Prescription only

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

[30 mg Drug Product] 1 vial contains

Active Ingredient: carfilzomib (in-house) ……32 mg

Excipients: Sulfobutylether 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]

For the treatment of patients with multiple myeloma who have received at least one prior therapy in combination with:

- Lenalidomide and dexamethasone, or
- Dexamethasone, or
- Daratumumab and dexamethasone.

[DOSAGE AND ADMINISTRATION]

1. 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/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 27 mg/m^2 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 20/27 mg/m^2 Twice Weekly (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/m^2)	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/m^2)	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/m^2)	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.

2. THIS DRUG in Combination with Dexamethasone

Twice weekly 20/56 mg/m^2 regimen by 30-minute infusion

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/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 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 20/56 mg/m^2 Twice Weekly (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/m^2)	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/m^2)	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.

Once weekly 20/70 mg/m^2 regimen by 30-minute infusion

For the combination regimen with dexamethasone, administer THIS DRUG intravenously as a 30-minute infusion on first day, each week for three weeks followed by a 13-day rest period as shown in Table 3. Each 28-day period is considered one treatment cycle. Administer THIS DRUG by 30-miniute infusion at a starting dose of 20 mg/m^2 in Cycle 1 on Day 1. If tolerated, escalate the dose to 70 mg/m^2 on Day 8 of Cycle 1. Dexamethasone 40 mg is taken by mouth or intravenously on Day 1, 8, and 15 of all cycles and on Day 22 of Cycle 1 to 9. Administer dexamethasone 30 minutes to 4 hours before THIS DRUG.

Table 3. THIS DRUG 20/70 mg/m^2 Once Weekly (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/m^2)	20	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-	-

	Cycles 2 to 9											
	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/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-	-
	Cycles 10 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/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	-	-	-

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

3. THIS DRUG in Combination with Daratumumab (Intravenous) and Dexamethasone

Twice weekly 20/56 mg/m^2 regimen by 30-minute infusion

For the combination regimen with daratumumab (intravenous) and 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 4. Each 28-day period is considered one treatment cycle. The recommended starting dose of THIS DRUG is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Day 8 of Cycle 1. Daratumumab is administered intravenously at a dose of 16 mg/kg actual body weight, with a split dose of 8 mg/kg in Cycle 1 on Days 1 and 2. Administer 16 mg/kg once weekly on Days 8, 15 and 22 of Cycle 1 and Days 1, 8 and 15 and 22 of Cycle 2, then every 2 weeks for Cycle 3 to 6 and then every 4 weeks for the remaining cycles. Dexamethasone 20 mg is taken by mouth or intravenously on Days 1, 2, 8, 9, 15 and 16 and 40 mg by mouth or intravenously on Day 22 of each 28-day cycle. Administer dexamethasone 30 minutes to 4 hours before THIS DRUG and 1 to 3 hours before daratumumab (intravenous).

Table 4. THIS DRUG 20/56 mg/m^2 Twice Weekly (30-Minute Infusion) in Combination with Daratumumab (Intravenous) 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**	**Day 23**	**Days 24–28**
THIS DRUG (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-
	Cycles 2											
	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/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
	Cycles 3-6											
	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/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
	Cycles 7 and onwards											
	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/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-

*For patients > 75 years of age, administer 20 mg of dexamethasone orally or intravenously weekly after the first week.

Treatment may be continued until disease progression or unacceptable toxicity occurs. Refer to the Prescribing Information for daratumumab (intravenous) and dexamethasone for additional dosage information.

Once weekly 20/70 mg/m^2 regimen by 30-minute infusion

For the combination regimen with daratumumab (intravenous) and dexamethasone, administer THIS DRUG intravenously as a 30-minute infusion on first day, each week for three weeks followed by a 13-day rest period as shown in Table 5. Each 28-day period is considered one treatment cycle. The recommended starting dose of THIS DRUG is 20 mg/m^2 in Cycle 1 on Day 1. If tolerated, escalate the dose to 70 mg/m^2 on Day 8 of Cycle 1. Daratumumab is administered intravenously at a dose of 16 mg/kg actual body weight, with a split dose of 8 mg/kg in Cycle 1 on Days 1 and 2. Administer 16 mg/kg once weekly on Days 8, 15 and 22 of Cycle 1 and Days 1, 8 and 15 and 22 of Cycle 2, then every 2 weeks for Cycle 3 to 6 and then every 4 weeks for the remaining cycles. Dexamethasone 20 mg is taken by mouth or intravenously on Days 1, 2, 8, 9, 15, 16, 22 and 23 of Cycle 1 and 2. Dexamethasone 20 mg is taken by mouth or intravenously on Days 1, 2, 15 and 16 and 40 mg is taken by mouth or intravenously on Days 8 and 22 of Cycle 3 to 6. Dexamethasone 20 mg is taken by mouth or intravenously on Days 1 and 2 and 40 mg is taken by mouth or intravenously on Days 8, 15 and 22 of Cycle 7 and thereafter. Administer dexamethasone 30 minutes to 4 hours before THIS DRUG and 1 to 3 hours before daratumumab (intravenous).

Table 5. THIS DRUG 20/70 mg/m^2 Once Weekly (30-Minute Infusion) in Combination with Daratumumab (Intravenous) 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**	**Day 23**	**Days 24–28**
THIS DRUG (mg/m^2)	20	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	20	20	-
Daratumumab (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-
	Cycles 2											
	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/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	20	20	-
Daratumumab (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-

	Cycles 3-6											
	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/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	40	-	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
	Cycles 7 and thereafter											
	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/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	40	-	-	40	-	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-

*For patients > 75 years of age, administer 20 mg of dexamethasone orally or intravenously weekly after the first week.

Treatment may be continued until disease progression or unacceptable toxicity occurs. Refer to the Prescribing Information for daratumumab (intravenous) and dexamethasone for additional dosage information.

4. Dosage Modifications for Adverse Reactions

Recommended actions and dosage modifications for THIS DRUG are presented in Table 6. Dose level reductions are presented in Table 7. See the lenalidomide, daratumumab (intravenous) and dexamethasone Prescribing Information respectively for dosage modification associated with each product.

Table 6. Dosage Modifications for Adverse Reactions[a] during THIS DRUG Treatment

Hematologic Toxicity	Recommended Action
• ANC less than 0.5 x 10^9/L	• Withhold dose • If recovered to greater than or equal to 0.5 x 10^9/L, continue at the same dose level • For subsequent drops to less than 0.5 x 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting THIS DRUG[a]
• Febrile neutropenia ANC less than 0.5 × 10^9/L and an oral temperature more than 38.5°C or two consecutive readings of more than 38.0°C for 2 hours	• Withhold dose • If ANC returns to baseline grade and fever resolves, resume at the same dose level
• Platelets less than 10 x 10^9/L or evidence of bleeding with thrombocytopenia	• Withhold dose • If recovered to greater than or equal to 10 x 10^9/L and/or bleeding is controlled, continue at the same dose level • For subsequent drops to less than 10 x 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting THIS DRUG[a]
Renal Toxicity	**Recommended Action**

• Serum creatinine greater than or equal to 2 × 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
	• Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance)
	  • 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**
• All other severe or life-threatening[b] non-hematological toxicities	• 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 7 for dose level reductions

[b] CTCAE Grade 3 and 4

Table 7. Dose Level Reductions for Adverse Reactions during THIS DRUG Treatment

Regimen	Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
THIS DRUG, Lenalidomide, and Dexamethasone	27 mg/m^2	20 mg/m^2	15 mg/m^2[a]	—
THIS DRUG and Dexamethasone	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2[a]
	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2[a]
THIS DRUG, Daratumumab and Dexamethasone	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2[a]
	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2[a]

Note: Infusion times remain unchanged during dose reduction(s)
[a] If toxicity persists, discontinue THIS DRUG treatment

5. Dosage Modifications for Use in Hepatic Impairment

For patients with mild (total bilirubin > 1 to 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment, reduce the dose of THIS DRUG by 25%. It has not been evaluated in patients with severe hepatic impairment.

6. Recommended Dosage in Patients with End Stage Renal Disease

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

7. 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 m^2, calculate the dose based upon a BSA of 2.2 m^2.

- **Thromboprophylaxis -** Thromboprophylaxis is recommended for patients being treated with the combination of THIS DRUG with dexamethasone, with lenalidomide plus dexamethasone, or with daratumumab (intravenous) and 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-Related Reactions
- Hemorrhage
- Thrombocytopenia
- Hepatic Toxicity and Hepatic Failure
- Thrombotic Microangiopathy
- Posterior Reversible Encephalopathy Syndrome
- Hepatitis B Virus (HBV) Reactivation
- Progressive Multifocal Leukoencephalopathy
- 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.
The pooled safety population described in *3. General Cautions* reflect exposure to THIS DRUG in 1874 patients administered in combination with other drugs in Study 1, Study 2, Study 3, Study 4 and Study 5. The most common adverse reactions occurring in at least 20% of patients who received THIS DRUG in combination were anemia, diarrhea, fatigue, hypertension, pyrexia, upper respiratory tract infection, thrombocytopenia, cough, dyspnea, and insomnia.

