Announcement regarding harshment (safety information) in the Physician Leaflet

הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך: 06.12.2016

Name of the product:

שם תכשיר באנגלית: Kyprolis

Registration No's:

מספר רישום: 151-21-33948-00

Name of the registration owner:

שם בעל הרישום Amgen Europe B.V.

1. INDICATIONS AND USAGE **Kyprolis is a proteasome inhibitor that is indicated:** • in combination with lenalidomide plus dexamethasone for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy. • as a single agent for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.	**1. INDICATIONS AND USAGE** **Kyprolis (carfilzomib) is ~~a proteasome inhibitor that is~~ indicated:** • in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy [*see Clinical Studies (14.1)*]. • as a single agent for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.
2. DOSAGE AND ADMINISTRATION […] • **Premedications** - Premedicate with dexamethasone 4 mg for monotherapy or the recommended dexamethasone dose if on combination therapy [*see Dosage and Administration (2.2)*] 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 reactions [*see Warnings and Precautions (5.5)*]. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles. • **Administration** - Infuse over 10 minutes. Do not administer as a bolus. Flush the intravenous administration line with normal saline or 5% dextrose injection, USP immediately before and after Kyprolis administration. Do not mix Kyprolis with or administer as an infusion with other medicinal products.	**2. DOSAGE AND ADMINISTRATION** **[…]** • **Premedications** - Premedicate with dexamethasone 4 mg for monotherapy or the recommended dexamethasone dose if on 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 reactions [*see Warnings and Precautions (5.9)*]. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles. • **Administration** - Infuse over 10 or 30 minutes depending on the Kyprolis dose regimen [*see Dosage and Administration (2.2)*]. Do not administer as a bolus. Flush the intravenous administration line with normal saline or 5% dextrose injection, USP immediately before and after Kyprolis administration. Do not mix Kyprolis with or administer

• **Dose Calculation** - Calculate the Kyprolis dose [*see Dosage and Administration (2.2)*] using the patient's actual body surface area at baseline. Patients with a body surface area greater than 2.2 m^2 should receive a dose based upon a body surface area of 2.2 m^2. • **Thromboprophylaxis** - Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis, lenalidomide, and dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks [*see Warnings and Precautions (5.8)*].	as an infusion with other medicinal products. • **Dose Calculation** - Calculate the Kyprolis dose [*see Dosage and Administration (2.2)*] using the patient's actual body surface area at baseline. In patients with a body surface area greater than 2.2 m^2, calculate the dose based upon a body surface area of 2.2 m^2. • **Thromboprophylaxis** - Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks [*see Warnings and Precautions (5.8)*]. • **[**…] • **Patients on Hemodialysis** - Administer Kyprolis after the hemodialysis procedure.
2.2 Recommended Dosing Kyprolis in Combination with Lenalidomide and Dexamethasone	**2.2 Recommended Dosing** Kyprolis in Combination with Lenalidomide and Dexamethasone For the combination regimen with lenalidomide and dexamethasone, administer Kyprolis intravenously as a 10-minute infusion on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 1 **[…]** **Table 1: Kyprolis (10-Minute Infusion) in Combination with Lenalidomide and Dexamethasone** **[…]** Kyprolis in Combination with Dexamethasone For the combination regimen with dexamethasone, administer Kyprolis intravenously as a 30-minute infusion on two consecutive days, each week

For the combination regimen, administer Kyprolis intravenously as a 10 minute infusion on two consecutive days, each week for three weeks followed by a 12 day rest period as shown in Table 1.
[…]

Table 1: Kyprolis in Combination with Lenalidomide and Dexamethasone

[…]

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

Table 2: Kyprolis (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	-

Treatment may be continued until disease progression or unacceptable toxicity occurs [*see Dosage and Administration (2.3)*]. Refer to the dexamethasone Prescribing Information for other concomitant medications.

2.3 Dose Modifications Based on Toxicities

[…]

Dose level reductions are presented in Table 5.

[…]

Table 5: Dose Level Reductions for Kyprolis

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

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

2.5 Dosing in Patients with End Stage Renal Disease

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

2.6 Reconstitution and Preparation for Intravenous Administration

[…]

2.3 Dose Modifications Based on Toxicities

[…]

	3. Use a 21-gauge or larger gauge needle (0.8 mm or smaller external diameter needle) to aseptically reconstitute each vial by slowly injecting **29 mL** Sterile Water for Injection, USP, through the stopper and directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming **[…]** 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. **[…]** 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 [*see Dosage and Administration (2)*] from the vial and dilute into **50 mL** intravenous bag containing 5% Dextrose Injection, USP (based on the calculated total dose and infusion time). **[…]** **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), restrictive 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 a randomized, open-label, multicenter trial evaluating Kyprolis in combination with lenalidomide and dexamethasone (KRd) *versus* lenalidomide/dexamethasone (Rd), the incidence of cardiac

