FULL PRESCRIBING INFORMATION

KYPROLIS® (carfilzomib) powder for solution for infusion

1 INDICATIONS AND USAGE

Relapsed or Refractory Multiple Myeloma

- Kyprolis is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy in combination with:
  - Lenalidomide and dexamethasone; or
  - Dexamethasone; or
  - Daratumumab and dexamethasone.

2 DOSAGE AND ADMINISTRATION

2.1 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. Consider hydration with 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 Kyprolis 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 *[see Warnings and Precautions (5.1, 5.3)]*.

Electrolyte Monitoring

Monitor serum potassium levels regularly during treatment with Kyprolis *[see Adverse Reactions (6.1)]*.

Premedications and Concomitant Medications

Premedicate with dexamethasone administered as part of the combination therapy *[see Dosage and Administration (2.2)]*. Administer dexamethasone orally or intravenously at least

30 minutes but no more than 4 hours prior to all doses of Kyprolis during Cycle 1 to reduce the incidence and severity of infusion-related reactions *[see Warnings and Precautions (5.9)]*. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles.

Provide thromboprophylaxis for patients being treated with Kyprolis in combination with other therapies *[see Warnings and Precautions (5.8)]*.

Consider antiviral prophylaxis to decrease the risk of herpes zoster reactivation *[see Adverse Reactions (6.1)]*.

Dose Calculation

For patients with body surface area (BSA) of 2.2 m^2 or less, calculate the Kyprolis dose using actual BSA. Dose adjustments do not need to be made for weight changes of 20% or less.

For patients with a BSA greater than 2.2 m^2, calculate the Kyprolis dose using a BSA of 2.2 m^2.

2.2 Recommended Dosage

Kyprolis in Combination with Lenalidomide and Dexamethasone

Administer Kyprolis intravenously as a 10-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle in combination with lenalidomide and dexamethasone until Cycle 12 as shown in Table 1 *[see Clinical Studies (12.1)]*. The recommended starting dose of Kyprolis is 20 mg/m^2 on Cycle 1, Days 1 and 2. If tolerated, escalate the dose to 27 mg/m^2 on Cycle 1, Day 8. From Cycle 13, administer Kyprolis on Days 1, 2, 15, 16 until Cycle 18. Discontinue Kyprolis after Cycle 18. Continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity occurs. Refer to the Prescribing Information for lenalidomide and dexamethasone for additional dosage information.

Table 1: Kyprolis 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
Kyprolis (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
Kyprolis (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
Kyprolis (mg/m^2)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1–21									-	-

[a] Kyprolis is administered through Cycle 18; lenalidomide and dexamethasone continue thereafter.

Kyprolis in Combination with Dexamethasone

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

Administer Kyprolis intravenously as a 30-minute infusion on Days 1, 8, and 15 of each 28-day cycle in combination with dexamethasone until disease progression or unacceptable toxicity as shown in Table 2 *[see Clinical Studies (12.2)]*. The recommended starting dose of Kyprolis is 20 mg/m^2 on Cycle 1, Day 1. If tolerated, escalate the dose to 70 mg/m^2 on Cycle 1, Day 8. Administer dexamethasone 30 minutes to 4 hours before Kyprolis. Refer to Prescribing Information for dexamethasone for additional dosage information.

Table 2: Kyprolis 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**
Kyprolis (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**
Kyprolis (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**
Kyprolis (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	-	-	-

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

Administer Kyprolis intravenously as a 30-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle in combination with dexamethasone until disease progression or unacceptable toxicity as shown in Table 3 *[see Clinical Studies (12.2)]*. The recommended starting dose of Kyprolis is 20 mg/m^2 on Cycle 1, Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Cycle 1, Day 8. Administer dexamethasone 30 minutes to 4 hours before Kyprolis. Refer to the Prescribing Information for dexamethasone for additional dosage information.

Table 3: Kyprolis 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
Kyprolis (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**
Kyprolis (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

Kyprolis in Combination with Daratumumab and Dexamethasone

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

Administer Kyprolis intravenously as a 30-minute infusion on Days 1, 2, 8, 9, 15 and 16 of each 28-day cycle in combination with daratumumab and dexamethasone until disease progression or unacceptable toxicity as shown in Table 4 *[see Clinical Studies (12.3)]*. The recommended starting dose of Kyprolis is 20 mg/m^2 on Cycle 1, Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Cycle 1, Day 8 and thereafter. Administer dexamethasone 30 minutes to 4 hours before Kyprolis and 1 to 3 hours before daratumumab. Refer to the Prescribing Information for daratumumab and dexamethasone for additional dosage information.

Table 4: Kyprolis 20/56 mg/m^2 Twice Weekly (30-Minute Infusion) in Combination with Daratumumab 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

Kyprolis (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	20	20	-
	with daratumumab intravenous formulation											
Daratumumab intravenous (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-
	OR with daratumumab subcutaneous formulation											
Daratumumab subcutaneous (mg)	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-
	Cycle 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**
Kyprolis (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	20	20	-
	with daratumumab intravenous formulation											
Daratumumab intravenous (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
	OR with daratumumab subcutaneous formulation											
Daratumumab subcutaneous (mg)	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-
	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**
Kyprolis (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
	with daratumumab intravenous formulation											
Daratumumab intravenous (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
	OR with daratumumab subcutaneous formulation											
Daratumumab subcutaneuous (mg)	**1,800**	-	-	-	-	-	**1,800**	-	-	-	-	-

	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
Kyprolis (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
	with daratumumab intravenous formulation											
Daratumumab intravenous (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-
	OR with daratumumab subcutaneous formulation											
Daratumumab subcutaneous (mg)	**1,800**	-	-	-	-	-	-	-	-	-	-	-

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

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

Administer Kyprolis intravenously as a 30-minute infusion on Days 1, 8 and 15 of each 28-day cycle in combination with daratumumab and dexamethasone until disease progression or unacceptable toxicity as shown in Table 5 *[see Clinical Studies (12.3)]*. The recommended starting dose of Kyprolis is 20 mg/m^2 on Cycle 1, Day 1. If tolerated, escalate the dose to 70 mg/m^2 on Cycle 1, Day 8 and thereafter. Administer dexamethasone 30 minutes to 4 hours before Kyprolis and 1 to 3 hours before daratumumab. Refer to the Prescribing Information for daratumumab and dexamethasone for additional dosage information.

Table 5: Kyprolis 20/70 mg/m^2 Once Weekly (30-Minute Infusion) in Combination with Daratumumab 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
Kyprolis (mg/m^2)	20	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	20	20	-
	with daratumumab intravenous formulation											

Daratumumab intravenous (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-
	OR with daratumumab subcutaneous formulation											
Daratumumab subcutaneous (mg)	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-
	Cycle 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**
Kyprolis (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	20	20	-
	with daratumumab intravenous formulation											
Daratumumab intravenous (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
	OR with daratumumab subcutaneous formulation											
Daratumumab subcutaneous (mg)	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-
	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**
Kyprolis (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	40	-	-	20	20	-	40	-	-
	with daratumumab intravenous formulation											
Daratumumab intravenous (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
	OR with daratumumab subcutaneous formulation											
Daratumumab subcutaneous (mg)	**1,800**	-	-	-	-	-	**1,800**	-	-	-	-	-
	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**

Kyprolis (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	40	-	-	40	-	-	40	-	-
	with daratumumab intravenous formulation											
Daratumumab intravenous (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-
	OR with daratumumab subcutaneous formulation											
Daratumumab subcutaneous (mg)	**1,800**	-	-	-	-	-	-	-	-	-	-	-

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

2.3 Dosage Modifications for Adverse Reactions

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

Table 6: Dosage Modifications for Adverse Reactions[a]

Hematologic Toxicity *[see Warnings and Precautions (5.11), Adverse Reactions (6.1)]*	**Recommended Action**
• ANC less than 0.5 × 10^9/L	• Withhold dose • If recovered to greater than or equal to 0.5 × 10^9/L, continue at the same dose level • For subsequent drops to less than 0.5 × 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[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 10×10^9/L or evidence of bleeding with thrombocytopenia	• Withhold dose • If recovered to greater than or equal to 10×10^9/L and/or bleeding is controlled, continue at the same dose level • For subsequent drops to less than 10×10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
Renal Toxicity *[see Warnings and Precautions (5.2)]*	**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 Kyprolis, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction[a]
	  • If not attributable to Kyprolis, dosing may be resumed at the discretion of the healthcare provider
	• For patients on hemodialysis receiving Kyprolis, the dose is to be administered after the hemodialysis procedure

Other Non-hematologic Toxicity *[see Adverse Reactions (6.1)].*	**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] Grade 3 and 4.

Table 7: Dose Level Reductions for Adverse Reactions

Regimen	Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Kyprolis and Dexamethasone OR Kyprolis, Daratumumab and Dexamethasone (once weekly)	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^{2a}
Kyprolis and Dexamethasone OR Kyprolis, Daratumumab, and Dexamethasone (twice weekly)	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^{2a}
Kyprolis, Lenalidomide, and Dexamethasone (twice weekly)	27 mg/m^2	20 mg/m^2	15 mg/m^{2a}	—

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

2.4 Dosage Modifications for 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 Kyprolis by 25% *[see Use in Specific Populations (7.6), Clinical Pharmacology (10.3)]*.