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 (Study 1).

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 reactions 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%). The incidence of cardiac failure events was 7% in the KRd arm *versus* 4% in the Rd arm.

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 8.

Table 8. Adverse Reactions (≥ 10%) Occurring in Cycles 1–12 in Patients Who Received KRd (20/27 mg/m^2 Regimen) in Study 1

Adverse Reactions by Body System	KRd Arm (N = 392) n (%)		Rd Arm (N = 389) n (%)	
	Any Grade	≥ Grade 3	Any Grade	≥ 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)

Adverse Reactions by Body System	KRd Arm (N = 392) n (%)		Rd Arm (N = 389) n (%)	
	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3
Infections				
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)
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, pancreatitis acute (including pancreatitis and pancreatitis acute)
- **General disorders and administration site conditions:** chills, infusion site reaction, multi-organ failure, pain
- **Infections:** 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 (≥ 2%) between the two arms were neutropenia, thrombocytopenia, hypokalemia, and hypophosphatemia.

Laboratory Abnormalities

Table 9 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥ 10% in the KRd arm for patients who received combination therapy.

Table 9. Grade 3–4 Laboratory Abnormalities (≥ 10%) in Cycles 1–12 in Patients Who Received KRd (20/27 mg/m^2 Regimen) in Study 1

Laboratory Abnormality	KRd (N = 392) n (%)	Rd (N = 389) n (%)
Decreased lymphocytes	182 (46)	119 (31)
Decreased absolute neutrophil count	152 (39)	141 (36)

Laboratory Abnormality	KRd (N = 392) n (%)	Rd (N = 389) n (%)
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 two open-label, randomized trials of patients with relapsed multiple myeloma (Study 2 and Study 3). Details of the study treatment are described in Section 12, 2.2.

Study 2

The safety of THIS DRUG 20/56 mg/m^2 twice weekly in combination with dexamethasone (Kd) was evaluated in Study 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 reactions 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 frequent adverse reaction leading to discontinuation was cardiac failure in the Kd arm (n = 8, 2%) and peripheral neuropathy in the Vd arm (n = 22, 5%). The incidence of cardiac failure events was 11% in the Kd arm *versus* 3% in the Vd arm.

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 10.

Table 10. Adverse Reactions (≥ 10%) Occurring in Months 1–6 in Patients Who Received Kd (20/56 mg/m^2 Regimen) in Study 2

Adverse Reactions by Body System	Kd (N = 463) n (%)		Vd (N = 456) n (%)	
	Any Grade	≥ Grade 3	Any Grade	≥ 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				
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)

Adverse Reactions by Body System	Kd (N = 463) n (%)		Vd (N = 456) n (%)	
	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3
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 ≥ 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, pancreatitis acute (including pancreatitis and pancreatitis acute)
- **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:** 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 11 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥ 10% in the Kd arm.

Table 11. Grade 3–4 Laboratory Abnormalities (≥ 10%) in Months 1–6 in Patients Who Received Kd (20/56 mg/m^2 Regimen) in Study 2

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)
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

Study 3

The safety of THIS DRUG in combination with dexamethasone was evaluated in Study 3. Patients received treatment for a median duration of 38 weeks in the Kd 20/70 mg/m^2 arm once weekly and 29.1 weeks in the Kd 20/27 mg/m^2 twice weekly arm. The safety profile for the once weekly Kd 20/70 mg/m^2 regimen was similar to the twice weekly Kd 20/27 mg/m^2 regimen.

Deaths due to adverse reactions within 30 days of last study treatment occurred in 22/238 (9%) patients in the Kd 20/70 mg/m^2 arm and 18/235 (8%) patients in the Kd 20/27 mg/m^2 arm. The most frequent fatal adverse reactions occurring in patients (%) in the two arms (once weekly Kd 20/70 mg/m^2 *versus* twice weekly Kd 20/27 mg/m^2) were sepsis 2 (< 1%) *versus* 2 (< 1%), septic shock 2 (< 1%) *versus* 1 (< 1%), and infection 2 (< 1%) *versus* 0 (0%). Serious adverse reactions were reported in 43% of the patients in the Kd 20/70 mg/m^2 arm and 41% of the patients in the Kd 20/27 mg/m^2 arm. In both arms, pneumonia was the most frequently reported serious adverse reaction (8% *versus* 7%).

Discontinuation due to any adverse reaction occurred in 13% in the Kd 20/70 mg/m^2 arm *versus* 12% in the Kd 20/27 mg/m^2 arm. The most frequent adverse reaction leading to discontinuation was acute kidney injury (2% *versus* 2%). The incidence of cardiac failure events was 3.8% in the once weekly Kd 20/70 mg/m^2 arm *versus* 5.1% in the twice weekly Kd 20/27 mg/m^2 arm.

Adverse reactions that occurred at a rate of 10% or greater in either Kd arm are presented in Table 12.

Table 12. Adverse Reactions in Patients Who Received Kd (≥ 10% in either Kd Arm) in Study 3

Adverse Reactions by Body System	Once weekly Kd 20/70 mg/m^2 (N = 238) n (%)		Twice weekly Kd 20/27 mg/m^2 (N = 235) n (%)	
	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3
Blood and Lymphatic System Disorders				
Anemia[a]	64 (27)	42 (18)	76 (32)	42 (18)
Thrombocytopenia[b]	53 (22)	26 (11)	41 (17)	27 (12)
Neutropenia[c]	30 (13)	21 (9)	27 (12)	17 (7)
Gastrointestinal Disorders				
Diarrhea	44 (19)	2 (1)	47 (20)	3 (1)
Nausea	34 (14)	1 (< 1)	26 (11)	2 (1)
General Disorders and Administration Site Conditions				
Pyrexia	55 (23)	2 (1)	38 (16)	4 (2)
Fatigue	48 (20)	11 (5)	47 (20)	5 (2)
Asthenia	24 (10)	3 (1)	25 (11)	2 (1)
Peripheral edema	18 (8)	0 (0)	25 (11)	2 (1)
Infections				
Respiratory tract infection[d]	70 (29)	7 (3)	79 (34)	7 (3)
Pneumonia	28 (12)	24 (10)	20 (9)	16 (7)
Bronchitis	27 (11)	2 (1)	25 (11)	5 (2)
Musculoskeletal and Connective Tissue Disorders				
Back pain	28 (12)	2 (1)	28 (12)	4 (2)
Nervous System Disorders				
Headache	25 (11)	1 (< 1)	23 (10)	1 (< 1)
Psychiatric Disorders				
Insomnia	35 (15)	2 (1)	47 (20)	0 (0)

Adverse Reactions by Body System	Once weekly Kd 20/70 mg/m^2 (N = 238) n (%)		Twice weekly Kd 20/27 mg/m^2 (N = 235) n (%)	
	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3
Respiratory, Thoracic and Mediastinal Disorders				
Cough[e]	37 (16)	2 (1)	31 (13)	0 (0)
Dyspnea[f]	28 (12)	1 (< 1)	26 (11)	2 (1)
Vascular Disorders				
Hypertension[g]	51 (21)	13 (6)	48 (20)	12 (5)

Kd = THIS DRUG and dexamethasone

[a] Anemia includes anemia, hematocrit decreased, and hemoglobin decreased.

[b] Thrombocytopenia includes platelet count decreased and thrombocytopenia.

[c] Neutropenia includes neutrophil count decreased and neutropenia.

[d] Respiratory tract infection includes respiratory tract infection, lower respiratory tract infection, upper respiratory tract infection, and viral upper respiratory tract infection.

[e] Cough includes cough and productive cough

[f] Dyspnea includes dyspnea and dyspnea exertional.

[g] Hypertension includes hypertension and hypertensive crisis.

Adverse Reactions Occurring at a Frequency of < 10%

- **Blood and lymphatic system disorders:** febrile neutropenia, leukopenia, lymphopenia, neutropenia, thrombotic microangiopathy
- **Cardiac disorders:** atrial fibrillation, cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia, palpitations, pericardial effusion, tachycardia
- **Ear and labyrinth disorders:** tinnitus
- **Eye disorders:** cataract, vision blurred
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, constipation, dyspepsia, toothache, vomiting
- **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
- **Infections:** clostridium difficile colitis, gastroenteritis, influenza, lung infection, nasopharyngitis, rhinitis, sepsis, septic shock, urinary tract infection, viral infection
- **Metabolism and nutrition disorders:** decreased appetite, dehydration, hypercalcemia, hyperglycemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders:** muscle spasms, muscular weakness, musculoskeletal chest pain, musculoskeletal pain, myalgia
- **Nervous system disorders:** cerebrovascular accident, dizziness, paresthesia, peripheral neuropathy
- **Psychiatric disorders:** anxiety, delirium
- **Renal and urinary disorders:** acute kidney injury, renal failure, renal impairment

- **Respiratory, thoracic and mediastinal disorders:** acute respiratory distress syndrome, dysphonia, epistaxis, interstitial lung disease, oropharyngeal pain, pneumonitis, pulmonary hemorrhage, pulmonary embolism, pulmonary hypertension, pulmonary edema, wheezing
- **Skin and subcutaneous tissue disorders:** erythema, hyperhidrosis, pruritus, rash
- **Vascular disorders:** deep vein thrombosis, flushing, hypotension

1.3) Safety Experience with THIS DRUG in Combination with Daratumumab (Intravenous) and Dexamethasone in Patients with Multiple Myeloma

The safety of THIS DRUG in combination with intravenous daratumumab and dexamethasone was evaluated in two trials of patients with relapsed multiple myeloma (Study 4 and Study 5). Details of the study treatment are described in Section 12, 2.3

Study 4

The safety of THIS DRUG 20/56 mg/m^2 twice weekly in combination with daratumumab (intravenous) and dexamethasone (KdD) was evaluated in Study 4. Patients received THIS DRUG for a median duration of 58 weeks in the KdD arm and 40 weeks in the Kd arm.

