^b		
N with response	345	264
ORR (%) (95% CI) ^f	87 (83, 90)	67 (62, 71)
P-value (2-sided) ^g	< 0.0001	
Response Category, n (%)		
sCR	56 (14)	17 (4)

	Combination Therapy	
	KRd Arm (N = 396)	Rd Arm (N = 396)
CR	70 (18)	20 (5)
VGPR	151 (38)	123 (31)
PR	68 (17)	104 (26)

CI = confidence interval; CR = complete response; HR = hazard ratio; KRd = THIS DRUG, lenalidomide, and dexamethasone; PFS = progression-free survival; PR = partial response; Rd = lenalidomide and dexamethasone; sCR = stringent CR; VGPR = very good partial response

^a Eligible patients had 1–3 prior lines of therapy

^b As determined by an Independent Review Committee

^c Based on Kaplan - Meier estimates

^d Based on stratified Cox's model

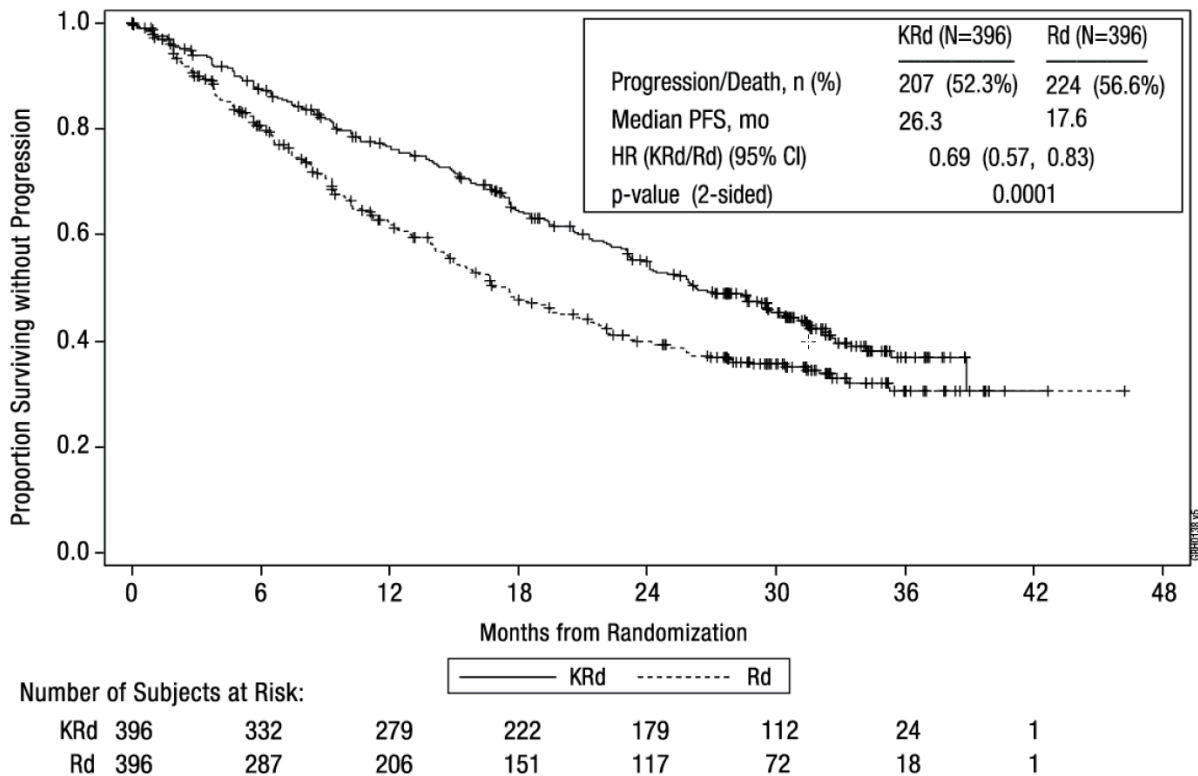
^e The P-value was derived using stratified log-rank test

^f Exact confidence interval

^g The P-value was derived using Cochran Mantel Haenszel test

The median duration of response (DOR) was 28.6 months (95% CI: 24.9, 31.3) for the 345 patients achieving a response in the KRd arm and 21.2 months (95% CI: 16.7, 25.8) for the 264 patients achieving a response in the Rd arm. The median time to response was 1 month (range 1 to 14 months) in the KRd arm and 1 month (range 1 to 16 months) in the Rd arm.