2.5 Recommended Dosage for End Stage Renal Disease

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

2.6 Preparation and Administration

Kyprolis vials contain no antimicrobial preservatives and are intended for single-dose only. 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 Kyprolis required using the patient's BSA at baseline.
3. Aseptically reconstitute each Kyprolis vial only with Sterile Water for Injection, USP using the volumes described in Table 8. Use a 21-gauge or larger needle (0.8 mm or smaller external diameter needle) to reconstitute each vial by slowly injecting Sterile Water for Injection, USP through the stopper and directing the Sterile Water for Injection, USP onto the INSIDE WALL OF THE VIAL to minimize foaming. **There is no data to support the use of closed system transfer devices with Kyprolis.**

Table 8: Reconstitution Volumes

Strength	Amount of Sterile Water for Injection, USP 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. Administer Kyprolis directly by intravenous infusion or in a 50 mL to 100 mL intravenous bag containing **5% Dextrose Injection, USP**. 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, USP** (based on the calculated total dose and infusion time).
9. Flush the intravenous administration line with normal saline or 5% Dextrose Injection, USP immediately before and after Kyprolis administration.
10. Do not mix Kyprolis with or administer as an infusion with other medicinal products.

The stabilities of reconstituted Kyprolis under various temperature and container conditions are shown in Table 9.

Table 9: Stability of Reconstituted Kyprolis

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

[a] Total time from reconstitution to administration should not exceed 24 hours.
[b] 5% Dextrose Injection, USP.

3 DOSAGE FORMS AND STRENGTHS

For injection: 30 mg and 60 mg as a lyophilized cake or powder in single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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 Kyprolis. Some events occurred in patients with normal baseline ventricular function. In clinical studies with Kyprolis, these events occurred throughout the course of Kyprolis therapy. Death due to cardiac arrest has occurred within one day of Kyprolis 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) *[see Adverse Reactions (6.1)]*.

Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold Kyprolis for Grade 3 or 4 cardiac adverse reactions until recovery and consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment *[see Dosage and Administration (2.3)]*.

While adequate hydration is required prior to each dose in Cycle 1, monitor all patients 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 *[see Dosage and Administration (2.1)]*.

In patients ≥ 75 years of age, the risk of cardiac failure is increased compared to younger patients. 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; for these patients, complete a comprehensive medical assessment (including blood pressure control and fluid management) prior to starting treatment with Kyprolis and remain under close follow-up *[see Use in Specific Populations (7.5)]*.

5.2 Acute Renal Failure

Cases of acute renal failure have occurred in patients receiving Kyprolis. Some of these events have been fatal. Renal insufficiency (including renal failure) has occurred in approximately 9% of patients who received Kyprolis. The risk of fatal renal failure was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft-Gault equation).

Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate *[see Dosage and Administration (2.3)]*.

5.3 Tumor Lysis Syndrome

Cases of TLS, including fatal outcomes, have been reported in patients who received Kyprolis. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS.

Administer oral and intravenous fluids before administration of Kyprolis in Cycle 1 and in subsequent cycles as needed. Consider uric acid-lowering drugs in patients at risk for TLS. Monitor for TLS during treatment and manage promptly, including interruption of Kyprolis until TLS is resolved *[see Dosage and Administration (2.1)]*.

5.4 Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS) and acute respiratory failure have occurred in approximately 2% of patients who received Kyprolis. In addition, acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease occurred in approximately 2% of patients who received Kyprolis. Some events were fatal.

In the event of drug-induced pulmonary toxicity, discontinue Kyprolis.

5.5 Pulmonary Hypertension

Pulmonary arterial hypertension was reported in approximately 2% of patients who received Kyprolis, with Grade 3 or greater in less than 1%.

Evaluate with cardiac imaging and/or other tests as indicated. Withhold Kyprolis for pulmonary hypertension until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment.

5.6 Dyspnea

Dyspnea was reported in 25% of patients treated with Kyprolis, with Grade 3 or greater in 4%.

Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Kyprolis for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart Kyprolis based on a benefit/risk assessment *[see Warnings and Precautions (5.1, 5.4) and Adverse Reactions (6.1)]*.

5.7 Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. In ASPIRE, the incidence of hypertension events was 17% in the KRd arm *versus* 9% in the Rd arm. In ENDEAVOR, the incidence of hypertension events was 34% in the Kd arm *versus* 11% in the Vd arm. In CANDOR, the incidence of hypertension events was 31% in the DKd arm *versus* 28% in the Kd arm. Some of these events have been fatal.

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

5.8 Venous Thrombosis

Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Kyprolis. In ASPIRE, 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 ENDEAVOR, the incidence of venous thromboembolic events in months 1–6 was 9% in the Kd arm *versus* 2% in the Vd arm.

Provide thromboprophylaxis for patients being treated with Kyprolis in combination with lenalidomide and dexamethasone; with dexamethasone; or with intravenous daratumumab and dexamethasone. Select the thromboprophylaxis regimen based on the patient's underlying risks.

For patients using oral contraceptives or hormonal contraception associated with a risk of thrombosis, consider non-hormonal contraception during treatment when Kyprolis is administered in combination *[see Use in Specific Populations (7.3)]*.

5.9 Infusion-Related Reactions

Infusion-related reactions, including life-threatening reactions, have occurred in patients receiving Kyprolis. 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 Kyprolis.

Administer dexamethasone prior to Kyprolis to reduce the incidence and severity of infusion-related reactions *[see Dosage and Administration (2.1, 2.2), Adverse Reactions (6.1)]*.

5.10 Hemorrhage

Fatal or serious cases of hemorrhage have been reported in patients treated with Kyprolis *[see Adverse Reactions (6.1)]*. 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 *[see Dosage and Administration (2.3)]*.

5.11 Thrombocytopenia

Kyprolis causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle with recovery to baseline platelet count usually by the start of the next cycle *[see Adverse Reactions (6.1)]*. Thrombocytopenia was reported in approximately 32% of patients in clinical trials with Kyprolis. Hemorrhage may occur *[see Adverse Reactions (6.1), Warnings and Precautions (5.10)]*.

Monitor platelet counts frequently during treatment with Kyprolis. Reduce or withhold dose as appropriate *[see Dosage and Administration (2.3)]*.

5.12 Hepatic Toxicity and Hepatic Failure

Cases of hepatic failure, including fatal cases, have been reported (2%) during treatment with Kyprolis. Kyprolis can cause increased serum transaminases *[see Adverse Reactions (6.1)]*.

Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold dose as appropriate *[see Dosage and Administration (2.3)]*.

5.13 Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received Kyprolis. Some of these events have been fatal.

Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Kyprolis and evaluate. If the diagnosis of TTP/HUS is excluded, Kyprolis may be restarted. The safety of reinitiating Kyprolis therapy in patients previously experiencing TTP/HUS is not known.

5.14 Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving Kyprolis. 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 Kyprolis if PRES is suspected and evaluate. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known.

5.15 Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML), which can be fatal, has been reported with Kyprolis. In addition to Kyprolis, other possible contributory factors include prior or concurrent immunosuppressive therapy that may cause immunosuppression.

Consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms. If PML is suspected, discontinue Kyprolis and initiate evaluation for PML including neurology consultation.

5.16 Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients

In CLARION, a clinical trial of 955 transplant-ineligible patients with newly diagnosed multiple myeloma randomized to Kyprolis (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), 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 (PFS) for the KMP arm. Kyprolis in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

5.17 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, Kyprolis can cause fetal harm when administered to a pregnant woman. Carfilzomib administered intravenously to pregnant rabbits during organogenesis at a dose approximately 40% of the clinical dose of 27 mg/m^2 based on BSA caused post-implantation loss and a decrease in fetal weight.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Kyprolis and for 6 months following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Kyprolis and for 3 months following the last dose *[see Use in Specific Populations (7.1, 7.3), Nonclinical Toxicology (11.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cardiac Toxicities *[see Warnings and Precautions (5.1)]*
- Acute Renal Failure *[see Warnings and Precautions (5.2)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.4)]*
- Pulmonary Hypertension *[see Warnings and Precautions (5.5)]*
- Dyspnea *[see Warnings and Precautions (5.6)]*
- Hypertension *[see Warnings and Precautions (5.7)]*
- Venous Thrombosis *[see Warnings and Precautions (5.8)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*
- Hemorrhage *[see Warnings and Precautions (5.10)]*
- Thrombocytopenia *[see Warnings and Precautions (5.11)]*
- Hepatic Toxicity and Hepatic Failure *[see Warnings and Precautions (5.12)]*
- Thrombotic Microangiopathy *[see Warnings and Precautions (5.13)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.14)]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (5.15)]*

6.1 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 practice.

The pooled safety population described in the Warnings and Precautions reflect exposure to Kyprolis in 1789 patients administered in combination with other drugs in ASPIRE, ENDEAVOR, A.R.R.O.W., and CANDOR. The most common adverse reactions occurring in at least 20% of patients who received Kyprolis in combination were anemia, diarrhea, fatigue, hypertension, pyrexia, upper respiratory tract infection, thrombocytopenia, cough, dyspnea, and insomnia.