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), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of Kyprolis. In clinical studies with Kyprolis, these events typically occurred early in the course of Kyprolis therapy (< 5 cycles). Death due to cardiac arrest has occurred within a day of Kyprolis administration. **[…]**	failure events was 6% in the KRd arm *versus* 4% in the Rd arm. In a randomized, open-label, multicenter trial of Kyprolis plus dexamethasone (Kd) *versus* bortezomib plus dexamethasone (Vd), the incidence of cardiac failure events was 8% in the Kd arm *versus* 3% in the Vd arm. […] **5.7 Hypertension** Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with KRd *versus* Rd, the incidence of hypertension events was 16% in the KRd arm *versus* 8% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of hypertension events was 26% in the Kd arm *versus* 10% in the Vd arm. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold Kyprolis and evaluate. Consider whether to restart Kyprolis based on a benefit/risk assessment [*see Dosage and Administration (2)*]. In patients ≥ 75 years of age, the risk of cardiac failure is increased compared to patients < 75 years of age. […] **5.2 Acute Renal Failure** Cases of acute renal failure have occurred in patients receiving Kyprolis. Renal insufficiency adverse events (~~renal impairment, acute renal failure~~, including renal failure) have occurred in approximately 10% of patients treated with Kyprolis. […] **5.7 Hypertension**

5.7 Hypertension Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold Kyprolis and evaluate. Consider whether to restart Kyprolis based on a benefit/risk assessment [*see Dosage and Administration (2)*].	Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with KRd *versus* Rd, the incidence of hypertension events was 16% in the KRd arm *versus* 8% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of hypertension events was 26% in the Kd arm *versus* 10% in the Vd arm. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold Kyprolis and evaluate. Consider whether to restart Kyprolis based on a benefit/risk assessment [*see Dosage and Administration (2)*].
	5.8 Venous Thrombosis Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating KRd *versus* Rd (with thromboprophylaxis used in both arms), the incidence of venous thromboembolic events in the first 12 cycles was 13% in the KRd arm *versus* 6% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of venous thromboembolic events in months 1–6 was 9% in the Kd arm *versus* 2% in the Vd arm. With Kyprolis monotherapy, the incidence of venous thromboembolic events was 2%. Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks. Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with Kyprolis in combination with dexamethasone or lenalidomide plus dexamethasone *see Use in*
5.2 Acute Renal Failure Cases of acute renal failure have occurred in patients receiving Kyprolis. Renal insufficiency adverse events (renal impairment, acute renal failure, renal failure) have occurred in approximately 10% of patients treated with Kyprolis. […]	
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have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold Kyprolis and evaluate. Consider whether to restart Kyprolis based on a benefit/risk assessment [*see Dosage and Administration (2)*].	*Specific Population (8.3)*]. […]
	5.10 Hemorrhage Fatal or serious cases of hemorrhage have been reported in patients treated with Kyprolis. 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) and Adverse Reactions (6.1)*].
5.8 Venous Thrombosis Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Kyprolis. In the combination study, the incidence of venous thromboembolic events in the first 12 cycles was 13% in the Kyprolis combination arm versus 6% in the control arm. With Kyprolis monotherapy, the incidence of venous thromboembolic events was 2%. Thromboprophylaxis is recommended and should be based on an assessment of the patient's underlying risks, treatment regimen, and clinical status.	**5.11 Thrombocytopenia** […] Hemorrhage may occur [*see Adverse Reactions (6.1) and Warnings and Precautions (5.10)*]. […]
	5.15 Embryo-Fetal Toxicity Kyprolis can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using Kyprolis. Advise females of reproductive potential to avoid becoming pregnant while being treated with Kyprolis. Advise males of reproductive potential to avoid fathering a child while being treated with Kyprolis. Advise women who use Kyprolis during pregnancy or become pregnant during treatment with Kyprolis of the potential hazard to the fetus [*see Use in Specific Populations (8.1, 8.3)*].

5.14 Embryo-fetal Toxicity Kyprolis can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using Kyprolis. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [*see Use in Specific Populations (8.1)*].	

6. ADVERSE REACTIONS The following adverse reactions are discussed in greater detail in other sections of the labeling: • […] • Thrombotic Thrombocytopenic Purpura /Hemolytic Uremic Syndrome [*see Warnings and Precautions (5.12)]* • […]	**6. ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of the labeling: • […] • Hemorrhage [*see Warnings and Precautions (5.10)*] • […] • Microangiopathy [*see Warnings and Precautions (5.13)]* […] **6.1. Clinical Trials Experience** […] Safety Experience with Kyprolis in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma […] **Table 7: Most Common Adverse Reactions (≥ 10% in the KRd Arm) Occurring in Cycles 1–12 (20/27 mg/m^2 Regimen In Combination with Lenalidomide and Dexamethasone)** *Adverse Reactions Occurring at a Frequency of < 10%* *[…]* • **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, gastrointestinal hemorrhage, toothache • **[…]** • **Infections and infestations:** influenza, lung infection, rhinitis, sepsis, urinary tract infection, viral infection • **[…]** • **Nervous system disorders:** hypoesthesia, intracranial hemorrhage, paresthesia, deafness