Serious adverse reactions were reported in 56% of the patients in the KdD arm and 46% of the patients in the Kd arm. The most frequent serious adverse reactions reported in the KdD arm as compared with the Kd arm were pneumonia (14% *versus* 9%), pyrexia (4.2% *versus* 2.0%), influenza (3.9% *versus* 1.3%), sepsis (3.9% *versus* 1.3%), anemia (2.3% *versus* 0.7%), bronchitis (1.9% *versus* 0%), diarrhea (1.6% *versus* 0%). Fatal adverse reactions within 30 days of the last dose of any study treatment occurred in 10% of 308 patients in the KdD arm compared with 5% of 153 patients in the Kd arm. The most frequent fatal adverse reaction (KdD versus Kd) was infection 4.5% *versus* 2.6%. Permanent discontinuation due to an adverse reaction in patients who received THIS DRUG occurred in 21% of patients in the KdD arm *versus* 22% in the Kd arm. The most frequent adverse reactions leading to discontinuation of THIS DRUG were cardiac failure (1.9%) and fatigue (1.9%) in the KdD arm and cardiac failure (2.0%), hypertension (2.0%) and acute kidney injury (2.0%) in the Kd arm. Interruption of THIS DRUG due to adverse reactions occurred in 71% of patients in KdD arm *versus* 63% in the Kd arm. Dose reduction of THIS DRUG due to adverse reactions occurred in 25% of patients in KdD arm *versus* 20% in the Kd arm.

Infusion-related reactions that occurred following the first THIS DRUG dose was 13% in the KdD arm *versus* 1% in the Kd arm.

Adverse reactions that occurred at a rate of 15% or greater in either KdD or Kd arm are presented in Table 13.

Table 13. Adverse Reactions (≥ 15%) in Patients Who Received either KdD or Kd (20/56 mg/m^2 Regimen) in Study 4

Adverse Reactions by Body System	Twice weekly KdD (N = 308)		Twice weekly Kd (N = 153)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
General Disorders and Administration Site Conditions				
Infusion-related reaction[a]	126 (41)	38 (12)	43 (28)	8 (5)
Fatigue[b]	98 (32)	33 (11)	43 (28)	12 (8)
Pyrexia	60 (20)	6 (2)	23 (15)	1 (1)
Infections				
Respiratory tract infection[c]	124 (40)[g]	21 (7)	45 (29)	5 (3)
Pneumonia	55 (18)[g]	41 (13)	19 (12)	13 (9)
Bronchitis	52 (17)	8 (3)	18 (12)	2 (1)
Blood and lymphatic system disorders				
Thrombocytopenia[d]	115 (37)	76 (25)	46 (30)	25 (16)
Anemia[e]	101 (33)	51 (17)	48 (31)	22 (14)
Gastrointestinal Disorders				
Diarrhea	97 (32)	12 (4)	22 (14)	1 (1)
Nausea	56 (18)	0 (0)	20 (13)	1 (1)
Vascular Disorders				
Hypertension	94 (31)	54 (18)	42 (28)	20 (13)
Respiratory, Thoracic and Mediastinal Disorders				
Cough[f]	63 (21)	0 (0)	32 (21)	0 (0)
Dyspnea	61 (20)	12 (4)	34 (22)	4 (3)
Psychiatric Disorders				
Insomnia	55 (18)	12 (4)	17 (11)	3 (2)

Adverse Reactions by Body System	Twice weekly KdD (N = 308)		Twice weekly Kd (N = 153)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Musculoskeletal and Connective Tissue Disorders				
Back pain	50 (16)	6 (2)	15 (10)	2 (1)

KdD = THIS DRUG, daratumumab, and dexamethasone; Kd = THIS DRUG and dexamethasone

[a] The incidence of infusion related reactions is based on a group of symptoms (including hypertension, pyrexia, rash, myalgia, hypotension, blood pressure increased, urticaria, acute kidney injury, bronchospasm, face edema, hypersensitivity, syncope, wheezing, eye pruritus, eyelid edema, renal failure, swelling face) related to infusion reactions which occurred within 1 day after KdD or Kd administration

[b] Fatigue includes fatigue and asthenia.

[c] Respiratory tract infection includes respiratory tract infection, lower respiratory tract infection, upper respiratory tract infection and viral upper respiratory tract infection.

[d] Thrombocytopenia includes platelet count decreased and thrombocytopenia.

[e] Anemia includes anemia, hematocrit decreased and hemoglobin decreased.

[f] Cough includes productive cough and cough.

[g] Includes fatal adverse reactions.

Adverse Reactions Occurring at a Frequency of < 15%

- **Blood and lymphatic system disorders:** febrile neutropenia, thrombotic thrombocytopenic purpura
- **Cardiac disorders:** atrial fibrillation, cardiac arrest, cardiac failure, cardiomyopathy, myocardial infarction, myocardial ischemia, tachycardia
- **Eye disorders:** cataract
- **Gastrointestinal disorders:** abdominal pain, gastrointestinal hemorrhage
- **General disorders and administration site conditions:** chest pain, malaise
- **Infections:** gastroenteritis, influenza, lung infection, nasopharyngitis, sepsis, septic shock, urinary tract infection, viral infection
- **Investigations:** alanine aminotransferase increased, blood creatinine increased, C-reactive protein increased, ejection fraction decreased
- **Metabolism and nutrition disorders:** dehydration, hyperglycemia, hyperkalemia, hypokalemia, hyponatremia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders:** pain in extremity
- **Nervous system disorders:** cerebrovascular accident, intracranial hemorrhage, posterior reversible encephalopathy syndrome, peripheral neuropathy
- **Psychiatric disorders:** anxiety
- **Renal and urinary disorders:** acute kidney injury, renal failure, renal impairment
- **Respiratory, thoracic and mediastinal disorders:** acute respiratory failure, epistaxis, interstitial lung disease, pneumonitis, pulmonary embolism, pulmonary hypertension, pulmonary edema
- **Skin and subcutaneous tissue disorders:** rash
- **Vascular disorders:** deep vein thrombosis, hypertensive crisis

Study 5
The safety of THIS DRUG 20/70 mg/m^2 once weekly in combination with daratumumab and dexamethasone (KdD) was evaluated in Study 5. Patients received THIS DRUG for a median duration of 66 weeks.

Serious adverse reactions were reported in 48% of patients. The most frequent serious adverse reactions reported were pneumonia (4.7%), upper respiratory tract infection (4.7%), basal cell carcinoma (4.7%), influenza (3.5%), general physical health deterioration (3.5%) and hypercalcemia (3.5%). Fatal adverse reactions within 30 days of the last dose of any study treatment occurred in 3.5% of patients who died of general physical health deterioration, multi-organ failure secondary to pulmonary aspergillosis, and disease progression. Discontinuation of THIS DRUG occurred in 19% of patients. The most frequent adverse reaction leading to discontinuation was asthenia (2%). Interruption of THIS DRUG due to adverse reactions occurred in 77% of patients. Dose reduction of THIS DRUG due to adverse reactions occurred in 31% of patients in KdD.
Infusion-related reactions that occurred following the first THIS DRUG dose was 11%. Pulmonary hypertension adverse reactions were reported in 4.7% of patients in Study 5.
Adverse reactions that occurred at a rate of 15% or greater in the KdD arm are presented in Table 14.

Table 14. Adverse Reactions (≥ 15%) in Patients Who Received KdD (20/70 mg/m^2 Regimen) in Study 5

Adverse Reactions by Body System	Once weekly KdD (N = 85)	
	All Grades (%)	Grade 3 or 4 (%)
Blood and Lymphatic System Disorders		
Thrombocytopenia[a]	58 (68)	27 (32)
Anemia[b]	44 (52)	18 (21)
Neutropenia[c]	26 (31)	18 (21)
Lymphopenia[d]	25 (29)	21 (25)
General Disorders and Administration Site Conditions		
Fatigue[e]	46 (54)	15 (18)
Infusion-related reaction[f]	45 (53)	10 (12)
Pyrexia	31 (37)	1 (1)

Adverse Reactions by Body System	Once weekly KdD (N = 85)	
	All Grades (%)	Grade 3 or 4 (%)
Infections		
Respiratory tract infection[g]	45 (53)	3 (4)
Bronchitis	16 (19)	0 (0)
Nasopharyngitis	15 (18)	0 (0)
Influenza	14 (17)	3 (4)
Gastrointestinal Disorders		
Nausea	36 (42)	1 (1)
Vomiting	34 (40)	1 (1)
Diarrhea	32 (38)	2 (2)
Constipation	14 (17)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	30 (35)	3 (4)
Cough[h]	28 (33)	0 (0)
Vascular Disorders		
Hypertension	28 (33)	17 (20)
Psychiatric Disorders		
Insomnia	28 (33)	4 (5)
Nervous System Disorders		
Headache	23 (27)	1 (1)
Musculoskeletal and Connective Tissue Disorders		
Back pain	21 (25)	0 (0)
Pain in extremity	13 (15)	0 (0)

KdD = THIS DRUG, daratumumab, and dexamethasone; Kd = THIS DRUG and dexamethasone

[a] Thrombocytopenia includes platelet count decreased and thrombocytopenia.