Kyprolis in Combination with Lenalidomide and Dexamethasone

The safety of Kyprolis 20/27 mg/m^2 twice weekly in combination with lenalidomide and dexamethasone (KRd) was evaluated in ASPIRE *[see Clinical Studies (12.1)]*. The median number of cycles initiated was 22 cycles for the KRd arm and 14 cycles for the Rd arm.

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 frequent 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 frequent 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 Kyprolis 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.

Table 10 summarizes the adverse reactions in the first 12 cycles in ASPIRE.

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

Adverse Reactions	KRd (N = 392) n (%)		Rd (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)
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)

Adverse Reactions	KRd (N = 392) n (%)		Rd (N = 389) n (%)	
	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3
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 = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone.
[a] Pneumonia includes pneumonia and bronchopneumonia.
[b] Peripheral neuropathies includes peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.
[c] Cough includes cough and productive cough.
[d] Dyspnea includes dyspnea and dyspnea exertional.
[e] Embolic and thrombotic events, venous includes deep vein thrombosis, pulmonary embolism, thrombophlebitis superficial, thrombophlebitis, venous thrombosis limb, post thrombotic syndrome, venous thrombosis.
[f] Hypertension includes hypertension, hypertensive crisis.

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

Adverse Reactions Occurring at a Frequency of < 10%

- **Blood and lymphatic system disorders:** febrile neutropenia, lymphopenia
- **Cardiac disorders:** cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia, pericardial effusion
- **Ear and labyrinth disorders:** deafness, tinnitus
- **Eye disorders:** cataract, vision blurred
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, gastrointestinal hemorrhage, toothache
- **General disorders and administration site conditions:** chills, infusion site reaction, multi-organ failure, pain
- **Infections:** 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.

Table 11 describes Grade 3–4 laboratory abnormalities reported in ASPIRE.

Table 11: Grade 3–4 Laboratory Abnormalities (≥ 10%) in Cycles 1–12 in Patients Who Received KRd (20/27 mg/m^2 Regimen) in ASPIRE

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

KRd = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone.

Kyprolis in Combination with Dexamethasone

The safety of Kyprolis in combination with dexamethasone was evaluated in two open-label, randomized trials (ENDEAVOR and A.R.R.O.W.).

ENDEAVOR

The safety of Kyprolis 20/56 mg/m^2 twice weekly in combination with dexamethasone (Kd) was evaluated in ENDEAVOR *[see Clinical Studies (*12.2*)]*. Patients received treatment for a median duration of 48 weeks in the 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 arms, pneumonia was the most frequently 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 12.

Table 12: Adverse Reactions (≥ 10%) Occurring in Months 1–6 in Patients Who Received Kd (20/56 mg/m^2 Regimen) in ENDEAVOR

Adverse Reactions	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)

Adverse Reactions	Kd (N = 463) n (%)		Vd (N = 456) n (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
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)	8 (2)	61 (13)	10 (2)
Nervous System Disorders				
Headache	67 (15)	4 (1)	39 (9)	2 (0)
Peripheral neuropathies[b,c]	56 (12)	7 (2)	170 (37)	23 (5)
Psychiatric Disorders				
Insomnia	105 (23)	5 (1)	116 (25)	10 (2)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[d]	128 (28)	23 (5)	69 (15)	8 (2)
Cough[e]	97 (21)	0 (0)	61 (13)	2 (0)
Vascular Disorders				
Hypertension[f]	83 (18)	30 (7)	33 (7)	12 (3)

Kd = Kyprolis 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 (12.2).

[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
- **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

Table 13 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥ 10% in the Kd arm.

Table 13: Grade 3–4 Laboratory Abnormalities (≥ 10%) in Months 1–6 in Patients Who Received Kd (20/56 mg/m^2 Regimen) in ENDEAVOR

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 = Kyprolis and dexamethasone; Vd = bortezomib and dexamethasone.
[a] Calculated using the Cockcroft-Gault formula.

A.R.R.O.W.

The safety of Kyprolis in combination with dexamethasone was evaluated in A.R.R.O.W. *[see Clinical Studies (12.2)]*. 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 14.

Table 14: Adverse Reactions in Patients Who Received Kd (≥ 10% in either Kd Arm) in A.R.R.O.W.

Adverse Reactions	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)
Respiratory, Thoracic and Mediastinal Disorders				
Cough[e]	37 (16)	2 (1)	31 (13)	0 (0)

Adverse Reactions	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
Dyspnea[f]	28 (12)	1 (< 1)	26 (11)	2 (1)
Vascular Disorders				
Hypertension[g]	51 (21)	13 (6)	48 (20)	12 (5)

Kd = Kyprolis 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

Kyprolis in Combination with Intravenous Daratumumab and Dexamethasone

The safety of Kyprolis in combination with intravenous daratumumab and dexamethasone was evaluated in two trials (CANDOR and EQUULEUS).

CANDOR

The safety of Kyprolis 20/56 mg/m^2 twice weekly in combination with intravenous daratumumab and dexamethasone (DKd) was evaluated in CANDOR *[see Clinical Studies (12.3)]*. Patients received Kyprolis for a median duration of 58 weeks in the DKd arm and 40 weeks in the Kd arm.

Serious adverse reactions were reported in 56% of the patients in the DKd arm and 46% of the patients in the Kd arm. The most frequent serious adverse reactions reported in the DKd 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%) and 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 DKd arm compared with 5% of 153 patients in the Kd arm. The most frequent fatal adverse reaction (DKd versus Kd) was infection 4.5% *versus* 2.6%.

Permanent discontinuation due to an adverse reaction in patients who received Kyprolis occurred in 21% of patients in the DKd arm *versus* 22% in the Kd arm. The most frequent adverse reactions leading to discontinuation of Kyprolis were cardiac failure (1.9%) and fatigue (1.9%) in the DKd arm and cardiac failure (2.0%), hypertension (2.0%) and acute kidney injury (2.0%) in the Kd arm. Interruption of Kyprolis due to adverse reactions occurred in 71% of patients in

DKd arm *versus* 63% in the Kd arm. Dose reduction of Kyprolis due to adverse reactions occurred in 25% of patients in DKd arm *versus* 20% in the Kd arm.

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

Table 15 summarizes the adverse reactions in CANDOR.

Table 15: Adverse Reactions (≥ 15%) in Patients Who Received either DKd or Kd (20/56 mg/m^2 Regimen) in CANDOR

Adverse Reactions	Twice weekly DKd (N = 308)		Twice weekly Kd (N = 153)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General Disorders and Administration Site Conditions				
Infusion-related reaction[a]	41	12	28	5
Fatigue[b]	32	11	28	8
Pyrexia	20	1.9	15	0.7
Infections				
Respiratory tract infection[c]	40[g]	7	29	3.3
Pneumonia	18[g]	13	12	9
Bronchitis	17	2.6	12	1.3
Blood and Lymphatic System Disorders				
Thrombocytopenia[d]	37	25	30	16
Anemia[e]	33	17	31	14
Gastrointestinal Disorders				
Diarrhea	32	3.9	14	0.7
Nausea	18	0	13	0.7
Vascular Disorders				
Hypertension	31	18	28	13
Respiratory, Thoracic and Mediastinal Disorders				
Cough[f]	21	0	21	0
Dyspnea	20	3.9	22	2.6
Psychiatric Disorders				
Insomnia	18	3.9	11	2.0

Adverse Reactions	Twice weekly DKd (N = 308)		Twice weekly Kd (N = 153)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and Connective Tissue Disorders				
Back pain	16	1.9	10	1.3

DKd = Kyprolis, daratumumab, and dexamethasone; Kd = Kyprolis 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, rash, syncope, wheezing, eye pruritus, eyelid edema, renal failure, swelling face) related to infusion reactions which occurred within 1 day after DKd 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

EQUULEUS

The safety of Kyprolis 20/70 mg/m^2 once weekly in combination with intravenous daratumumab and dexamethasone (DKd) was evaluated in EQUULEUS *[see Clinical Studies (12.3)]*. Patients received Kyprolis 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 Kyprolis occurred in 19% of patients. The most frequent adverse reaction leading to discontinuation was asthenia (2%). Interruption of Kyprolis due to adverse reactions occurred in 77% of patients. Dose reduction of Kyprolis due to adverse reactions occurred in 31% of patients in DKd.

Infusion-related reactions that occurred following the first Kyprolis dose was 11%. Pulmonary hypertension adverse reactions were reported in 4.7% of patients in EQUULEUS.

Table 16 summarizes the adverse reactions in EQUULEUS.

Table 16: Adverse Reactions (≥ 15%) in Patients Who Received DKd (20/70 mg/m^2 Regimen) in EQUULEUS

Adverse Reactions	Once weekly DKd (N = 85)	
	All Grades (%)	Grade 3 or 4 (%)
Blood and Lymphatic System Disorders		
Thrombocytopenia[a]	68	32
Anemia[b]	52	21
Neutropenia[c]	31	21
Lymphopenia[d]	29	25
General Disorders and Administration Site Conditions		
Fatigue[e]	54	18
Infusion-related reaction[f]	53	12
Pyrexia	37	1.2
Infections		
Respiratory tract infection[g]	53	3.5
Bronchitis	19	0
Nasopharyngitis	18	0
Influenza	17	3.5
Gastrointestinal Disorders		
Nausea	42	1.2
Vomiting	40	1.2
Diarrhea	38	2.4
Constipation	17	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	35	3.5
Cough[h]	33	0
Vascular Disorders		
Hypertension	33	20
Psychiatric Disorders		
Insomnia	33	4.7
Nervous System Disorders		
Headache	27	1.2
Musculoskeletal and Connective Tissue Disorders		
Back pain	25	0

Adverse Reactions	Once weekly DKd (N = 85)	
	All Grades (%)	Grade 3 or 4 (%)
Pain in extremity	15	0

DKd = Kyprolis, daratumumab, and dexamethasone; Kd = Kyprolis 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, rash, syncope, wheezing, eye pruritus, eyelid edema, renal failure, swelling face) related to infusion reactions which occurred within 1 day after DKd 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

Kyprolis in Combination with Subcutaneous Daratumumab and Dexamethasone

The safety of Kyprolis in combination with subcutaneous daratumumab and dexamethasone was evaluated in PLEIADES *[see Clinical Studies (12.3)]*.