	• **Respiratory, thoracic and mediastinal disorders:** dysphonia, epistaxis, , oropharyngeal pain, pulmonary embolism, pulmonary edema, , pulmonary hemorrhage • **[…]** • **Vascular disorders:** deep vein thrombosis, hemorrhage, hypotension […] **Table 8: Grade 3–4 Laboratory Abnormalities (≥ 10% in the KRd Arm) in Cycles 1-12 (20/27 mg/m^2 Regimen In Combination with Lenalidomide and Dexamethasone)** Safety Experience with Kyprolis in Combination with Dexamethasone in Patients with Multiple Myeloma The safety of Kyprolis in combination with dexamethasone was evaluated in an open-label, randomized trial of patients with relapsed multiple myeloma. The study treatment is described in Section 14.2. Patients received treatment for a median duration of 40 weeks in the Kyprolis/dexamethasone (Kd) arm and 27 weeks in the bortezomib/dexamethasone (Vd) arm. Deaths due to adverse reactions within 30 days of last study treatment occurred in 22/463 (5%) 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 7 (2%) *versus* 5 (1%), infections 5 (1%) *versus* 8 (2%), disease progression 6 (1%) *versus* 4 (1%), pulmonary 3 (1%) *versus* 2 (< 1%), renal 1 (< 1%) *versus* 0 (0%), and other adverse events 2 (< 1%) *versus* 2 (< 1%). Serious adverse reactions were reported in 48% of the patients in the Kd arm and 36% of the patients in the Vd arm. In both treatment arms, pneumonia was the most commonly reported serious adverse reaction (6% *versus* 9%). Discontinuation due to any adverse reaction occurred in 20% in the Kd

arm *versus* 21% in the Vd arm. The most common reaction leading to discontinuation was cardiac failure in the Kd arm (n = 6, 1.3%) and peripheral neuropathy in the Vd arm (n = 19, 4.2%).

Common Adverse Reactions (≥ 10%)

Adverse reactions in the first 6 months of therapy that occurred at a rate of 10% or greater in the Kd arm are presented in Table 9.

Table 9: Most Common Adverse Reactions (≥ 10% in the Kd Arm) Occurring in Months 1–6 (20/56 mg/m^2 Regimen In Combination with Dexamethasone

	Kd (N = 463)		Vd (N = 456)	
Adverse Reaction by Body System	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	160 (35)	57 (12)	112 (25)	43 (9)
Thrombocytopenia[a]	127 (27)	46 (10)	112 (25)	65 (14)
Gastrointestinal Disorders				
Diarrhea	111 (24)	14 (3)	150 (33)	26 (6)
Nausea	69 (15)	4 (1)	66 (15)	3 (1)
Constipation	58 (13)	1 (0)	109 (24)	6 (1)
Vomiting	45 (10)	5 (1)	32 (7)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	112 (24)	13 (3)	124 (27)	25 (6)
Pyrexia	102 (22)	9 (2)	52 (11)	3 (1)
Peripheral edema	75 (16)	3 (1)	73 (16)	3 (1)
Asthenia	71 (15)	9 (2)	66 (14)	13 (3)

Infections and Infestations				
Upper respiratory tract infection	66 (14)	4 (1)	54 (12)	3 (1)
Bronchitis	54 (12)	5 (1)	26 (6)	2 (0)
Nasopharyngitis	45 (10)	0 (0)	42 (9)	1 (0)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	66 (14)	1 (0)	22 (5)	3 (1)
Back pain	58 (13)	7 (2)	60 (13)	8 (2)
Nervous System Disorders				
Headache	68 (15)	4 (1)	38 (8)	2 (0)
Peripheral neuropathies[b,c]	54 (12)	7 (2)	167 (37)	23 (5)
Psychiatric Disorders				
Insomnia	103 (22)	5 (1)	113 (25)	10 (2)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[d]	123 (27)	23 (5)	66 (15)	8 (2)
Cough[e]	91 (20)	0 (0)	61 (13)	2 (0)
Vascular Disorders				
Hypertension[f]	80 (17)	29 (6)	33 (7)	12 (3)

Kd = Kyprolis and dexamethasone; Vd = bortezomib and dexamethasone

[a] Thrombocytopenia includes platelet count decreased and thrombocytopenia.

[b] Peripheral neuropathies include peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] See Clinical Studies (14.2).