[b] Anemia includes anemia, hematocrit decreased and hemoglobin decreased.

[c] Neutropenia includes neutrophil count decreased and neutropenia.

[d] Lymphopenia includes lymphocyte count decreased and lymphopenia

[e] Fatigue includes fatigue and asthenia.

[f] The incidence of infusion related reactions is based on a group of symptoms (including hypertension, pyrexia, rash, myalgia, hypotension, blood pressure increased, urticaria, acute kidney injury, bronchospasm, face edema, hypersensitivity, syncope, wheezing, eye pruritus, eyelid edema, renal failure, swelling face) related to infusion reactions which occurred within 1 day after KdD administration

[g] Respiratory tract infection includes respiratory tract infection, lower respiratory tract infection, upper respiratory tract infection and viral upper respiratory tract infection.

[h] Cough includes productive cough and cough.

Adverse Reactions Occurring at a Frequency of < 15%

- **Blood and lymphatic system disorders:** febrile neutropenia, thrombotic microangiopathy
- **Cardiac disorders:** cardiac failure, myocardial ischemia
- **Gastrointestinal disorders:** abdominal pain
- **General disorders and administration site conditions:** multiple organ dysfunction syndrome
- **Infections:** pneumonia, sepsis, septic shock
- **Metabolism and nutrition disorders:** dehydration, hypercalcemia
- **Renal and urinary disorders:** acute kidney injury, renal failure, renal impairment
- **Respiratory, thoracic and mediastinal disorders:** pulmonary embolism, pulmonary hypertension
- **Vascular disorders:** hypotension

2) Post-marketing Experience

The following adverse reactions have been identified during post approval use of 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, and intestinal obstruction.

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), 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 randomized, open-label, multicenter trials for combination therapies, the incidence of cardiac failure events was 8% and that of arrythmias was 8% (majority of which were atrial fibrillation and sinus tachycardia).

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 reactions 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 (including renal failure) has occurred in approximately 9% 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) and acute respiratory failure have occurred in approximately 2% of patients receiving THIS DRUG. In addition acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in approximately 2% 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 2% 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 25% of patients treated with THIS DRUG and was Grade 3 or greater in 4% 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 twice-weekly Kd *versus* Vd, the incidence of hypertension events was 34% in the Kd arm *versus* 11% in the Vd arm. In a randomized, open label, multicenter trial evaluating twice weekly KdD versus twice weekly Kd, the incidence of hypertension events was 31% in the KdD arm *versus* 28% in the Kd 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 twice-weekly 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, with lenalidomide plus dexamethasone or daratumumab (intravenous) and 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 lenalidomide plus dexamethasone, or daratumumab (intravenous) and dexamethasone.

9) Infusion-Related Reactions

Infusion-related 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-related reactions.

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 32% of patients in clinical trials with THIS DRUG. Hemorrhage may occur.

Monitor platelet counts frequently during treatment with THIS DRUG. Reduce or withhold dose as appropriate.

12) Hepatic Toxicity and Hepatic Failure

Cases of hepatic failure, including fatal cases, have been reported (2%) 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), which can be fatal, have been reported in patients treated with THIS DRUG. In addition to THIS DRUG, other possible contributary factors include prior or concurrent immunosuppressive therapy that may cause immunosuppression.

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, withhold administration of THIS DRUG and 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/m^2 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.

19) Electrocardiographic Changes

There have been cases of QT interval prolongation reported in clinical studies and post-marketing. Cases of ventricular tachycardia have been reported in patients receiving THIS DRUG.

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 (total bilirubin > 1 to 1.5×ULN and any AST or total bilirubin ≤ ULN and AST > ULN), moderate (total bilirubin > 1.5 to 3×ULN and any AST), or severe (total bilirubin > 3×ULN and any AST) 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 reactions 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/m^2 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. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with THIS DRUG and for 2 weeks after treatment.

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 6 months following completion of therapy. Advise male patients and/or their female partners 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 3 months 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 the 2,387 patients in clinical studies of THIS DRUG, 51% were 65 years and older, while 14% were 75 years and older. The incidence of serious adverse reactions was 49% in patients < 65 years of age, 58% in patients 65 to 74 years of age, and 63% in patients ≥ 75 years of age. Of the 308 patients treated with THIS DRUG dosed at 20/56 mg/m^2 twice weekly with daratumumab (intravenous) and dexamethasone, 47% of patients were 65 years and older, while 9% were 75 years and older. Fatal adverse reactions in KdD arm occurred in 6% of patients < 65 years of age, 14% of patients between 65 to 74 years of age, and 14% of 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/m^2) and number of vials of THIS DRUG required using the patient's BSA at baseline. Patients with a BSA greater than 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2. 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 15. 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 15. 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).

⑨ Do not mix THIS DRUG with or administer as an infusion with other medicinal products.

The stabilities of reconstituted drug under various temperature and container conditions are shown in Table 16.

Table 16. 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

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

THIS DRUG at doses between 20 mg/m^2 and 70 mg/m^2 administered as a 30 minute infusion resulted in dose dependent increases in maximum plasma concentrations (C_{max}) and area under the curve over time to infinity ($AUC_{0\text{-}INF}$) in patients with multiple myeloma. A dose dependent increase in C_{max} and $AUC_{0\text{-}INF}$ was also observed between THIS DRUG 20 mg/m^2 and 56 mg/m^2 as a 2 to 10 minute infusion in patients with relapsed or refractory multiple myeloma. A 30 minute infusion resulted in a similar $AUC_{0\text{-}INF}$, but 2 to 3 fold lower C_{max} than that observed with a 2 to 10 minute infusion at the same dose. There was no evidence of accumulation of THIS DRUG following repeated administration of THIS DRUG 70 mg/m^2 as a 30 minute once weekly infusion or 15 and 20 mg/m^2 as a 2 to 10 minute twice weekly infusion.

Table 17 lists the estimated mean average daily area under the curve in the first cycle ($AUC_{C1,avg}$), average daily area under the curve at steady state (AUC_{ss}) and C_{max} at the highest dose in the first cycle ($C_{max,C1}$) for the different dosing regimens.

Table 17. THIS DRUG Exposure Parameters for Different Dosing Regimens

Estimated Parameters (%CV)	20/27 mg/m^2 twice weekly with 2- to 10-minute infusion	20/56 mg/m^2 twice weekly with 30-minute infusion	20/70 mg/m^2 once weekly with 30-minute infusion
$AUC_{C1,avg}$ (ng•hr/mL)	95 (40)	170 (35)	114 (36)
AUC_{ss} (ng•hr/mL)	111 (34)	228 (28)	150 (35)
$C_{max,C1}$ (ng/mL)	1282 (17)	1166 (29)	1595 (36)

CV = Coefficient of variation

Distribution: The mean steady-state volume of distribution of a 20 mg/m^2 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/m^2, 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 (35–89 years), gender, and race.

Hepatic Impairment: The pharmacokinetics of carfilzomib was studied in patients with relapsed or progressive advanced malignancies with mild (total bilirubin > 1 to 1.5×ULN and any AST or total bilirubin ≤ ULN and AST > ULN) or moderate (total bilirubin > 1.5 to 3×ULN and any AST) 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 (total bilirubin > 3×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 (Ki = 1.7 micromolar) and time-dependent inhibition (Ki = 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 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 × ULN and bilirubin > 2 × 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/m^2, which was increased to 27 mg/m^2 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 18). 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 18. 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)

Characteristics	KRd Combination Therapy	
	KRd Arm (N = 396)	Rd Arm (N = 396)
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)
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 19 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 19 and Figure 2).