PLEIADES

The safety of Kyprolis in combination with subcutaneous daratumumab and dexamethasone (DKd) was evaluated in a single-arm cohort of PLEIADES. Patients received Kyprolis as a 30-minute IV infusion once weekly for three weeks (Days 1, 8, and 15), followed by a 13-day rest period (Days 16 to 28) and continued until disease progression or unacceptable toxicity (N=66) in combination with subcutaneous daratumumab and dexamethasone. Among these patients, 77% were exposed for 6 months or longer and 27% were exposed for greater than one year.

Serious adverse reactions occurred in 27% of patients who received Kyprolis in combination with subcutaneous daratumumab and dexamethasone. Fatal adverse reactions occurred in 3% of patients who received Kyprolis in combination with subcutaneous daratumumab and dexamethasone.

Permanent discontinuation of Kyprolis due to an adverse reaction occurred in 6% of patients who received Kyprolis.

Dosage interruptions due to an adverse reaction occurred in 46% of patients who received Kyprolis.

The most common adverse reactions (≥ 20%) were upper respiratory tract infection, fatigue, insomnia, hypertension, diarrhea, cough, dyspnea, headache, pyrexia, nausea and edema peripheral.

Table 17 summarizes the adverse reactions in patients who received Kyprolis with subcutaneous daratumumab and dexamethasone (DKd) in PLEIADES.

Table 17: Adverse Reactions (≥ 10%) in Patients Who Received Kyprolis with Subcutaneous Daratumumab and Dexamethasone (DKd) in PLEIADES

	DKd (N=66)	
Adverse Reaction	**All Grades (%)**	**Grade ≥3 (%)**
Infections and infestations		
Upper respiratory tract infection[a]	52	0
Bronchitis[b]	12	2[#]
General disorders and administration site conditions		

Fatigue[c]	39	2[#]
Pyrexia	21	2[#]
Edema peripheral[d]	20	0
Psychiatric disorders		
Insomnia	33	6[#]
Vascular disorders		
Hypertension[e]	32	21[#]
Gastrointestinal disorders		
Diarrhea	29	0
Nausea	21	0
Vomiting	15	0
Respiratory, thoracic and mediastinal disorders		
Cough[f]	24	0
Dyspnea[g]	23	2[#]
Nervous system disorders		
Headache	23	0
Peripheral sensory neuropathy	11	0
Musculoskeletal and connective tissue disorders		
Back pain	17	2[#]
Musculoskeletal chest pain	11	0

[a] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, viral pharyngitis, and viral upper respiratory tract infection.

[b] Bronchitis includes bronchitis, and bronchitis viral.

[c] Fatigue includes asthenia, and fatigue.

[d] Edema peripheral includes generalized edema, edema peripheral, and peripheral swelling.

[e] Hypertension includes blood pressure increased, and hypertension.

[f] Cough includes cough, and productive cough.

[g] Dyspnea includes dyspnea, and dyspnea exertional.

[#] Only Grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in < 10% of patients who received Kyprolis with subcutaneous daratumumab and dexamethasone include:

- **Gastrointestinal disorders:** abdominal pain, constipation, pancreatitis
- **Infection and infestations:** pneumonia, influenza, urinary tract infection, herpes zoster, sepsis
- **Metabolism and nutrition disorders:** hyperglycemia, decreased appetite, hypocalcemia
- **Musculoskeletal and connective tissue disorders:** muscle spasms, arthralgia

- **Nervous system disorders:** paresthesia, dizziness, syncope
- **General disorders and administration site conditions:** injection site reaction, infusion reactions, chills
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Cardiac disorders:** cardiac failure
- **Vascular disorders:** hypotension

Table 18 summarizes the laboratory abnormalities in patients who received Kyprolis with subcutaneous daratumumab and dexamethasone in PLEIADES.

Table 18: Select Laboratory Abnormalities (≥ 30%) Worsening from Baseline in Patients Who Received DKd in PLEIADES

Laboratory Abnormality	DKd[a]	
	All Grades (%)	Grades 3-4 (%)
Decreased platelets	88	18
Decreased lymphocytes	83	50
Decreased leukocytes	68	18
Decreased neutrophils	55	15
Decreased hemoglobin	47	6
Decreased corrected calcium	45	2
Increased alanine aminotransferase (ALT)	35	5

[a] Denominator is based on the safety population treated with DKd (N=66).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Kyprolis. 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: hemolytic uremic syndrome (HUS), hepatitis B virus reactivation, gastrointestinal perforation, pericarditis, and cytomegalovirus infection including chorioretinitis, pneumonitis, enterocolitis, viremia, intestinal obstruction, and acute pancreatitis.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

Kyprolis can cause fetal harm based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (10.1)]*. There are no available data on Kyprolis use in pregnant women to evaluate for drug-associated risks. Kyprolis caused embryo-fetal lethality in rabbits at doses lower than the clinical dose *(see Data)*. Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Data

Animal Data

Carfilzomib 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. 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.

7.2 Lactation

Risk Summary

There are no data on the presence of Kyprolis in human milk, the effects on the breastfed child, or the effects of the drug on milk production. Because of the potential for serious adverse

reactions in the breastfed child, advise women not to breastfeed during treatment with Kyprolis and for 2 weeks after treatment.

7.3 Females and Males of Reproductive Potential

Based on its mechanism of action and findings in animals, Kyprolis can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (7.1)]*.

Pregnancy Testing

Conduct pregnancy testing on females of reproductive potential prior to initiating Kyprolis treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Kyprolis and for 6 months following the last dose.

Males

Advise males with female sexual partners of reproductive potential to use effective contraception during treatment with Kyprolis and for 3 months following the last dose.

Infertility

Based on the mechanism of action, Kyprolis may have an effect on either male or female fertility *[see Clinical Pharmacology (10.1), Nonclinical Toxicology (11.1)]*. There are no data on the effect of Kyprolis on human fertility.

7.4 Pediatric Use

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

7.5 Geriatric Use

Of the 2,387 patients in clinical studies of Kyprolis, 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 in CANDOR who received DKd, 47% of patients were 65 years and older, while

9% were 75 years and older. Fatal adverse reactions in the DKd arm of CANDOR 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 *[see Adverse Reactions (6.1)]*. No overall differences in effectiveness were observed between older and younger patients.

7.6 Hepatic Impairment

Reduce the dose of Kyprolis by 25% in 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. A recommended dosage of Kyprolis has not been established for patients with severe hepatic impairment (total bilirubin > 3 × ULN and any AST) *[see Dosage and Administration (2.4), Clinical Pharmacology (10.3)]*.

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%) *[see Warnings and Precautions (5.12), Clinical Pharmacology (10.3)]*.

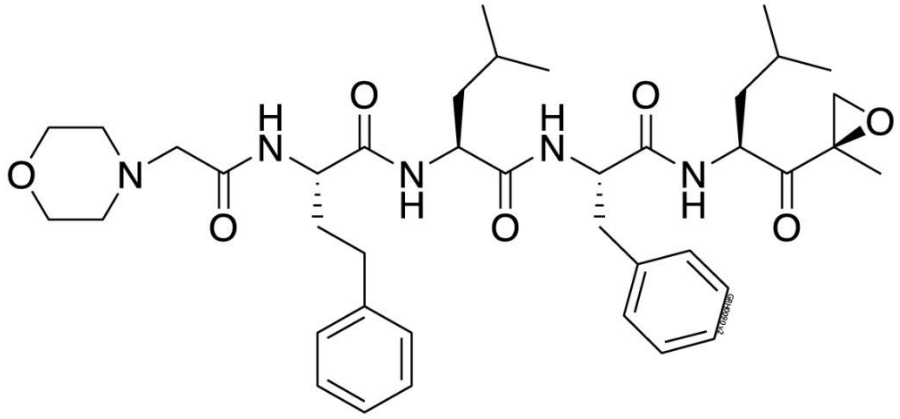
8 OVERDOSAGE

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

There is no known specific antidote for Kyprolis overdosage. In the event of overdose, monitor patients for adverse reactions and provide supportive care as appropriate.

9 DESCRIPTION

Carfilzomib is a proteasome inhibitor. The chemical name for carfilzomib is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. Carfilzomib has the following structure:



Carfilzomib is a crystalline substance with a molecular weight of 719.9. The molecular formula is $C_{40}H_{57}N_5O_7$. Carfilzomib is practically insoluble in water and very slightly soluble in acidic conditions.