Figure 1. Kaplan-Meier Curve of Progression-Free Survival in Study 1



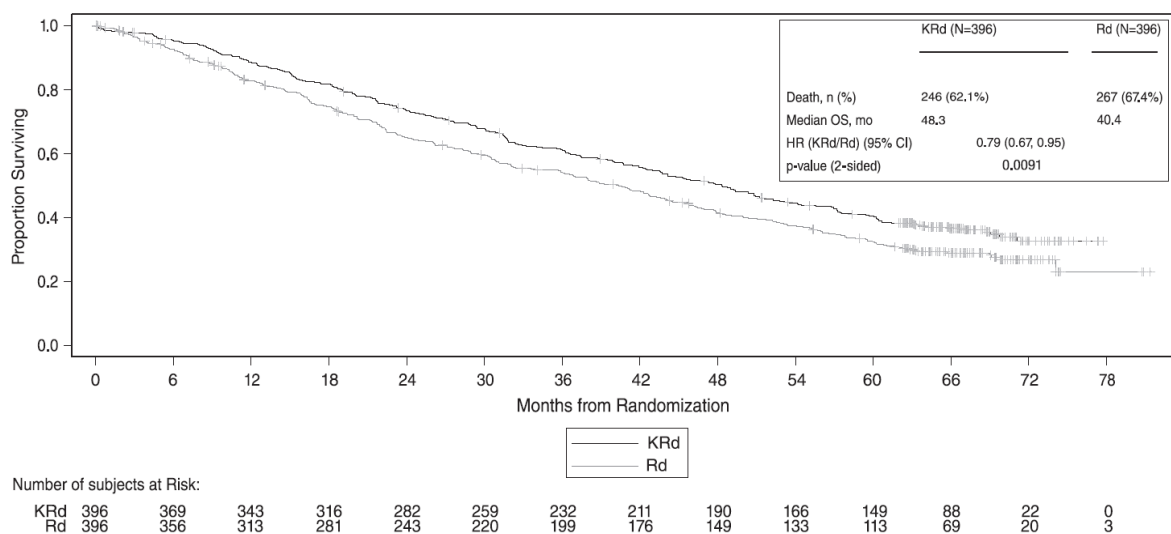
CI = confidence interval; EBMT = European Blood and Marrow Transplantation; HR = hazard ratio;

IMWG = International Myeloma Working Group; KRd = THIS DRUG, lenalidomide, and dexamethasone;

mo = months; PFS = progression-free survival; Rd = lenalidomide and dexamethasone arm

Note: The response and PD outcomes were determined using standard objective IMWG/EBMT response criteria

Figure 2. Kaplan-Meier Curve of Overall Survival in Study 1



CI = confidence interval; HR = hazard ratio; KRd = THIS DRUG, lenalidomide, and dexamethasone; mo = month; OS = overall survival; Rd = lenalidomide and dexamethasone arm

2.2) In Combination with Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (Study 2)

Study 2 was a randomized, open-label, multicenter superiority trial of THIS DRUG plus dexamethasone (Kd) *versus* bortezomib plus dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 lines of therapy. A total of 929 patients were enrolled and randomized (464 in the Kd arm; 465 in the Vd arm). Randomization was stratified by prior proteasome inhibitor therapy (yes *versus* no), prior lines of therapy (1 *versus* 2 or 3), current International Staging System stage (1 *versus* 2 or 3), and planned route of bortezomib administration. Patients were excluded if they had less than PR to all prior regimens; creatinine clearance < 15 mL/min; hepatic transaminases $\geq 3 \times$ ULN; or left-ventricular ejection fraction < 40% or other significant cardiac conditions. This trial evaluated THIS DRUG at a starting dose of 20 mg/m², which was increased to 56 mg/m² on Cycle 1, Day 8 onward. THIS DRUG was administered twice weekly as a 30-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. Dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each cycle. In the Vd arm, bortezomib was dosed at 1.3 mg/m² intravenously or subcutaneously on Days 1, 4, 8, and 11 of a 21-day cycle, and dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle. Concurrent use of thromboprophylaxis was optional, and prophylaxis with an antiviral agent and proton pump inhibitor was required. Of the 465 patients in the Vd arm, 381 received bortezomib subcutaneously. Treatment continued until disease progression or unacceptable toxicity.