Table 19. 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	

	Combination Therapy	
	KRd Arm (N = 396)	**Rd Arm (N = 396)**
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)
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

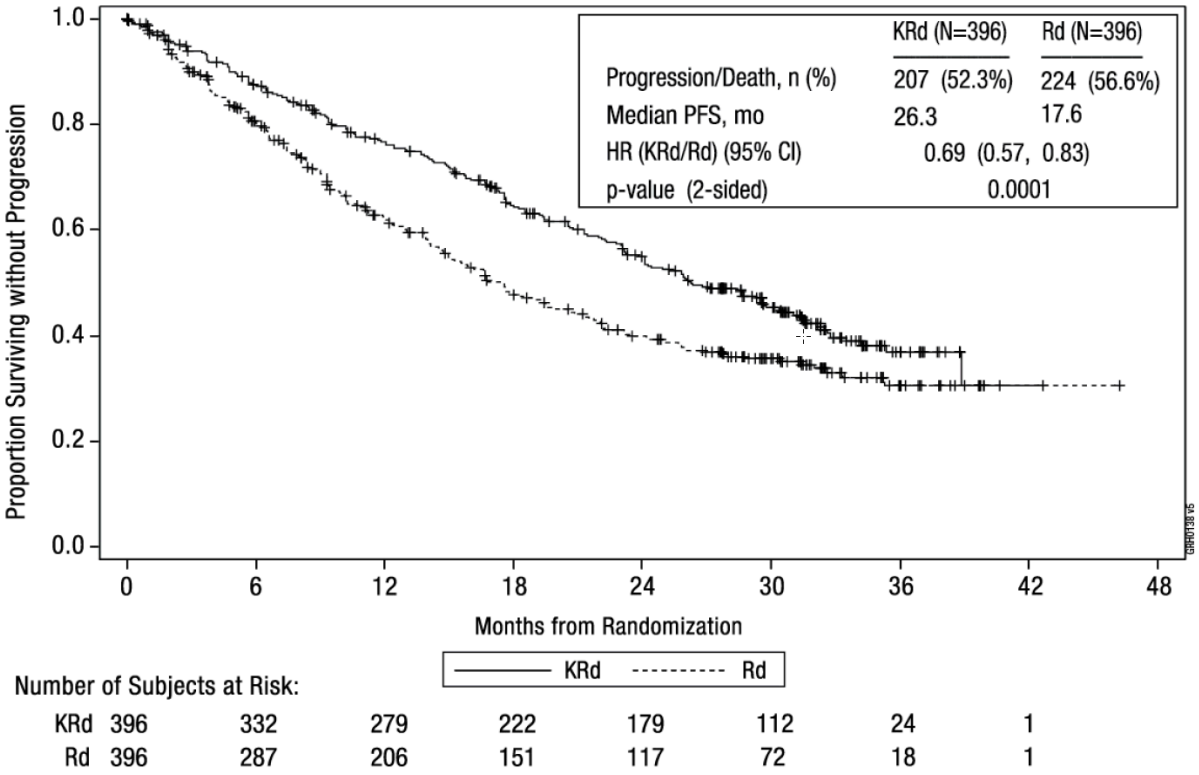
[e] The P-value was derived using stratified log-rank test

[f] Exact confidence interval

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

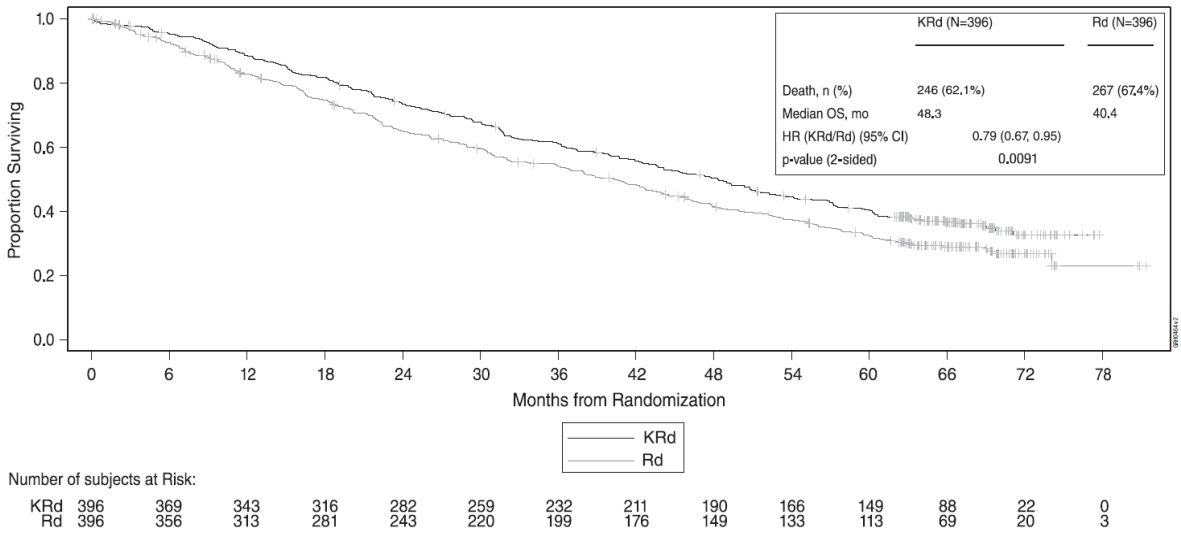
The median duration of response (DOR) was 28.6 months (95% CI: 24.9, 31.3) for the 345 patients achieving a response in the KRd arm and 21.2 months (95% CI: 16.7, 25.8) for the 264 patients achieving a response in the Rd arm. The median time to response was 1 month (range 1 to 14 months) in the KRd arm 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 Relapsed or Refractory Multiple Myeloma (Study 2 and Study 3)

The efficacy of THIS DRUG in combination with dexamethasone was evaluated in two open-label randomized trials.

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 ≥ 3 × ULN; or left-ventricular ejection fraction < 40% or other significant cardiac conditions.

This trial evaluated THIS DRUG at a starting dose of 20 mg/m^2, which was increased to 56 mg/m^2 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/m^2 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 20.

Table 20. 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)

Characteristics	Kd Arm (N = 464)	Vd Arm (N = 465)
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)

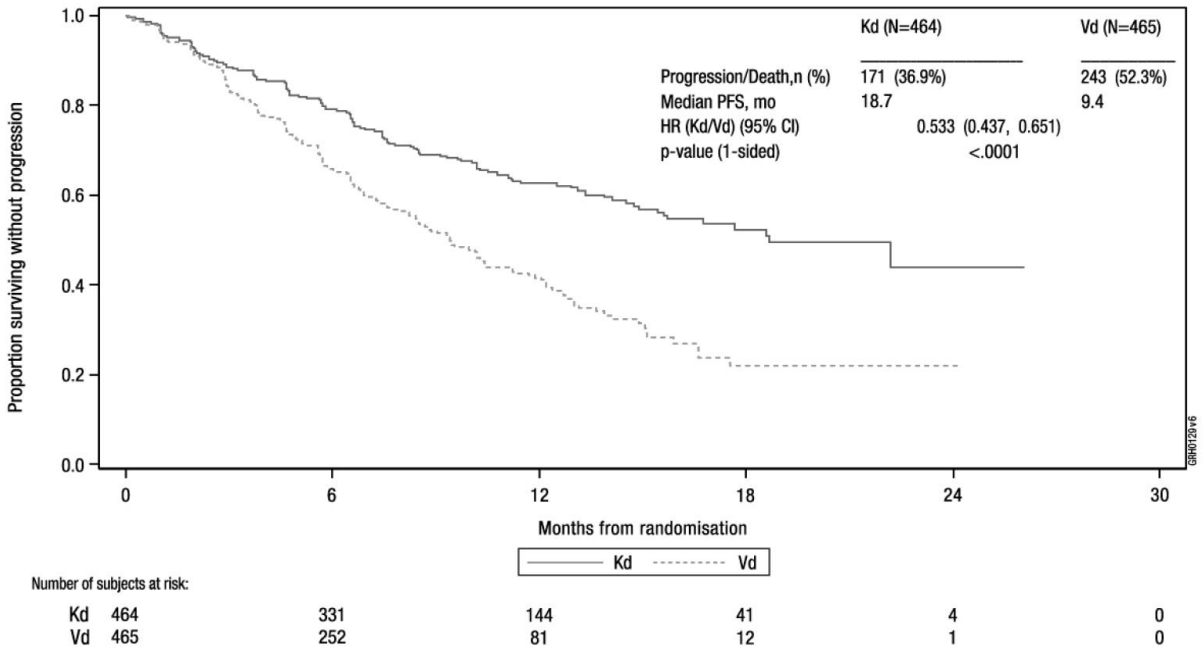
Characteristics	Kd Arm (N = 464)	Vd Arm (N = 465)
Prior Therapies, n (%)	464 (100)	465 (100)
Bortezomib	250 (54)	252 (54)
Transplant for Multiple Myeloma	266 (57)	272 (59)
Thalidomide	212 (46)	249 (54)
Lenalidomide	177 (38)	178 (38)
Bortezomib + immunomodulatory agent	159 (34)	168 (36)
Refractory to 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 21 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 21 and Figure 4).

ORR was 77% for patients in the Kd arm and 63% for patients in the Vd arm (see Table 21).