[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 6% (95% CI: 4, 8) *versus* 32% (95% CI: 28, 36) 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 • **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, infusion site reactions (including inflammation, pain, and erythema), pain • **Hepatobiliary disorders:** cholestasis, hepatic failure, hyperbilirubinemia • **Immune system disorders:** drug hypersensitivity • **Infections and infestations:** bronchopneumonia, influenza, lung infection, pneumonia, rhinitis, sepsis, urinary tract infection, viral infection • **Metabolism and nutrition disorders:** decreased appetite, dehydration, hypercalcemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia, tumor lysis syndrome • **Musculoskeletal and connective tissue disorders:** muscular weakness, musculoskeletal chest pain, musculoskeletal pain, myalgia • **Nervous system disorders:** cerebrovascular accident, dizziness, hypoesthesia, paresthesia, posterior reversible encephalopathy syndrome

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

Laboratory Abnormalities

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

Table 10: Grades 3–4 Laboratory Abnormalities (≥ 10%) in Months 1–6 (20/56 mg/m^2 Regimen In Combination with Dexamethasone)

Laboratory Abnormality	Kd (N = 463)	Vd (N = 456)
Decreased lymphocytes	248 (54)	180 (40)
Increase uric acid	243 (53)	198 (43)
Decreased hemoglobin	79 (17)	68 (15)
Decreased platelets	85 (18)	77 (17)
Decreased phosphorus	73 (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.

Safety Experience with Kyprolis in Patients with Multiple Myeloma who Received Monotherapy

The safety of Kyprolis, dosed at 20/27 mg/m^2 by up to 10-minute infusion, was evaluated in clinical trials in which 598 patients with relapsed and/or refractory myeloma received Kyprolis monotherapy starting with the 20 mg/m^2 dose in Cycle 1, Day 1 and escalating to 27 mg/m^2 on Cycle 1, Day 8 or Cycle 2, Day 1.

[…]

Safety of Kyprolis monotherapy dosed at 20/56 mg/m^2 by 30-minute infusion was evaluated in a multicenter, open-label study in patients with relapsed and/or refractory multiple myeloma. The study treatment is described in Section 14.3. The patients received a median of 4 (range 1–10) prior regimens.

The common adverse reactions occurring at a rate of 20% or greater with Kyprolis monotherapy are presented in Table 11.

Table 11: Most Common Adverse Reactions (≥ 20%) with Kyprolis Monotherapy

[…]

Safety Experience with Kyprolis in Patients with Multiple Myeloma who Received Monotherapy

[…]

The common adverse events occurring at a rate of 10% or greater with Kyprolis monotherapy are presented in Table 7

	20/56 mg/m^2 by 30-minute infusion (N = 24)		20/27 mg/m^2 by 2- to 10-minute infusion (N = 598)	
Adverse Reaction	**Any Grade n (%)**	**Grades 3 - 5 n (%)**	**Any Grade n (%)**	**Grades 3 - 5 n (%)**
Fatigue	14 (58)	2 (8)	238 (40)	25 (4)
Dyspnea[a]	14 (58)	2 (8)	202 (34)	21 (4)
Pyrexia	14 (58)	0	177 (30)	11 (2)
Thrombocytopenia	13 (54)	13 (54)	220 (37)	152 (25)
Nausea	13 (54)	0	211 (35)	7 (1)
Anemia	10 (42)	7 (29)	291 (49)	141 (24)
Hypertension[b]	10 (42)	3 (13)	90 (15)	22 (4)
Chills	9 (38)	0	73 (12)	1 (< 1)
Headache	8 (33)	0	141 (24)	7 (1)
Cough[c]	8 (33)	0	134 (22)	2 (< 1)
Vomiting	8 (33)	0	104 (17)	4 (1)
Lymphopenia	8 (33)	8 (33)	85 (14)	73 (12)
Insomnia	7 (29)	0	75 (13)	0
Dizziness	7 (29)	0	64 (11)	5 (1)
Diarrhea	6 (25)	1 (4)	160 (27)	8 (1)
Blood creatinine increased	6 (25)	1 (4)	103 (17)	15 (3)
Peripheral edema	5 (21)	0	118 (20)	1 (< 1)
Back pain	5 (21)	1 (4)	115 (19)	19 (3)
Upper respiratory tract infection	5 (21)	1 (4)	112 (19)	15 (3)
Decreased appetite	5 (21)	0	89 (15)	2 (< 1)
Muscle spasms	5 (21)	0	62 (10)	2 (< 1)
Chest pain	5 (21)	0	20 (3)	1 (< 1)