The demographics and baseline characteristics are summarized in Table 13.

Table 13. Demographics and Baseline Characteristics in Study 2 (Combination Therapy for Relapsed or Refractory Multiple Myeloma)

Characteristics	Kd Arm (N = 464)	Vd Arm (N = 465)
Age, Years		
Median (min, max)	65 (35, 89)	65 (30, 88)
< 65, n (%)	223 (48)	210 (45)
65–74, n (%)	164 (35)	189 (41)
≥ 75, n (%)	77 (17)	66 (14)
Sex, n (%)		
Female	224 (48)	236 (51)
Male	240 (52)	229 (49)
Race, n (%)		
White	353 (76)	361 (78)
Black	7 (2)	9 (2)
Asian	56 (12)	57 (12)
Other or Not Reported	48 (10)	38 (8)
ECOG Performance Status, n (%)		
0	221 (48)	232 (50)
1	210 (45)	203 (44)
2	33 (7)	30 (6)
Creatinine Clearance (mL/min)		
Median (min, max)	73 (14, 185)	72 (12, 208)
< 30, n (%)	28 (6)	28 (6)
30 – < 50, n (%)	57 (12)	71 (15)
50 – < 80, n (%)	186 (40)	177 (38)
≥ 80, n (%)	193 (42)	189 (41)
FISH, n (%)		
High-risk	97 (21)	113 (24)
Standard-risk	284 (61)	291 (63)
Unknown-risk	83 (18)	61 (13)
ISS Stage at Study Baseline, n (%)		
ISS I	219 (47)	212 (46)
ISS II	138 (30)	153 (33)
ISS III	107 (23)	100 (22)
Number of Prior Regimens, n (%)		
1	232 (50)	231 (50)
2	158 (34)	144 (31)
3	74 (16)	88 (19)
4	0 (0)	2 (0.4)
Prior Therapies, n (%)		
Bortezomib	250 (54)	252 (54)
Transplant for Multiple Myeloma	266 (57)	272 (59)

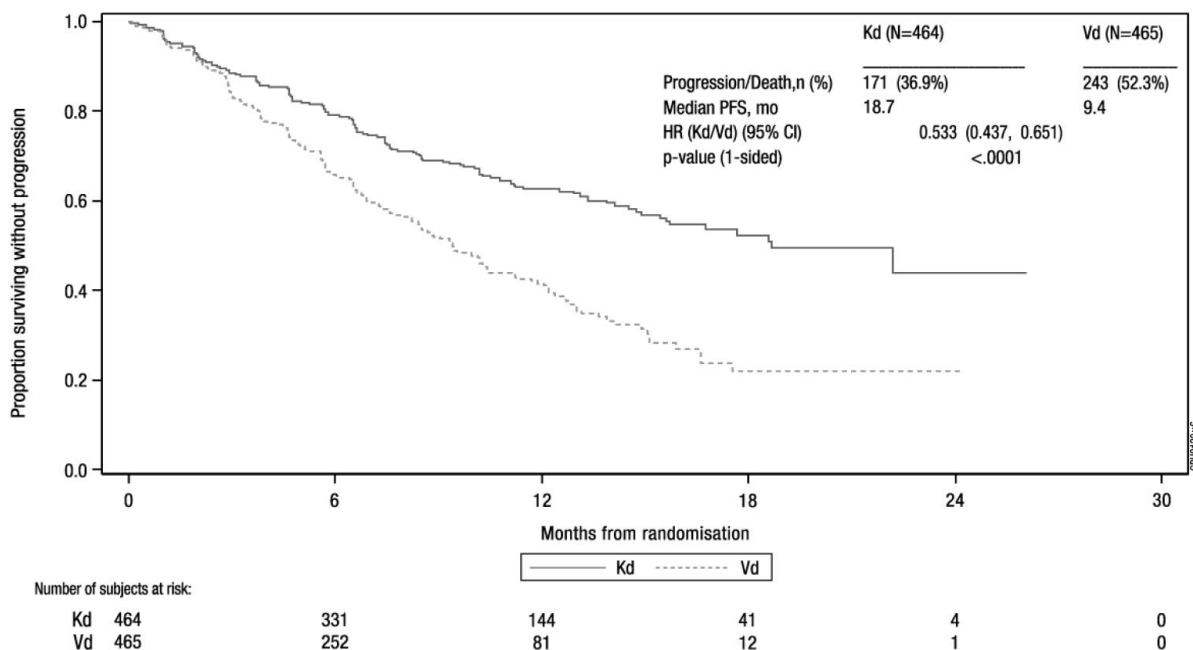
Characteristics	Kd Arm (N = 464)	Vd Arm (N = 465)
Thalidomide	212 (46)	249 (54)
Lenalidomide	177 (38)	178 (38)
Bortezomib + immunomodulatory agent	159 (34)	168 (36)
Refractory to last prior therapy, n (%) ^a	184 (40)	189 (41)

ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence *in situ* hybridization; ISS = International Staging System; Kd = THIS DRUG plus dexamethasone; Vd = bortezomib and dexamethasone

^a Refractory = disease not achieving a minimal response or better, progressing during therapy, or progressing within 60 days after completion of therapy

The efficacy of THIS DRUG was evaluated by PFS as determined by an IRC using IMWG response criteria. The trial showed a median PFS of 18.7 months in the Kd arm *versus* 9.4 months in the Vd arm (see Table 14 and Figure 3).

Figure 3. Kaplan-Meier Plot of Progression-Free Survival in Study 2



CI = confidence interval; HR = hazard ratio; Kd = THIS DRUG plus dexamethasone; mo = month; PFS = progression-free survival; Vd = bortezomib and dexamethasone

Other endpoints included OS and overall response rate (ORR).

A pre-planned OS analysis was performed after 189 deaths in the Kd arm and 209 deaths in the Vd arm. The median follow-up was approximately 37 months. A significantly longer OS was observed in patients in the Kd arm compared to patients in the Vd arm (HR = 0.79; 95% CI: 0.65, 0.96; P-value = 0.01) (see Table 14 and Figure 4).

ORR was 77% for patients in the Kd arm and 63% for patients in the Vd arm (see Table 14).

**Table 14. Summary of Key Results in Study 2
(Intent-to-Treat Population)^a**

	Kd Arm (N = 464)	Vd Arm (N = 465)
PFS^b		
Number of events (%)	171 (37)	243 (52)
Median ^c , Months (95% CI)	18.7 (15.6, NE)	9.4 (8.4, 10.4)
Hazard Ratio (Kd/Vd) (95% CI) ^d	0.53 (0.44, 0.65)	
P-value (1-sided) ^e	< 0.0001	
Overall Survival		
Number of deaths (%)	189 (41)	209 (45)
Median ^c , Months (95% CI)	47.6 (42.5, NE)	40.0 (32.6, 42.3)
Hazard Ratio (Kd/Vd) (95% CI) ^d	0.79 (0.65, 0.96)	
P-value (1-sided) ^e	0.01	
Overall Response^b		
N with Response	357	291
ORR (%) (95% CI) ^f	77 (73, 81)	63 (58, 67)
P-value (1-sided) ^g	< 0.0001	
Response Category, n (%)		
sCR	8 (2)	9 (2)
CR	50 (11)	20 (4)
VGPR	194 (42)	104 (22)
PR ^h	105 (23)	158 (34)

CI = confidence interval; CR = complete response; Kd = THIS DRUG and dexamethasone; ORR = overall response rate; PFS = progression-free survival; PR = partial response; sCR = stringent CR; Vd = bortezomib and dexamethasone; VGPR = very good partial response; NE = non-estimable