Table 21. 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

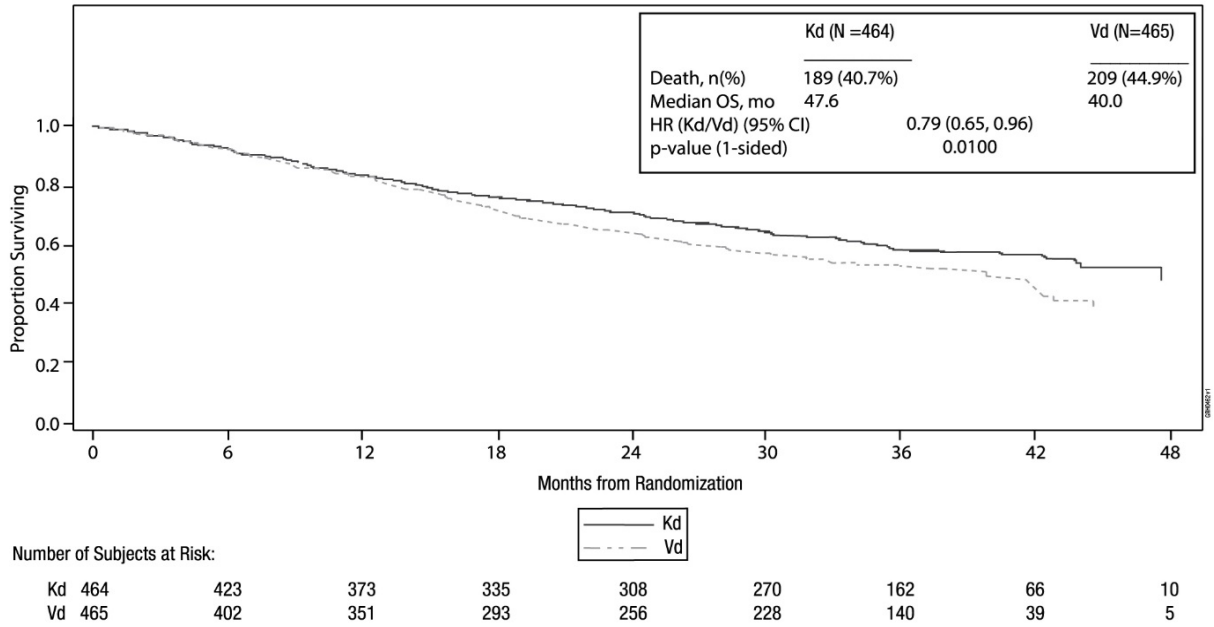
[e] P-value was derived using a stratified log-rank test

[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 Surival in Study 2



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.

Study 3

Study 3 was a randomized, open label, multicenter superiority trial of THIS DRUG and dexamethasone (Kd) once weekly (20/70 mg/m^2) *versus* Kd twice weekly (20/27 mg/m^2) in patients with relapsed and refractory multiple myeloma who had received 2 to 3 prior lines of therapy. Patients were excluded if they had less than PR to at least one prior line; creatinine clearance < 30 mL/min; hepatic transaminases ≥ 3 × ULN; or left ventricular ejection fraction < 40% or other significant cardiac conditions. A total of 478 patients were enrolled and randomized (240 in 20/70 mg/m^2 arm; 238 in 20/27 mg/m^2 arm). Randomization was stratified by current International Staging System stage (stage 1 *versus* stages 2 or 3), refractory to bortezomib treatment (yes *versus* no), and age (< 65 *versus* ≥ 65 years).

Arm 1 of this trial evaluated THIS DRUG at a starting dose of 20 mg/m^2, which was increased to 70 mg/m^2 on Cycle 1, Day 8 onward. Arm 1 THIS DRUG was administered once weekly as a 30 minute infusion on Days 1, 8 and 15, of each 28 day cycle. Arm 2 of this trial evaluated THIS DRUG at a starting dose of 20 mg/m^2, which was increased to 27 mg/m^2 on Cycle 1, Day 8 onward. Arm 2 THIS DRUG was administered twice weekly as a 10 minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28 day cycle. In both regimens, dexamethasone 40 mg was administered orally or intravenously on Days 1, 8, 15 for all cycles and on Day 22 for cycles 1 to 9 only. Concurrent use of thromboprophylaxis was optional, prophylaxis with an antiviral agent was recommended, and prophylaxis with a proton pump inhibitor was required. Treatment continued until disease progression or unacceptable toxicity.

The demographics and baseline characteristics are summarized in Table 22.

Table 22. Demographics and Baseline Characteristics in Study 3 (Combination Therapy for Relapsed and Refractory Multiple Myeloma)

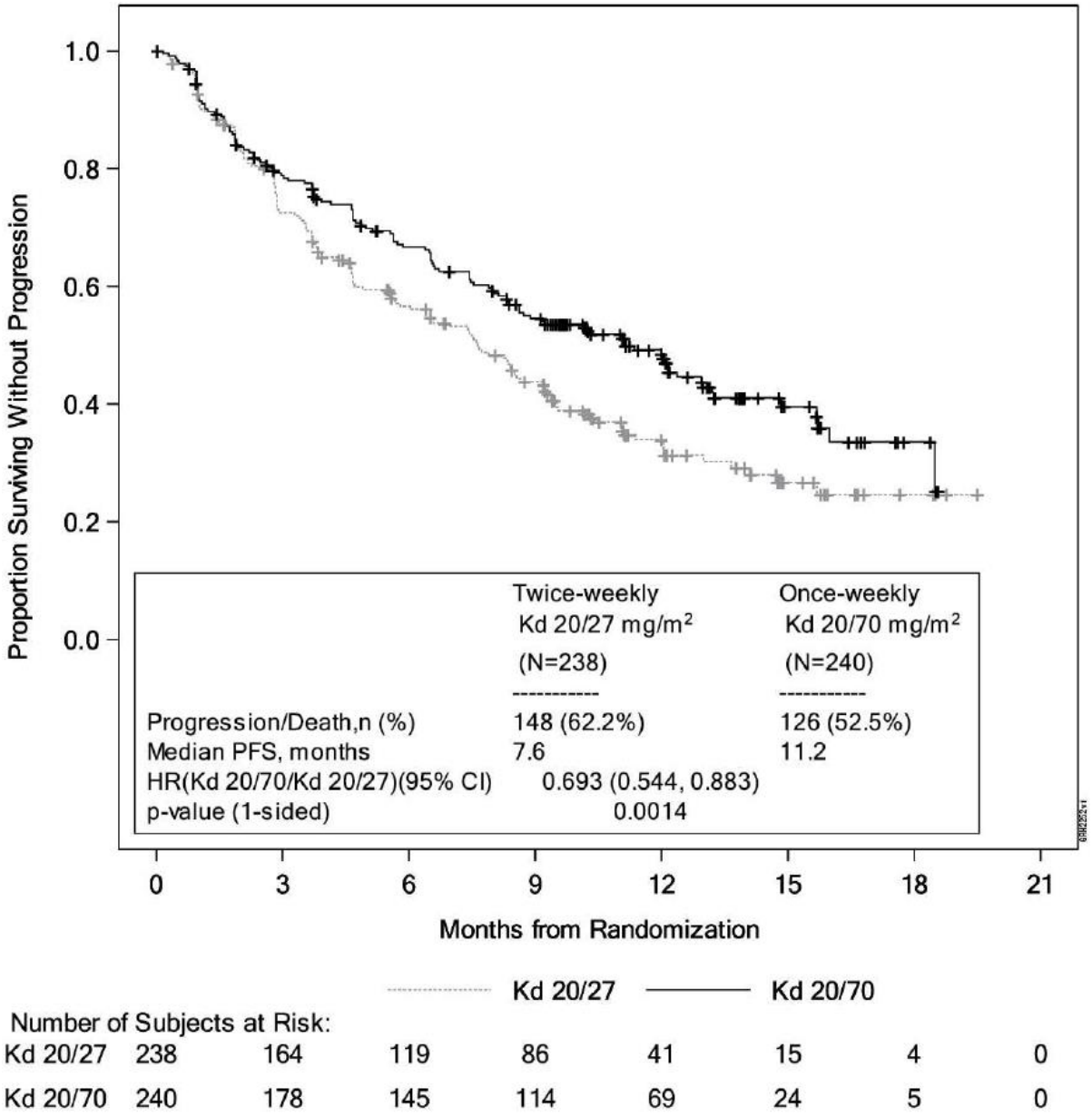
Characteristics	Once weekly Kd 20/70 mg/m^2 (N = 240)	Twice weekly Kd 20/27 mg/m^2 (N = 238)
Age, Years		
Median (min, max)	66 (39, 85)	66 (35, 83)
< 65, n (%)	104 (43)	104 (44)
65 – 74, n (%)	90 (38)	102 (43)
≥ 75, n (%)	46 (19)	32 (13)
Sex, n (%)		
Female	108 (45)	110 (46)
Male	132 (55)	128 (54)
Race, n (%)		
White	200 (83)	202 (85)
Black	3 (1)	2 (1)
Asian	30 (13)	15 (6)
Other or Not Reported	7 (3)	19 (8)
ECOG Performance Status, n (%)		
0	118 (49)	118 (50)
1	121 (50)	120 (50)
2	1 (0.4)	0 (0)
Creatinine Clearance (mL/min)		
Median (min, max)	70.80 (28, 212)	73.20 (29, 181)
< 30, n (%)	2 (1)	1 (0.4)
30 – < 50, n (%)	48 (20)	34 (14)
50 – < 80, n (%)	91 (38)	111 (47)
≥ 80, n (%)	99 (41)	91 (38)

Characteristics	Once weekly Kd 20/70 mg/m^2 (N = 240)	Twice weekly Kd 20/27 mg/m^2 (N = 238)
FISH, n (%)		
High-risk	34 (14)	47 (20)
Standard-risk	47 (20)	53 (22)
Unknown-risk	159 (66)	138 (58)
ISS Stage at Study Baseline, n (%)		
ISS I	94 (39)	99 (42)
ISS II	80 (33)	81 (34)
ISS III	63 (26)	54 (23)
Number of Prior Regimens, n (%)		
2	116 (48)	125 (53)
3	124 (52)	112 (47)
>3	0 (0)	1 (0.4)
Prior Therapies, n (%)		
Bortezomib	236 (98)	237 (100)
Transplantation	146 (61)	157 (66)
Thalidomide	119 (50)	119 (50)
Lenalidomide	207 (86)	194 (82)

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

The efficacy of THIS DRUG was evaluated by PFS using IMWG response criteria. Efficacy results are provided in Table 23 and Figure 5.