	Adverse Reactions Occurring at a Frequency of < 20% • **Blood and lymphatic system disorders:** febrile neutropenia, leukopenia, neutropenia • **Cardiac disorders:** cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia • **[…]** • **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, constipation, dyspepsia, gastrointestinal hemorrhage, toothache • **General disorders and administration site conditions:** asthenia, infusion site reaction, multi-organ failure, pain • **[…]** • **Infections and infestations:** bronchitis, bronchopneumonia, influenza, lung infection, pneumonia, nasopharyngitis, respiratory tract infection, rhinitis, sepsis, urinary tract infection • **Metabolism and nutrition disorders:** hypercalcemia, hyperglycemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, tumor lysis syndrome • **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal pain, musculoskeletal chest pain, myalgia, pain in extremity • **Nervous system disorders:** hypoesthesia, intracranial hemorrhage, paresthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathy • **[…]** • **Renal and urinary disorders:** acute renal failure, renal failure, renal impairment • **Respiratory, thoracic and mediastinal disorders:** dysphonia, epistaxis, oropharyngeal pain, pulmonary edema, pulmonary

hemorrhage

- **[…]**
- **Vascular disorders:** embolic and thrombotic events, venous (including deep vein thrombosis and pulmonary embolism), hemorrhage, hypotension

[…]

Table 12: Grade 3–4 Laboratory Abnormalities (> 10%) with Kyprolis Monotherapy

Laboratory Abnormality	Kyprolis 20/56 mg/m^2 (N = 24)	Kyprolis 20/27 mg/m^2 (N = 598)
Decreased lymphocytes	15 (63)	151 (25)
Decreased platelets	11 (46)	184 (31)
Decreased hemoglobin	7 (29)	132 (22)
Decreased total white blood cell count	3 (13)	71 (12)
Decreased sodium	2 (8)	69 (12)
Decreased absolute neutrophil count	2 (8)	67 11)

6.2 Postmarketing Experience

[…]

8. USE IN SPECIFIC POPULATIONS

[…]

8. USE IN SPECIFIC POPULATIONS […] **8.5 Geriatric Use** […]	**8.5 Geriatric Use** Of 598 patients in clinical studies of Kyprolis monotherapy dosed at 20/27 mg/m^2 by up to 10-minute infusion, 49% were 65 and over, while 16% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 55% in patients 65 to 74 years of age, and 56% in patients ≥ 75 years of age [*see Warnings and Precautions (5.1)*]. In a single-arm, multicenter clinical trial of Kyprolis monotherapy dosed at 20/27 mg/m^2 (N = 266), no overall differences in effectiveness were observed between older and younger patients. Of 392 patients treated with Kyprolis in combination with lenalidomide and dexamethasone, 47% were 65 and over and 11% were 75 years and over. The incidence of serious adverse events was 50% in patients < 65 years of age, 70% in patients 65 to 74 years of age, and 74% in patients ≥ 75 years of age [*see Warnings and Precautions (5.1)*]. No overall differences in effectiveness were observed between older and younger patients. Of 463 patients treated with Kyprolis dosed at 20/56 mg/m^2 by 30-minute infusion in combination with dexamethasone, 52% were 65 and over and 17% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 50% in patients 65 to 74 years of age, and 57% in patients ≥ 75 years of age [*see Warnings and Precautions (5.1)*]. No overall differences in effectiveness were observed between older and younger patients. **8.6 Hepatic Impairment** The pharmacokinetics and safety of Kyprolis were evaluated in patients

	with advanced malignancies who had either normal hepatic function, or mild (bilirubin > 1 to 1.5 × ULN or AST > ULN), moderate (bilirubin > 1.5 to 3 × ULN), or severe (bilirubin > 3 × ULN) hepatic impairment. The AUC of carfilzomib increased by approximately 50% in patients with mild and moderate hepatic impairment compared to patients with normal hepatic function. PK data were not collected in patients with severe hepatic impairment. The incidence of serious adverse events was higher in patients with mild, moderate, and severe hepatic impairment combined (22/35 or 63%) than in patients with normal hepatic function (3/11 or 27%) [*see Warnings and Precautions (5.12), Clinical Pharmacology (12.3)*]. Monitor liver enzymes regularly, regardless of baseline values, and modify dose based on toxicity [*see Dosage and Administration (2.3)*]. **8.7 Renal Impairment** No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic hemodialysis. The pharmacokinetics and safety of Kyprolis were evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic hemodialysis. In addition, a pharmacokinetic study was conducted in patients with normal renal function and end-stage renal disease (ESRD) [*see Clinical Pharmacology (12.3)*]. In these studies, the pharmacokinetics of Kyprolis was not influenced by the degree of baseline renal impairment, including the patients on hemodialysis. Since dialysis clearance of Kyprolis concentrations has not been studied, the drug should be administered after the hemodialysis procedure [*see Clinical Pharmacology (12.3)*].