Kyprolis for injection, for intravenous use is a sterile, white to off-white lyophilized powder in a single-dose vial. Each 30 mg vial contains 30 mg of carfilzomib, 1500 mg sulfobutylether beta-cyclodextrin sodium, and 28.8 mg anhydrous citric acid and sodium hydroxide for pH adjustment (target pH 3.5). Each 60 mg vial contains 60 mg of carfilzomib, 3000 mg sulfobutylether beta-cyclodextrin sodium, 57.7 mg citric acid, and sodium hydroxide for pH adjustment (target pH 3.5).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib had antiproliferative and proapoptotic activities *in vitro* in solid and hematologic tumor cells. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth in models of multiple myeloma, hematologic, and solid tumors.

10.2 Pharmacodynamics

Intravenous carfilzomib administration resulted in suppression of proteasome chymotrypsin-like (CT-L) activity when measured in blood 1 hour after the first dose. Doses of carfilzomib

≥ 15 mg/m^2 with or without lenalidomide and dexamethasone induced a ≥ 80% inhibition of the CT-L activity of the proteasome. In addition, carfilzomib, 20 mg/m^2 intravenously as a single agent, resulted in a mean inhibition of the low molecular mass polypeptide 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) subunits of the proteasome ranging from 26% to 32% and 41% to 49%, respectively. Proteasome inhibition was maintained for ≥ 48 hours following the first dose of carfilzomib for each week of dosing.

10.3 Pharmacokinetics

Carfilzomib 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 carfilzomib 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 carfilzomib accumulation following repeated administration of carfilzomib 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 19 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 19: Carfilzomib 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 carfilzomib was 28 L. Carfilzomib is 97% bound to human plasma proteins over the concentration range of 0.4 to 4 micromolar *in vitro*.

Elimination

Carfilzomib has a half-life of ≤ 1 hour on Day 1 of Cycle 1 following intravenous doses ≥ 15 mg/m^2. The half-life was similar when administered either as a 30-minute infusion or a 2- to 10-minute infusion. The systemic clearance ranged from 151 to 263 L/hour.

Metabolism

Carfilzomib is rapidly metabolized. Peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450 (CYP)-mediated mechanisms contribute a minor role in overall carfilzomib metabolism.

Excretion

Approximately 25% of the administered dose of carfilzomib was excreted in urine as metabolites in 24 hours. Urinary and fecal excretion of the parent compound was negligible (0.3% of total dose).

Specific Populations

Age (35-89 years), sex, race or ethnicity (80% White, 11% Black, 6% Asians, 3% Hispanics), and mild to severe renal impairment (creatinine clearance 15-89 mL/min) did not have clinically meaningful effects on the pharmacokinetics of carfilzomib.

Patients with Hepatic Impairment

Compared to patients with normal hepatic function, patients with mild (total bilirubin > 1 to 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN) and moderate (total bilirubin > 1.5 to 3 × ULN and any AST) 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).

Patients with Renal Impairment

Relative to patients with normal renal function, ESRD patients on hemodialysis showed 33% higher carfilzomib AUC. Since hemodialysis clearance of Kyprolis concentrations has not been studied, the drug should be administered after the hemodialysis procedure.

Drug Interaction Studies

Clinical Studies

Effect of Carfilzomib on Sensitive CYP3A Substrate: Midazolam (a sensitive CYP3A substrate) pharmacokinetics was not affected by concomitant administration of carfilzomib.

In Vitro Studies

Effect of Carfilzomib on Cytochrome P450 (CYP) Enzymes: Carfilzomib showed direct and time-dependent inhibition of CYP3A but did not induce CYP1A2 and CYP3A4 *in vitro*.

Effect of Transporters on Carfilzomib: Carfilzomib is a P-glycoprotein (P-gp) substrate *in vitro*.

Effect of Carfilzomib on Transporters: Carfilzomib inhibits P-gp *in vitro*. However, given that Kyprolis is administered intravenously and is extensively metabolized, the pharmacokinetics of Kyprolis is unlikely to be affected by P-gp inhibitors or inducers.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with carfilzomib.

Carfilzomib was clastogenic in the *in vitro* chromosomal aberration test in peripheral blood lymphocytes. Carfilzomib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) test and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay.

Fertility studies with carfilzomib have not been conducted. No effects on reproductive tissues were noted during 28-day repeat-dose rat and monkey toxicity studies or in 6-month rat and 9-month monkey chronic toxicity studies.

11.2 Animal Toxicology and/or Pharmacology

Cardiovascular Toxicity

Monkeys administered a single bolus intravenous dose of carfilzomib 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 carfilzomib 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.

12 CLINICAL STUDIES

12.1 In Combination with Lenalidomide and Dexamethasone for Relapsed or Refractory Multiple Myeloma

ASPIRE (NCT01080391)

ASPIRE was a randomized, open-label, multicenter trial which evaluated the combination of Kyprolis 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, Kyprolis 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. Kyprolis 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. Kyprolis 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. Kyprolis 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 ASPIRE were randomized 1:1 to the KRd or Rd arm. The demographics and baseline characteristics were well-balanced between the two arms (see Table 20). 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 20: Demographics and Baseline Characteristics in ASPIRE

Characteristics	KRd (N = 396)	Rd (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)

Characteristics	KRd (N = 396)	Rd (N = 396)
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)
Creatinine Clearance 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; IgG = immunoglobulin G; ISS = International Staging System; KRd = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone.
[a] Including 2 patients with 4 prior regimens.

Patients in the KRd arm demonstrated improved 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 21 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 21 and Figure 2).

Table 21: Efficacy Outcomes in ASPIRE[a]

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

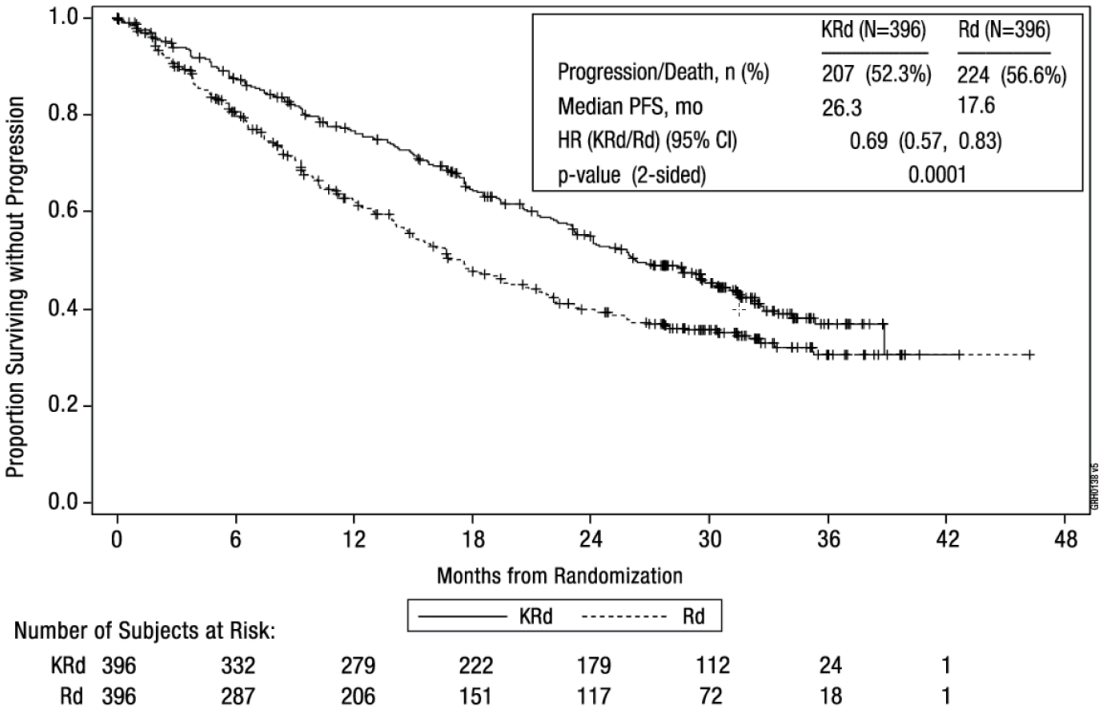
[e] The P-value was derived using stratified log-rank test.

[f] Exact confidence interval.