Figure 5. Kaplan-Meier Plot of Progression-Free Survival in Study 3



CI = confidence interval; HR = hazard ratio; Kd = THIS DRUG and dexamethasone; PFS = progression-free survival

Table 23 Summary of Key Results in Study 3
(Intent-to-Treat Population)

	Once weekly Kd 20/70 mg/m^2 (N = 240)	**Twice weekly Kd 20/27 mg/m^2 (N = 238)**
PFS		
Number of events, n (%)	126 (52.5)	148 (62.2)
Median, Months (95% CI)	11.2 (8.6, 13.0)	7.6 (5.8, 9.2)
HR (95% CI)	0.69 (0.54, 0.88)	
P-value (1-sided)	0.0014	

	Once weekly Kd 20/70 mg/m^2 (N = 240)	Twice weekly Kd 20/27 mg/m^2 (N = 238)
Overall Response[a]		
N with Response	151	97
ORR (%) (95% CI)	62.9 (56.5, 69.0)	40.8 (34.5, 47.3)
P-value (1-sided)	< 0.0001	
Response Category, n (%)		
sCR	4 (1.7)	0 (0.0)
CR	13 (5.4)	4 (1.7)
VGPR	65 (27.1)	28 (11.8)
PR	69 (28.8)	65 (27.3)

CI = confidence interval; CR = complete response; HR = hazard ratio; Kd = THIS DRUG and dexamethasone; ORR = overall response rate; PFS = progression free survival; PR = partial response; sCR = stringent complete response; VGPR = very good partial response

[a] Overall response is defined as achieving a best overall response of PR, VGPR, CR or sCR.

The median DOR in subjects achieving PR or better was 15 months (95% CI: 12.2, not estimable) in the Kd 20/70 mg/m^2 arm and 13.8 months (95% CI: 9.5, not estimable) in the Kd 20/27 mg/m^2 arm. The median time to response was 1.1 months in the Kd 20/70 mg/m^2 arm and 1.9 months in the Kd 20/27 mg/m^2 arm.

THIS DRUG is not approved for twice weekly 20/27 mg/m^2 administration in combination with dexamethasone alone.

2.3) In Combination with Daratumumab (Intravenous) and Dexamethasone for Relapsed or Refractory Multiple Myeloma (Study 4 and Study 5)

The efficacy of THIS DRUG in combination with daratumumab and dexamethasone (KdD) was evaluated in two open label clinical trials.

Study 4

Study 4 was a randomized, open label, multicenter trial which evaluated the combination of THIS DRUG 20/56 mg/m^2 twice weekly with daratumumab (intravenous) and dexamethasone (KdD) *versus* THIS DRUG 20/56 mg/m^2 twice weekly and dexamethasone (Kd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 lines of therapy. Patients who had the following were excluded from the trial: known moderate or severe persistent asthma within the past 2 years, known chronic obstructive pulmonary disease (COPD) with a FEV1 < 50% of predicted normal, and active congestive heart failure. Randomization was stratified by the ISS (stage 1 or 2 vs stage 3) at screening, prior proteasome inhibitor exposure (yes vs no), number of prior lines of therapy (1 vs ≥ 2), or prior cluster differentiation antigen 38 (CD38) antibody therapy (yes vs no).

THIS DRUG was administered intravenously over 30 minutes at a dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2; at a dose of 56 mg/m^2 in Cycle 1 on Days 8, 9, 15 and 16; and on Days 1, 2, 8, 9, 15 and 16 of each 28-day cycle thereafter. Dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 8, 9, 15 and 16 and then 40 mg orally or intravenously on Day 22 of each 28-day cycle. In the KdD arm, daratumumab was administered intravenously at a dose of 8 mg/kg in Cycle 1 on Days 1 and 2. Thereafter, daratumumab was administered intravenously at a dose of 16 mg/kg on Days 8, 15 and 22 of Cycle 1; Days 1, 8 and 15 and 22 of Cycle 2; Days 1 and 15 of Cycles 3 to 6; and Day 1 for the remaining cycles or until disease progression. For patients > 75 years on a reduced dexamethasone dose of 20 mg, the entire 20 mg dose was given as a daratumumab pre-infusion medication on days when daratumumab was administered. Dosing of dexamethasone was otherwise split across days when THIS DRUG was administered in both study arms. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 466 patients were randomized; 312 to the KdD arm and 154 to the Kd arm. The demographics and baseline characteristics are summarized in Table 24.

Table 24. Demographics and Baseline Characteristics in Study 4 (Combination Therapy for Relapsed or Refractory Multiple Myeloma)

Characteristics	KdD (N = 312)	Kd (N = 154)
Age at randomization (years)		
Median (min, max)	64 (29, 84)	65 (35, 83)
Age group – n (%)		
18 – 64 years	163 (52)	77 (50)
65 – 74 years	121 (39)	55 (36)
75 years and older	28 (9)	22 (14)
Sex – n (%)		
Male	177 (57)	91 (59)
Female	135 (43)	63 (41)
Race – n (%)		
Asian	46 (15)	20 (13)
Black or African American	7 (2.2)	2 (1.3)
White	243 (78)	123 (80)
Other	16 (5)	9 (6)

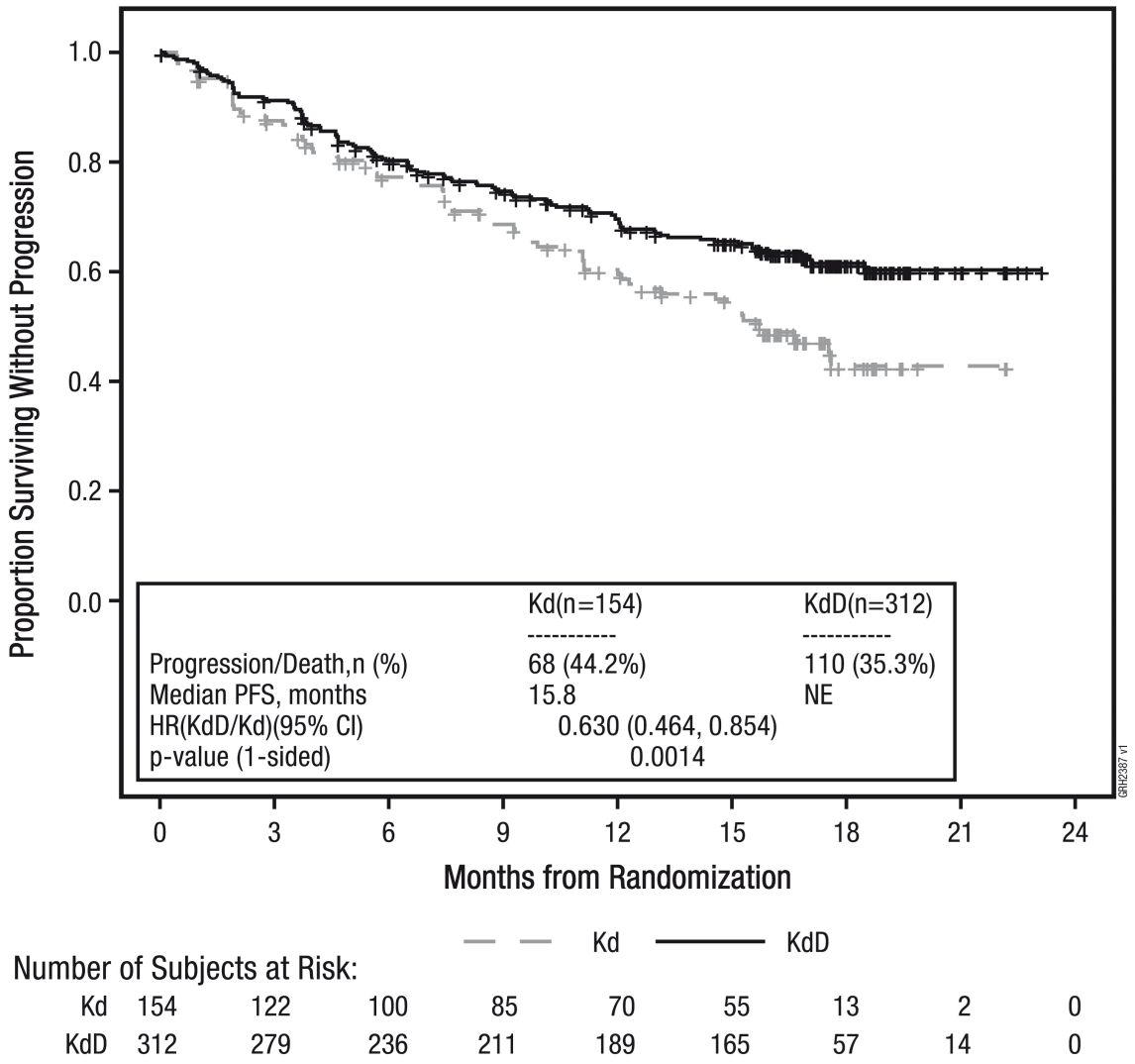
Characteristics	KdD (N = 312)	Kd (N = 154)
Geographic region – n (%)		
North America	21 (7)	12 (8)
Europe	207 (66)	103 (67)
Asia Pacific	84 (27)	39 (25)
ECOG performance status – n (%)		
0 or 1	295 (95)	147 (95)
2	15 (4.8)	7 (4.5)
Missing	2 (0.6)	0 (0.0)
Risk group as determined by FISH – n (%)		
High risk	48 (15)	26 (17)
Standard risk	104 (33)	52 (34)
Unknown	160 (51)	76 (49)
ISS stage per I x RS at screening – n (%)		
I or II	252 (81)	127 (82)
III	60 (19)	27 (17)
Number of prior regimens – n (%)		
1	144 (46)	70 (45)
2	99 (32)	46 (30)
3	69 (22)	37 (24)
Prior Therapies		
Lenalidomide	123 (39)	74 (48)
Refractory to lenalidomide	99 (32)	55 (36)
Bortezomib	287 (92)	134 (87)
Prior CD38 antibody therapy – n (%)	1 (0.3)	0 (0.0)
Prior stem cell transplant (ASCT) – n (%)	195 (62)	75 (49)

ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence *in situ* hybridization; ISS = International Staging System; KdD = THIS DRUG, daratumumab, and dexamethasone

*Subjects with number of prior regimens > 3 was 0 in the KdD arm and 1 in Kd arm

Efficacy was assessed by an IRC evaluation of PFS using the IMWG response criteria. Efficacy results are provided in Table 25 and Figure 6. The median duration of response was not estimable for the KdD arm and was 16.6 months (13.9, NE) for the Kd arm. The median (min, max) time to response was 1.0 (1, 14) months for the KdD arm and 1.0 (1, 10) months for the Kd arm.

Figure 6. Kaplan-Meier Plot of Progression-Free Survival in Study 4



KdD = THIS DRUG, daratumumab and dexamethasone; Kd= THIS DRUG and dexamethasone;

Table 25. Summary of Key Results in Study 4 (Intent-to-Treat Population)

	KdD (N = 312)	**Kd (N = 154)**
PFS		
Number of events (%)	110 (35)	68 (44)
Median, Months (95% CI)	NE (NE, NE)	15.8 (12.1, NE)
HR (95% CI)	0.63 (0.46, 0.85)	
P-value (1-sided)[a]	0.0014	

	KdD (N = 312)	Kd (N = 154)
Overall Response		
N with Response	263	115
ORR (%) (95% CI)	84 (80, 88)	75 (67, 81)
P-value (1-sided)[b]	0.0040	
CR	89 (28)	16 (10)
VGPR	127 (41)	59 (38)
PR	47 (15)	40 (26)
MRD [-] CR rate at 12 month n (%)[c] (95% CI)	39 (12) (9, 17)	2 (1.3) (0.2, 4.6)
P-value (1-sided)[b]	< 0.0001	
MRD [-] CR[d]	43 (14)	5 (3.2)

CI = confidence interval; CR = complete response; HR = hazard ratio; KdD = THIS DRUG, daratumumab, and dexamethasone; Kd = THIS DRUG and dexamethasone; ORR = overall response rate; PFS = progression-free survival; PR = partial response; MRD [-] CR = minimal residual disease negative-complete response; NE = non-estimable; VGPR = very good partial response

[a] The P-value was derived using stratified log-rank test

[b] The P-value was derived using stratified Cochran Mantel-Haenszel Chi-Squared test

[c] MRD [-] CR (at a 10^{-5} level) is defined as achievement of CR per IMWG-URC and MRD[-] status as assessed by the next generation sequencing assay (ClonoSEQ) at the 12 months landmark (from 8 months to 13 months window)

[d] MRD[-]CR (at a 10^{-5} level) is defined as achievement of CR per IMWG-URC and MRD[-] status as assessed by the next generation sequencing assay (ClonoSEQ) at any timepoint during the trial

Study 5

Study 5 was an open label, multi cohort trial which evaluated the combination of THIS DRUG with daratumumab (intravenous) and dexamethasone in patients with relapsed or refractory multiple myeloma who had received one to three prior lines of therapy. Patients who had the following were excluded from the trial: known moderate or severe persistent asthma within the past 2 years, known chronic obstructive pulmonary disease (COPD) with a FEV1 < 50% of predicted normal, or active congestive heart failure (defined as New York Heart Association Class III-IV).

THIS DRUG was administered intravenously over 30 minutes once weekly at a dose of 20 mg/m^2 on Cycle 1, Day 1 and escalated to a dose of 70 mg/m^2 on Cycle 1, Days 8 and 15; and on Days 1, 8, and 15 of each 28 day cycle. Ten patients were administered daratumumab at a dose of 16 mg/kg intravenously on Cycle 1, Day 1 and the remaining patients were administered daratumumab at a dose of 8 mg/kg intravenously on Cycle 1, Days 1 and 2. Thereafter, daratumumab was administered intravenously at a dose of 16 mg/kg on Days 8, 15 and 22 of Cycle 1; Days 1, 8, 15 and 22 of Cycle 2; Days 1 and 15 of Cycles 3 to 6; and then Day 1 for the remaining cycles of each 28 day cycle. In Cycles 1 and 2, dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 8, 9, 15, 16, 22 and 23; in cycles 3 to 6, dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 15 and 16 and at a dose of 40 mg on Day 8 and 22; and in cycles 7 and thereafter, dexamethasone 20 mg was administered orally or intravenously on Days 1 and 2 and at a dose of 40 mg on Days 8, 15,

and 22. For patients > 75 years of age, dexamethasone 20 mg was administered orally or intravenously weekly after the first week. Treatment continued until disease progression or unacceptable toxicity.

The Study 5 trial enrolled 85 patients. The demographics and baseline characteristics are summarized in Table 26.

Table 26. Demographics and Baseline Characteristics in KdD 20/70 mg/m^2 Regimen of Study 5 (Combination Therapy for Relapsed or Refractory Multiple Myeloma)

Characteristics	Number of Patients (%)
Age (years)	
Median (min, max)	66 (38, 85)
Age group – n (%)	
< 65 years	36 (42)
65 - < 75 years	41 (48)
≥ 75 years	8 (9)
Sex – n (%)	
Male	46 (54)
Female	39 (46)
Race – n (%)	
Asian	3 (3.5)
Black or African American	3 (3.5)
White	68 (80)
ECOG Score, n (%)	
0	32 (38)
1	46 (54)
2	7 (8)
FISH, n (%)	
N	67
Standard Risk	54 (81)
High Risk	13 (19)

Characteristics	Number of Patients (%)
Number of Prior regimens	
1	20 (23)
2	40 (47)
3	23 (27)
> 3	2 (2.4)
Prior Therapies	
Bortezomib	85 (100)
Lenalidomide	81 (95)
Prior stem cell transplant (ASCT)	62 (73)
Refractory to lenalidomide	51 (60)
Refractory to both a PI and IMiD	25 (29)

ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence *in situ* hybridization Efficacy results were based on overall response rate using IMWG criteria; PI = proteasome inhibitor; IMiD = immunomodulatory agent.

Efficacy results were based on overall response rate using IMWG criteria. Efficacy results are provided in Table 27. The median time to response was 0.95 months (range: 0.9, 14.3). The median duration of response was 28 months (95% CI: 20.5, not estimable).

Table 27. Summary of Key Results in Study 5 (Intent-to-Treat Population)

	Study Patients n (%)
Overall Response	
N with Response	69
ORR (%) (95% CI)	81 (71, 89)
Response category, n (%)	
sCR	18 (21)
CR	12 (14)
VGPR	28 (33)
PR	11 (13)

CI = confidence interval; sCR = stringent complete response; CR = complete response; ORR = overall response rate; PR = partial response; VGPR = very good partial response

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/m^2 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/m^2 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** 5900 Martin Luther King Jr. Highway, Greenville, NC 27834, USA **Amgen Technology (Ireland) UC (ADL)** Pottery Road, Dun Laoghaire Co, Dublin, Ireland 2) Packaging **Sharp Corporation (only for 60 mg/vial)** 7451 Keebler Way, Allentown, PA 18106, USA **Amgen Manufacturing Ltd (AML)** State Rd 31 Km 24.6, Juncos, Puerto Rico 00777, USA

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