12. CLINICAL PHARMACOLOGY **12.3 Pharmacokinetics** […] […]	**12. CLINICAL PHARMACOLOGY** **12.3 Pharmacokinetics** […] Following a 30-minute infusion of the 56 mg/m^2 dose, the mean (CV%) AUC of 948 ng•hr/mL (34%) was approximately twice that observed following a 2- to 10-minute infusion at the 27 mg/m^2 dose with a mean (CV%) of 379 ng•hr/mL (25%). The mean (CV%) C_{max} of 2079 ng/mL (44%) following a 30-minute infusion of the 56 mg/m^2 dose was lower compared to that of 27 mg/m^2 over the 2- to 10-minute infusion with a mean (CV%) of 4232 ng/mL (49%). At doses between 20 and 56 mg/m^2, there was a dose-dependent increase in exposure at either infusion duration. […] **Specific Populations:** **Age, Gender, and Race:** Clinically significant differences were not observed in the pharmacokinetics of carfilzomib based on age (35-88 years), gender, and race. **Hepatic Impairment:** The pharmacokinetics of carfilzomib was studied in patients with relapsed or progressive advanced malignancies with mild (bilirubin > 1 to 1.5 × ULN or AST > ULN) or moderate (bilirubin > 1.5 to 3 × ULN) chronic hepatic impairment relative to those with normal hepatic function. Compared to patients with normal hepatic function, patients with mild and moderate hepatic impairment had approximately 50% higher carfilzomib AUC. The pharmacokinetics of carfilzomib has not been evaluated in

	patients with severe hepatic impairment (bilirubin > 3 × ULN and any AST). **Renal Impairment:** The pharmacokinetics of carfilzomib was studied in relapsed multiple myeloma patients with normal renal function; mild, moderate or severe renal impairment; and patients with ESRD requiring hemodialysis. Exposures of carfilzomib (AUC and C_{max}) in patients with mild, moderate, and severe renal impairment were similar to those with normal renal function. Relative to patients with normal renal function, ESRD patients on hemodialysis showed 33% higher carfilzomib AUC. No starting dose adjustment is required in patients with baseline renal impairment. **Drug Interactions** Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs […] **14. CLINICAL STUDIES** […] **14.2 In Combination with Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (Study 2)** Study 2 was a randomized, open-label, multicenter superiority trial of Kyprolis plus dexamethasone (Kd) *versus* bortezomib plus dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 lines of therapy. A total of 929 patients were enrolled and randomized (464 in the Kd arm; 465 in the Vd arm). Randomization was

14. CLINICAL STUDIES

[…]

14.2 Monotherapy for Treatment of Patients with Relapsed and Refractory Multiple Myeloma

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 15.

Table 15: Demographics and Baseline Characteristics in Study 2 (Combination Therapy for Relapsed or Refractory Multiple Myeloma)

Characteristics	Kd Arm (N = 464)	Vd Arm (N = 465)
Age, Years		
Median (min, max)	65 (35, 89)	65 (30, 88)
< 65, n (%)	223 (48)	210 (45)
65–74, n (%)	164 (35)	189 (41)
≥ 75, n (%)	77 (17)	66 (14)

Sex, n (%)		
Female	224 (48)	236 (51)
Male	240 (52)	229 (49)
Race, n (%)		
White	348 (75)	353 (76)
Black	8 (2)	9 (2)
Asian	56 (12)	57 (12)
Other or Not Reported	52 (11)	46 (10)
ECOG Performance Status, n (%)		
0	221 (48)	232 (50)
1	211 (46)	203 (44)
2	32 (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	212 (46)	205 (44)
ISS II	138 (30)	151 (33)
ISS III	114 (25)	109 (23)
Number of Prior Regimens		
1	232 (50)	232 (50)

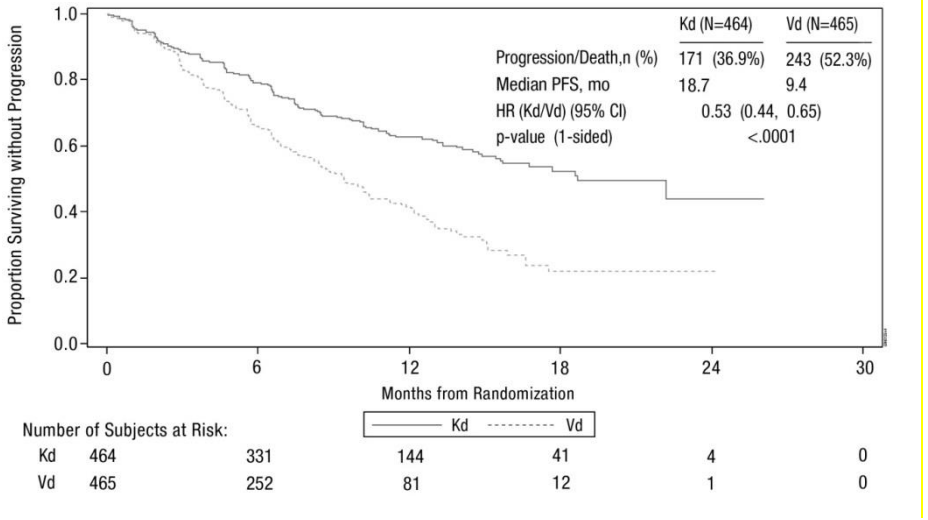
2	157 (34)	145 (31)
3	75 (16)	87 (19)
4	0 (0)	1 (0)
Prior Therapies, n (%)	464 (100)	465 (100)
Bortezomib	250 (54)	252 (54)
Transplant for Multiple Myeloma	266 (57)	272 (59)
Thalidomide	211 (46)	247 (53)
Lenalidomide	177 (38)	177 (38)
Bortezomib + immunomodulatory agent	158 (34)	167 (36)
Refractory to last prior therapy, n (%)[a]	184 (40)	188 (40)