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

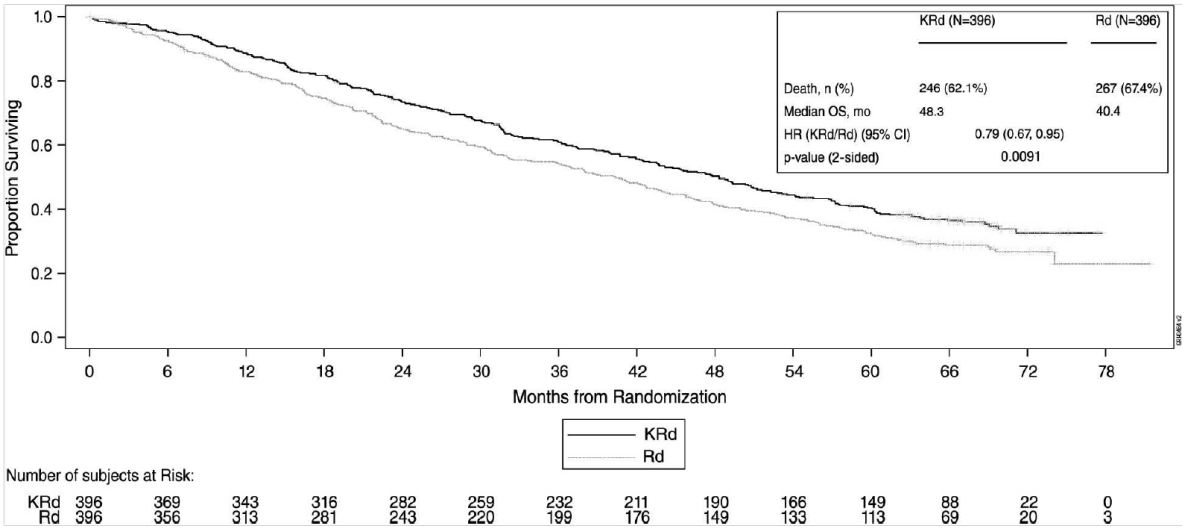
The median duration of response (DOR) was 28.6 months (95% CI: 24.9, 31.3) for the 345 patients achieving a response in the KRd arm and 21.2 months (95% CI: 16.7, 25.8) for the 264 patients achieving a response in the Rd arm. The median time to response was 1 month (range 1 to 14 months) in the KRd arm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

Figure 1: Kaplan-Meier Curve of Progression-Free Survival in ASPIRE



CI = confidence interval; EBMT = European Blood and Marrow Transplantation; HR = hazard ratio; IMWG = International Myeloma Working Group; KRd = Kyprolis, 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 ASPIRE



CI = confidence interval; HR = hazard ratio; KRd = Kyprolis, lenalidomide, and dexamethasone; mo = months; OS = overall survival; Rd = lenalidomide and dexamethasone arm.

12.2 In Combination with Dexamethasone for Relapsed or Refractory Multiple Myeloma

The efficacy of Kyprolis in combination with dexamethasone was evaluated in two open-label randomized trials (ENDEAVOR and A.R.R.O.W.).

ENDEAVOR (NCT01568866)

ENDEAVOR was a randomized, open-label, multicenter trial of Kyprolis and dexamethasone (Kd) *versus* bortezomib and 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 Kyprolis at a starting dose of 20 mg/m^2, which was increased to 56 mg/m^2 on Cycle 1, Day 8 onward. Kyprolis 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 22.

Table 22: Demographics and Baseline Characteristics in ENDEAVOR

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

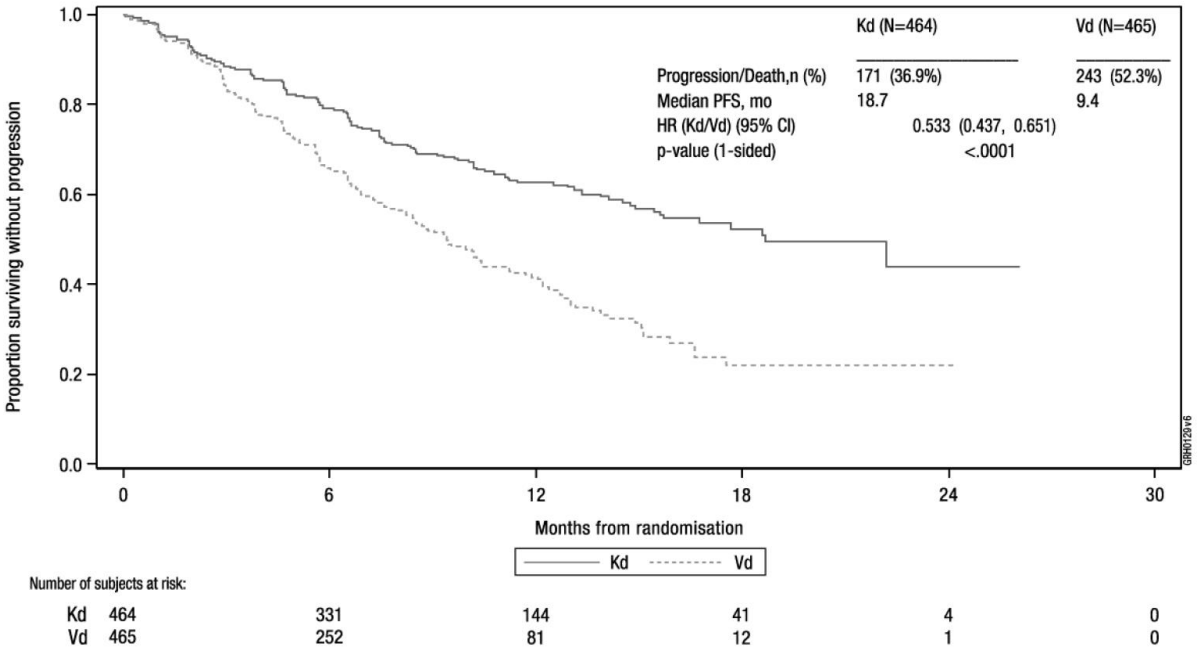
Characteristics	Kd (N = 464)	Vd (N = 465)
Number of Prior Regimens, n (%)		
1	232 (50)	231 (50)
2	158 (34)	144 (31)
3	74 (16)	88 (19)
4	0 (0)	2 (0.4)
Prior Therapies, n (%)	464 (100)	465 (100)
Bortezomib	250 (54)	252 (54)
Transplant for Multiple Myeloma	266 (57)	272 (59)
Thalidomide	212 (46)	249 (54)
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 = Kyprolis and 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 Kyprolis 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 23 and Figure 3).

Figure 3: Kaplan-Meier Plot of Progression-Free Survival in ENDEAVOR



CI = confidence interval; HR = hazard ratio; Kd = Kyprolis and dexamethasone; mo = months; 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). Results are provided in Table 23 and Figure 4.

Table 23: Summary of Key Results in ENDEAVOR
(Intent-to-Treat Population)[a]

	Kd (N = 464)	**Vd (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)
HR (Kd/Vd) (95% CI)[d]	0.53 (0.44, 0.65)	
P-value (1-sided)[e]	< 0.0001	

	Kd (N = 464)	Vd (N = 465)
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)
HR (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; HR= hazard ratio; Kd = Kyprolis and dexamethasone; ORR = overall response rate; PFS = progression-free survival; PR = partial response; sCR = stringent CR; Vd = bortezomib and dexamethasone; VGPR = very good partial response; NE = non-estimable.

[a] Eligible patients had 1–3 prior lines of therapy.

[b] PFS and ORR were determined by an Independent Review Committee.

[c] Based on Kaplan-Meier estimates.

[d] Based on a stratified Cox's model.

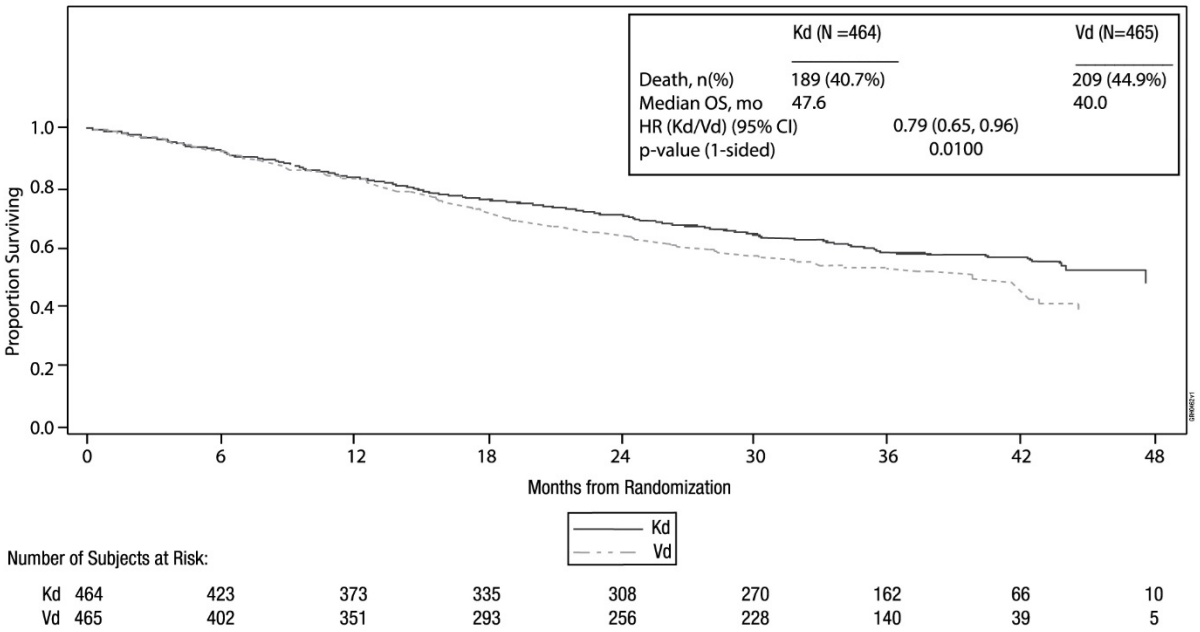
[e] P-value was derived using a stratified log-rank test.

[f] Exact confidence interval.

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

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

Figure 4: Kaplan-Meier Plot of Overall Survival in ENDEAVOR



CI = confidence interval; HR = hazard ratio; Kd = Kyprolis 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.