^a Eligible patients had 1-3 prior lines of therapy

^b PFS and ORR were determined by an Independent Review Committee

^c Based on Kaplan - Meier estimates

^d Based on a stratified Cox's model

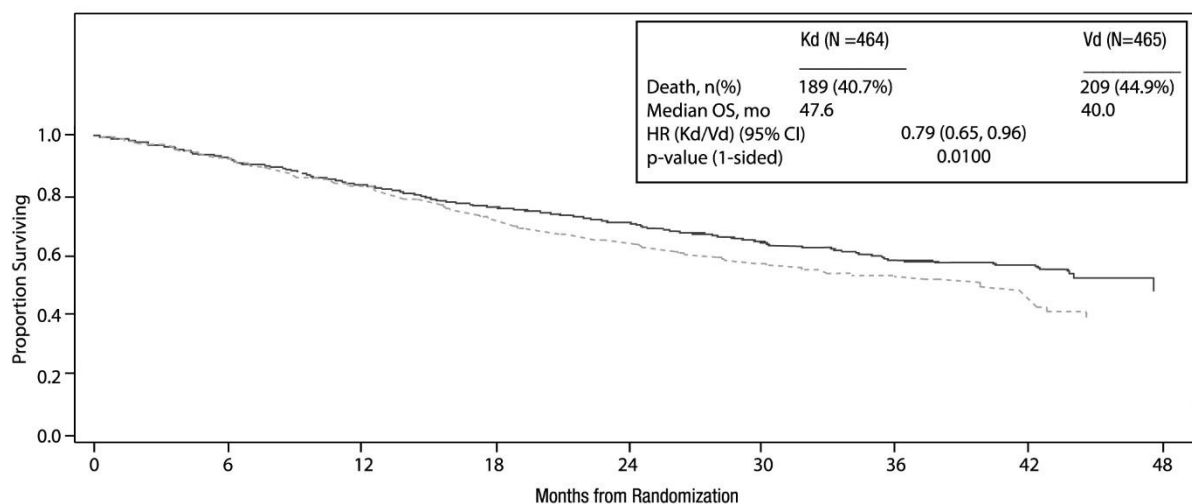
^e P-value was derived using a stratified log-rank test

^f Exact confidence interval

^g The P-value was derived using Cochran Mantel Haenszel test

^h Includes one patient in each arm with a confirmed PR which may not have been the best response

Figure 4. Kaplan-Meier Plot of Overall Survival in Study 2



Number of Subjects at Risk:										
		0	6	12	18	24	30	36	42	48
Kd	464	423	373	335	308	270	162	66	10	
Vd	465	402	351	293	256	228	140	39	5	

CI = confidence interval; HR = hazard ratio; Kd = THIS DRUG and dexamethasone; mo = month; OS = overall survival; Vd = bortezomib and dexamethasone

The median DOR in subjects achieving PR or better was 21.3 months (95% CI: 21.3, not estimable) in the Kd arm and 10.4 months (95% CI: 9.3, 13.8) in the Vd arm. The median time to response was 1 month (range < 1 to 8 months) in both arms.

3) Pharmacology and Toxicology Studies

Cardiovascular Toxicity: Monkeys administered a single bolus intravenous dose of THIS DRUG at 3 mg/kg (approximately 1.3 times recommended dose in humans of 27 mg/m² based on BSA) experienced hypotension, increased heart rate, and increased serum levels of troponin-T.

Chronic Administration: Repeated bolus intravenous administration of THIS DRUG at ≥ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac hemorrhage/degeneration), gastrointestinal (necrosis/hemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), and pulmonary (hemorrhage/inflammation) systems. The dose of 2 mg/kg/dose in rats is approximately half the recommended dose in humans of 27 mg/m² based on BSA. The dose of 2 mg/kg/dose in monkeys is approximately equivalent to the recommended dose in humans based on BSA.

[STORAGE CONDITION]

Hermetic container. Store refrigerated (2~8°C), protected from light.

[PACKAGING UNIT]

1 vial/Box

[EXPIRY DATE]

Refer to the outer package (YY/MM/DD)

[MANUFACTURER]

Product-license holder

Onyx Pharmaceuticals, Inc.
Thousand Oaks, CA 91320, USA

Manufacturers

1) Drug Product

Patheon Manufacturing Services LLC
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Amgen Technology (Ireland) UC (ADL)
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2) Packaging

Sharp Corporation (only for 60 mg/vial)
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Amgen Manufacturing Ltd (AML)
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