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

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

The efficacy of 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 16 and Figure 3).

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



HR = hazard ratio; Kd = Kyprolis plus dexamethasone; PFS = progression-free survival; Vd = bortezomib and dexamethasone

Other endpoints included OS and overall response rate (ORR). At the time of analysis, OS data were not mature. ORR was 77% for patients in the Kd arm and 63% for patients in the Vd arm (see Table 16).

Table 16: Summary of Key Results in Study 2 (Intent-to-Treat Population)[a]

	Kd Arm (N = 464)	**Vd Arm (N = 465)**
PFS[b]		
Median[c], Months (95% CI)	18.7 (15.6, —)	9.4 (8.4, 10.4)
Hazard Ratio (Kd/Vd) (95% CI)[d]	0.53 (0.44, 0.65)	
P-value (1-sided)[e]	< 0.0001	

Overall Response[b]		
N with Response	357	291
ORR (%) (95% CI)[f]	77 (73, 81)	63 (58, 67)
P-value (1-sided)[g]	< 0.0001	
Response Category, n (%)		
sCR	8 (2)	9 (2)
CR	50 (11)	20 (4)
VGPR	194 (42)	104 (22)
PR[h]	105 (23)	158 (34)

CI = confidence interval; CR = complete response; Kd = Kyprolis and dexamethasone; ORR = overall response rate; PFS = progression-free survival; sCR = stringent CR; Vd = bortezomib and dexamethasone; VGPR = very good partial response

[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] 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.

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

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..

14.3 Monotherapy for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (Study 3, Study 4, and Study 5)

Study 3

Study 3 was a multicenter, open-label, dose escalation, single-arm trial that evaluated the safety of carfilzomib monotherapy as a 30-minute infusion in patients with relapsed or refractory multiple myeloma after 2 or more lines of therapy. Patients were excluded if they had a creatinine clearance < 20 mL/min; ALT ≥ 3 × upper limit of normal (ULN), bilirubin ≥ 1.5 × ULN; New York Heart Association class III or IV congestive heart failure; or other significant cardiac conditions. A total of 24 subjects with multiple myeloma were enrolled at the maximum tolerated dose level of 20/56 mg/m^2. Carfilzomib was administered twice-weekly for 3 consecutive weeks (Days 1, 2, 8, 9, 15, and 16) of a 28-day cycle. In Cycle 13 onward, the Day 8 and 9 carfilzomib doses could be omitted. Patients received carfilzomib at a starting dose of 20 mg/m^2 on Days 1 and 2 of Cycle 1, which was increased to 56 mg/m^2 for all subsequent doses. Dexamethasone 8 mg orally or intravenously was required prior to each carfilzomib dose in Cycle 1 and was optional in subsequent cycles. Treatment was continued until disease progression or unacceptable toxicity.

Efficacy was evaluated by ORR and DOR. ORR by investigator assessment was 50% (95% CI: 29, 71) per IMWG criteria (see Table 17). The median DOR in subjects who achieved a PR or better was 8.0 months (Range: 1.4, 32.5).

Table 18: Response Categories in Study 3 (20/56 mg/m^2 Monotherapy Regimen)

Characteristic	Study Patients[a] n (%)
Number of Patients (%)	24 (100)
Overall Response[b]	12 (50)
95% CI[c]	(29, 71)
Response Category	

sCR	1 (4)
CR	0 (0)
VGPR	4 (17)
PR	7 (29)

sCR = stringent complete response; VGPR = very good partial response

[a] Eligible patients had 2 or more prior lines of therapy.

[b] Per investigator assessment.

[c] Exact confidence interval.

Study 4

Study 4 was a single-arm, multicenter clinical trial of Kyprolis monotherapy by up to 10-minute infusion.

[…]

Study 5

Study 5 was a single-arm, multicenter clinical trial of Kyprolis monotherapy by up to 10-minute infusion. Eligible patients were those with relapsed or refractory multiple myeloma who were bortezomib-naïve, had received one to three prior lines of therapy and had ≤ 25% response or progression during therapy or within 60 days after completion of therapy. Patients were excluded from the trial if they were refractory to standard first-line therapy or had a total bilirubin ≥ 2 × ULN; creatinine clearance < 30 mL/min; New York Heart Association Class III to IV congestive heart failure; symptomatic cardiac ischemia; myocardial infarction within the last 6 months; active infections requiring treatment; or pleural effusion.