A.R.R.O.W. (NCT02412878)

A.R.R.O.W. was a randomized, open-label, multicenter superiority trial of Kyprolis 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 Kyprolis 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 Kyprolis 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 Kyprolis 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 Kyprolis 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 24.

Table 24: Demographics and Baseline Characteristics in A.R.R.O.W.

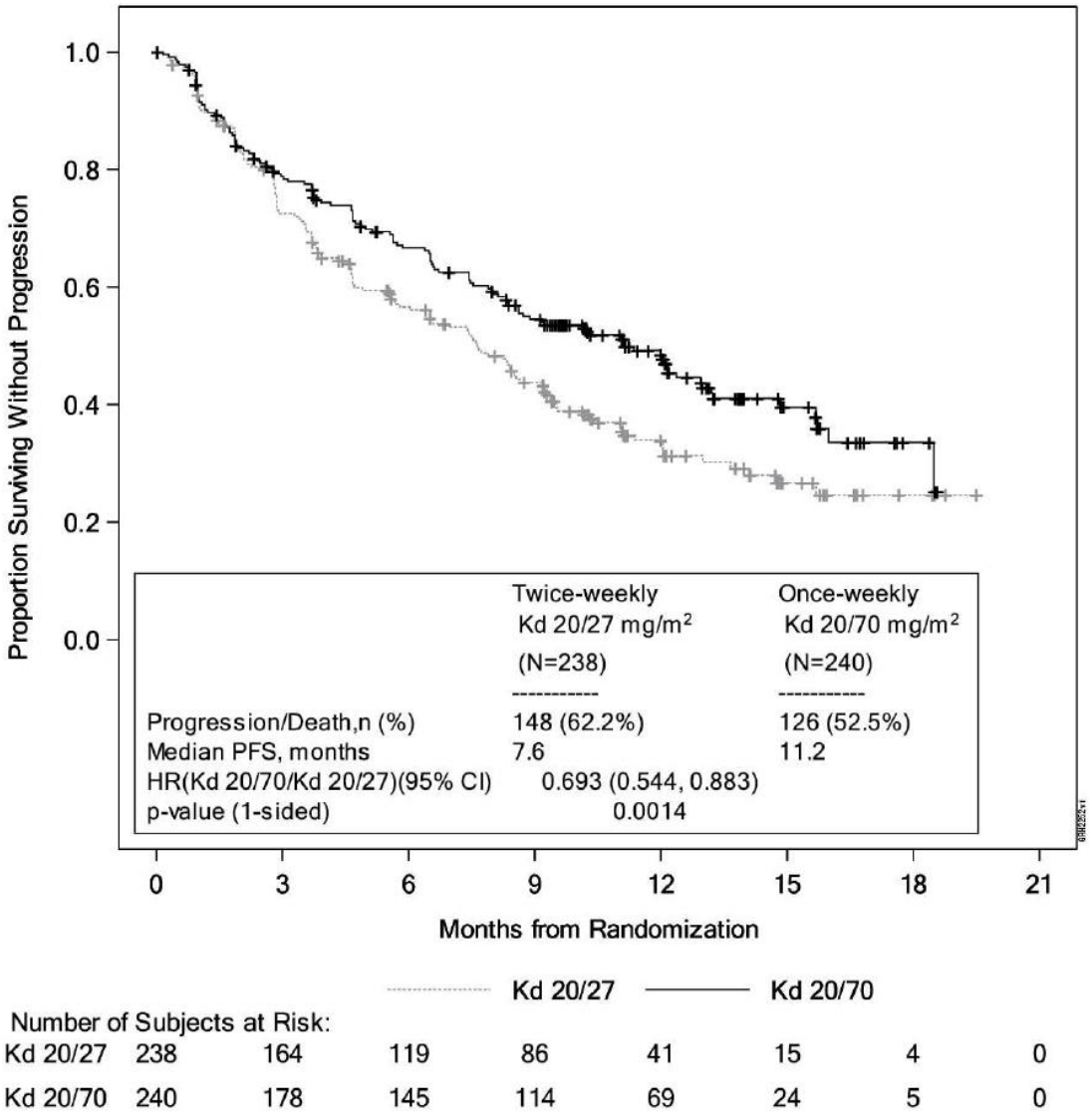
Characteristics	Once weekly Kd 20/70 mg/m^2 (N = 240)	Twice weekly Kd 20/27 mg/m^2 (N = 238)
Age, Years		
Median (min, max)	66 (39, 85)	66 (35, 83)
< 65, n (%)	104 (43)	104 (44)
65–74, n (%)	90 (38)	102 (43)
≥ 75, n (%)	46 (19)	32 (13)
Sex, n (%)		
Female	108 (45)	110 (46)
Male	132 (55)	128 (54)
Race, 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)

Characteristics	Once weekly Kd 20/70 mg/m^2 (N = 240)	Twice weekly Kd 20/27 mg/m^2 (N = 238)
< 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)
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 = Kyprolis and dexamethasone

The efficacy of Kyprolis was evaluated by PFS using IMWG response criteria. Efficacy results are provided in Table 25 and Figure 5.

Figure 5: Kaplan-Meier Plot of Progression-Free Survival in A.R.R.O.W.



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

Table 25: Summary of Key Results in A.R.R.O.W. (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	
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 = Kyprolis 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.

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

12.3 In Combination with Daratumumab and Dexamethasone for Relapsed or Refractory Multiple Myeloma

The efficacy of Kyprolis in combination with daratumumab and dexamethasone (DKd) was evaluated in three open-label clinical trials (CANDOR, EQUULEUS, and PLEIADES).

CANDOR (NCT03158688)

CANDOR was a randomized, open-label, multicenter trial which evaluated the combination of Kyprolis 20/56 mg/m^2 twice weekly with intravenous daratumumab and dexamethasone (DKd) *versus* Kyprolis 20/56 mg/m^2 twice weekly and dexamethasone (Kd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 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, 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).

Kyprolis 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 DKd 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 Kyprolis 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 DKd arm and 154 to the Kd arm. The demographics and baseline characteristics are summarized in Table 26.

Table 26: Demographics and Baseline Characteristics in CANDOR

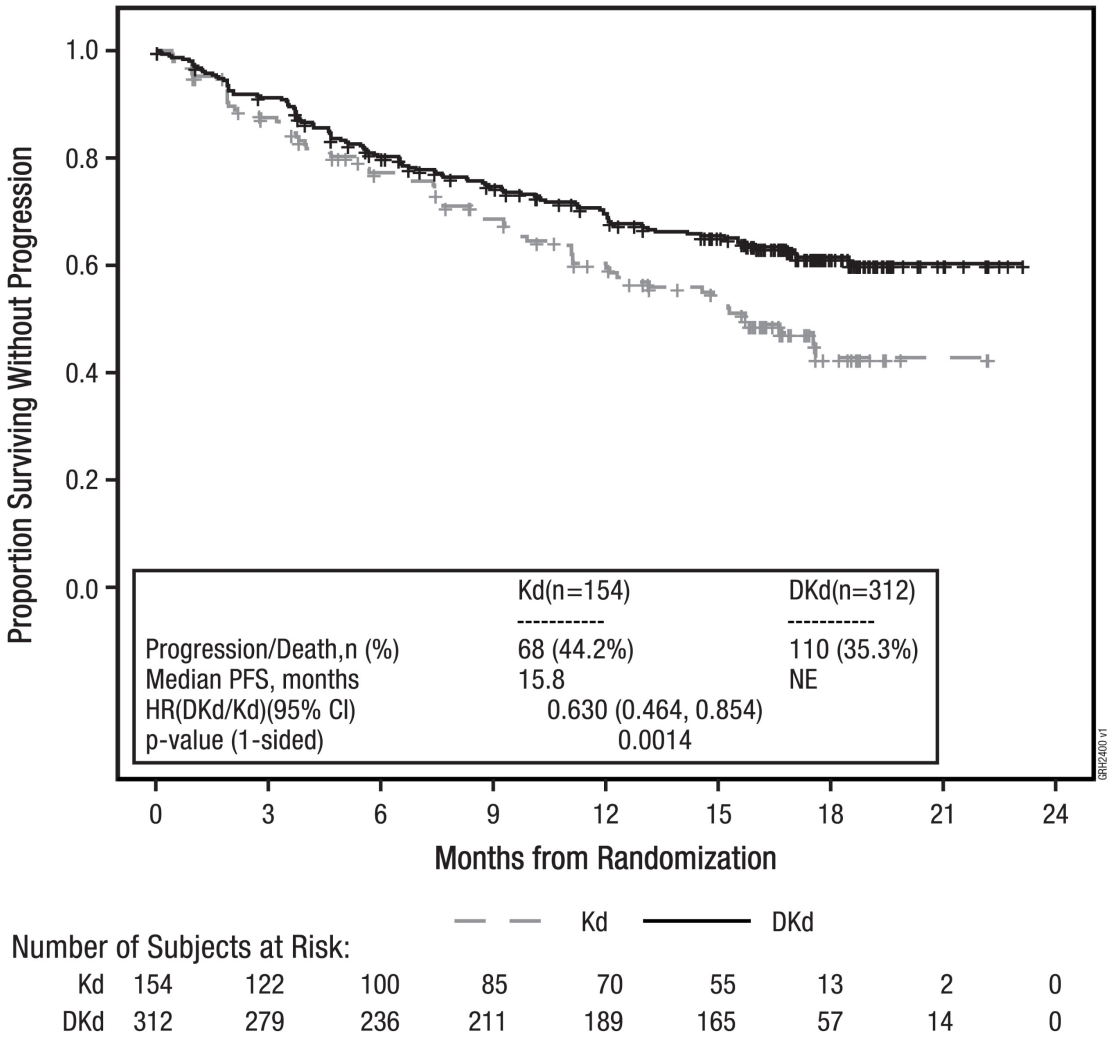
Characteristics	DKd (N = 312)	Kd (N = 154)
Age at randomization (years)		
Median (min, max)	64 (29, 84)	65 (35, 83)
Age group – n (%)		
18 – 64 years	163 (52)	77 (50)
65 – 74 years	121 (39)	55 (36)
75 years and older	28 (9)	22 (14)