Kyprolis was administered intravenously up to 10 minutes on two consecutive days each week for three weeks, followed by a 12-day rest period (28-day treatment cycle), until disease progression, unacceptable

[…]

toxicity, or for a maximum of 12 cycles. Patients received 20 mg/m^2 at each dose in Cycle 1, and 27 mg/m^2 in subsequent cycles. Dexamethasone 4 mg orally or intravenously was administered prior to Kyprolis doses in the first and second cycles.

A total of 70 patients were treated with this 20/27 mg/m^2 regimen. Baseline patient and disease characteristics are summarized in Table 20.

Table 20: Demographics and Baseline Characteristics in Study 5 (20/27 mg/m^2 Monotherapy Regimen for Relapsed or Refractory Multiple Myeloma

Characteristic	Number of Patients (%)
Patient Characteristics	
Enrolled patients	70 (100)
Median age, years (range)	66 (45, 85)
Age group, < 65 / ≥ 65 (years)	31 (44) / 39 (56)
Gender (male / female)	44 (63) / 26 (37)
Race (White / Black / Asian / Hispanic / Other)	52 (74) / 12 (17) / 3 (4) / 2 (3) / 1 (1)
Disease Characteristics	
Number of Prior Regimens (median)	2[a]
Prior Transplantation	47 (67)
Refractory Status to Most Recent Therapy[b]	
Refractory: Progression during most recent therapy	28 (40)
Refractory: Progression within 60 days after completion of most recent therapy	7 (10)
Refractory: ≤ 25% response to treatment	10 (14)
Relapsed: Progression after 60 days post treatment	23 (33)

No Signs of Progression	2 (3)
Years since diagnosis, median (range)	3.6 (0.7, 12.2)
Plasma cell involvement (< 50% / ≥ 50% / unknown)	54 (77) / 14 (20) / 1 (1)
ISS Stage at Study Baseline, n (%)	
I	28 (40)
II	25 (36)
III	16 (23)
Unknown	1 (1)
Cytogenetics or FISH analyses	
Normal/Favorable	57 (81)
Poor Prognosis	10 (14)
Unknown	3 (4)
Creatinine clearance < 30 mL/min	1 (1)

FISH = Fluorescence in situ hybridization; ISS = International Staging System

[a] Range: 1, 4.

[b] Categories for refractory status are derived by programmatic assessment using available laboratory data.

Efficacy was evaluated by ORR as determined by IRC assessment using IMWG criteria. The median number of cycles started was seven. The ORR (PR or better) was 50% (95% CI: 38, 62) (see Table 21). The median DOR was not reached.

Table 21: Response Categories in Study 5 (20/27 mg/m^2 Monotherapy Regimen)

Characteristic	Study Patients[a] n (%)
Number of Patients (%)	70 (100)
Overall Response[b]	35 (50)

	95% CI[c] | (38 - 62) Response Category | CR | 1 (1) VGPR | 18 (26) PR | 16 (23)

CR = complete response; VGPR = very good partial response

[a] Eligible patients had 1-3 prior lines of therapy and were refractory to the last regimen.

[b] As assessed by an Independent Review Committee.

[c] Exact confidence interval.

17. PATIENT COUNSELING INFORMATION Discuss the following with patients prior to treatment with Kyprolis: […]	**17. 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 physician 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 Reactions:** Advise patients of the risk of infusion reactions, and discuss the common signs and symptoms of infusion 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 physician 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 physician if they experience jaundice *[see Warnings and Precautions (5.12)]*. **Other:** Inform patients to contact their physician if they experience neurologic symptoms such as headaches, confusion, seizures, or visual loss [*see Adverse Reactions (6) and Warnings and Precautions (5)*]. **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)*]. **Pregnancy/Nursing:** Counsel females of reproductive potential to use effective contraceptive measures to prevent pregnancy during and for at least 30 days after treatment with Kyprolis. Counsel males of reproductive potential to use effective contraceptive measures to prevent pregnancy during and for at least 90 days after treatment with Kyprolis. Advise the patient to contact their physician immediately if pregnancy does occur during these times. Advise patients not to take Kyprolis treatment while

	pregnant or breastfeeding. If a patient wishes to restart breastfeeding after treatment, advise her to discuss the appropriate timing with her physician [*see Warnings and Precautions (5.15) and Use in Specific Populations (8.1, 8.3)*]. **Concomitant Medications:p** Advise patients to discuss with their physician any medication they are currently taking prior to starting treatment with Kyprolis, or prior to starting any new medication(s) during treatment with Kyprolis.