Characteristics	DKd (N = 312)	Kd (N = 154)
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)
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)

DKd = Kyprolis, daratumumab, and dexamethasone; ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence *in situ* hybridization; ISS = International Staging System; Kd = Kyprolis and dexamethasone
*Subjects with number of prior regimens > 3 was 0 in the DKd 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 27 and Figure 6. The median duration of response has not been reached for the DKd 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 DKd arm and 1.0 (1, 10) months for the Kd arm.

Figure 6: Kaplan-Meier Plot of Progression-Free Survival in CANDOR



CI = confidence interval; DKd = Kyprolis, daratumumab and dexamethasone; HR = hazard ratio; Kd= Kyprolis and dexamethasone

Table 27: Summary of Key Results in CANDOR (Intent-to-Treat Population)

	DKd (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	
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 months 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; DKd = Kyprolis, daratumumab, and dexamethasone; Kd = Kyprolis 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

EQUULEUS (NCT01998971)

EQUULEUS was an open-label, multi-cohort trial which evaluated the combination of Kyprolis with intravenous daratumumab and dexamethasone in patients with relapsed or refractory multiple myeloma who had received 1 to 3 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).

Kyprolis 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 EQUULEUS trial enrolled 85 patients. The demographics and baseline characteristics are summarized in Table 28.

Table 28: Demographics and Baseline Characteristics in DKd 20/70 mg/m^2 Regimen of EQUULEUS (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)

Characteristics	Number of Patients (%)
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)
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; PI = proteasome inhibitor; IMiD = immunomodulatory agent.

Efficacy results were based on overall response rate using IMWG criteria. Efficacy results are provided in Table 29. 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 29: Summary of Key Results in EQUULEUS

(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

PLEIADES (NCT03412565)

The efficacy of Kyprolis with subcutaneous daratumumab plus dexamethasone (DKd) was evaluated in a single-arm cohort of PLEIADES, a multi-cohort, open-label trial.

This cohort enrolled patients with relapsed or refractory multiple myeloma excluding patients with left ventricular ejection fraction (LVEF) less than 40%, myocardial infarction within 6 months, uncontrolled cardiac arrhythmia, or uncontrolled hypertension (systolic blood pressure > 159 mmHg or diastolic > 99 mmHg despite optimal treatment). Patients received Kyprolis administered by IV infusion at a dose of 20 mg/m^2 on Cycle 1 Day 1 and if a dose of 20 mg/m^2 was tolerated Kyprolis was administered at a dose of 70 mg/m^2 as a 30-minute IV infusion on Cycle 1 Day 8 and Day 15, and then Day 1, 8 and 15 of each cycle; daratumumab 1,800 mg administered subcutaneously once weekly from Weeks 1 to 8, once every 2 weeks from Weeks 9 to 24 and once every 4 weeks starting with Week 25 until disease progression or unacceptable toxicity; and dexamethasone 40 mg per week (or a reduced dose of 20 mg per week for patients ≥ 75 years or BMI < 18.5). The major efficacy outcome measure was ORR.

A total of 66 patients received the DKd regimen. The median age was 61 years (range: 42, 84); 52% were male; 73% were White and 3% Black or African American; and 68% had ISS Stage I,

18% had ISS Stage II, and 14% had ISS Stage III disease. A total of 79% of patients had a prior ASCT; 91% of patients received a prior PI. All patients received 1 prior line of therapy with exposure to lenalidomide and 62% of patients were refractory to lenalidomide.

Efficacy results are summarized in Table 30. At a median follow-up of 9.2 months, the median duration of response had not been reached and an estimated 85.2% (95% CI: 72.5, 92.3) maintained response for at least 6 months and 82.5% (95% CI: 68.9, 90.6) maintained response for at least 9 months.

Table 30: Efficacy Results from PLEIADES in Patients Who Received DKd

	DKd (N = 66)
Overall response rate (sCR+CR+VGPR+PR), n (%)[a]	56 (84.8%)
95% CI (%)[24]	(73.9%, 92.5%)
Stringent complete response (sCR)	11 (16.7%)
Complete response (CR)	14 (21.2%)
Very good partial response (VGPR)	26 (39.4%)
Partial response (PR)	5 (7.6%)

CI = confidence interval

Kyprolis monotherapy in patients with relapsed and refractory multiple myeloma

Additional clinical experience has been generated with Kyprolis monotherapy in patients with relapsed and refractory multiple myeloma. Study PX-171-011 was an open-label randomized phase 3 study (N = 315; exposure to ≥ 3 prior therapies required). Patients enrolled to study PX-171-011 were more heavily pre-treated with lower organ and marrow function as compared to those enrolled in Study 1. PX-171-011 evaluated Kyprolis monotherapy *versus* a control arm (corticosteroids and cyclophosphamide). The study did not meet its primary efficacy endpoint of demonstrating superiority of Kyprolis monotherapy over the active control arm in overall survival (HR = 0.975 [95% CI: 0.760–1.249]). PX-171-003A1 was a single-arm phase 2 study (N = 266; exposure to ≥ 2 prior therapies required), which met its primary efficacy endpoint of IRC-assessed ORR (22.9%).

13 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Kyprolis (carfilzomib) is supplied as:

- An individually packaged single-dose vial containing 30 mg of carfilzomib as a white to off-white lyophilized cake or powder.
- An individually packaged single-dose vial containing 60 mg of carfilzomib as a white to off-white lyophilized cake or powder.

(Not all product strengths may be available)

Storage and Handling

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

14 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to treatment with Kyprolis:

Cardiac Toxicities: Advise patients of the risks and symptoms of cardiac failure and ischemia *[see Warnings and Precautions (5.1)]*.

Dehydration: Counsel patients to avoid dehydration, since patients receiving Kyprolis therapy may experience vomiting and/or diarrhea. Instruct patients to seek medical advice if they experience symptoms of dehydration *[see Warnings and Precautions (5.3)]*.

Respiratory: Advise patients that they may experience cough or shortness of breath (dyspnea) during treatment with Kyprolis. This most commonly occurs within a day of dosing. Advise patients to contact their healthcare provider if they experience shortness of breath *[see Warnings and Precautions (5.6)]*.

Venous Thrombosis: Inform patients of the risk of venous thromboembolism and discuss the options for prophylaxis. Advise patients to seek immediate medical attention for symptoms of venous thrombosis or embolism *[see Warnings and Precautions (5.8)]*.

Infusion-Related Reactions: Advise patients of the risk of infusion-related reactions and discuss the common signs and symptoms of infusion-related reactions with the patients *[see Warnings and Precautions (5.9)]*.

Bleeding: Inform patients that they may bruise or bleed more easily or that it may take longer to stop bleeding and to report to their healthcare provider any prolonged, unusual or excessive bleeding. Instruct patients on the signs of occult bleeding *[see Warnings and Precautions (5.10)]*.

Hepatic: Inform patients of the risk of developing hepatic failure. Advise patients to contact their healthcare provider for symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes *[see Warnings and Precautions (5.12)]*.

Other: Inform patients to contact their healthcare provider if they experience neurologic symptoms such as headaches, confusion, dizziness or loss of balance, difficulty talking or walking, decreased strength or weakness on one side of the body, seizures, or visual loss *[see Warnings and Precautions (5) and Adverse Reactions (6)]*.

Driving/Operating Machines: Advise patients that Kyprolis may cause fatigue, dizziness, fainting, and/or drop in blood pressure. Advise patients not to drive or operate machinery if they experience any of these symptoms *[see Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity: Advise females of the potential risk to the fetus. Advise females of reproductive potential to inform their healthcare provider immediately of a known or suspected pregnancy. Advise female patients to use effective contraceptive during treatment with Kyprolis and for 6 months following the last dose. Advise male patients with female sexual partners of reproductive potential to use effective contraception during treatment with Kyprolis and for 3 months following the last dose *[see Warnings and Precautions (5.17), Use in Specific Populations (7.1, 7.3)]*.

Lactation: Advise patients to avoid breastfeeding while receiving Kyprolis and for 2 weeks after the last dose *[see Use in Specific Populations (7.2)]*.

Concomitant Medications: Advise patients to discuss with their healthcare provider any medication they are currently taking prior to starting treatment with Kyprolis, or prior to starting any new medication(s) during treatment with Kyprolis.

Kyprolis® (carfilzomib)

Product owner:

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