Kyprolis® (carfilzomib) for injection

Kd
2nd-generation PI doublet

At first relapse,

Kd provides superior progression-free survival for patients with multiple myeloma[1,*,†]

Look to KYPROLIS® for the way forward

***Median PFS: 18.7 months (Kd 56 mg/m²) vs 9.4 months (Vd); HR = 0.53; 95% CI: 0.44-0.65; *P* < 0.0001, one-sided.[1,2]**

†Median PFS: 11.2 months (Kd 70 mg/m² once weekly) vs 7.6 months (Kd 27 mg/m² twice weekly); HR = 0.69; 95% CI: 0.54-0.88; *P* = 0.0014, one-sided.[1]

* **Kd 56 mg/m² vs Vd study design (ENDEAVOR):** Phase 3, randomized, open-label superiority study (N = 929) comparing Kd 56 mg/m² twice weekly to Vd in relapsed or refractory multiple myeloma patients who had received 1 to 3 prior lines of therapy. The primary endpoint was PFS. Select secondary endpoints included OS, overall response rate, duration of response, and safety.[1,2]

† **Kd 70 mg/m² once weekly vs Kd 27 mg/m² twice weekly study design (A.R.R.O.W.):** Phase 3, randomized, multicenter, open-label study (N = 478) in patients with relapsed and refractory multiple myeloma who had received 2 to 3 prior lines of therapy, KYPROLIS®+dexamethasone 70 mg/m² once weekly (n = 240) vs KYPROLIS®+dexamethasone 27 mg/m² twice weekly (n = 238). The primary endpoint was PFS. Select secondary endpoints included ORR and safety.[1,3]

Note: Kd 27 mg/m² is not an FDA-approved dose for KYPROLIS®.[1]

Kd = KYPROLIS®+dexamethasone; PI = proteasome inhibitor; PFS = progression-free survival; Vd = Velcade® (bortezomib)+dexamethasone; HR = hazard ratio; CI = confidence interval; OS = overall survival; ORR = overall response rate; FDA = Food and Drug Administration.

INDICATION

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone or with daratumumab and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Cardiac Toxicities

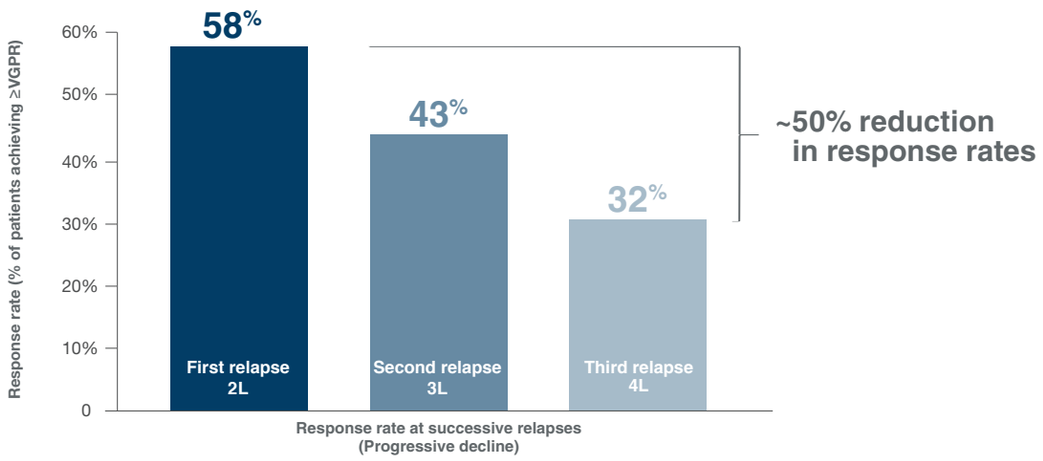
- New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of administration.
- Monitor patients for signs or symptoms of cardiac failure or 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 at 1 dose level reduction based on a benefit/risk assessment.

Please see additional Important Safety Information throughout.

For your patients with multiple myeloma, your choice of treatment at first relapse can impact their chances of survival[4,5]

In patients who receive treatment for subsequent relapses, response rates decline by almost HALF by the third relapse[5]

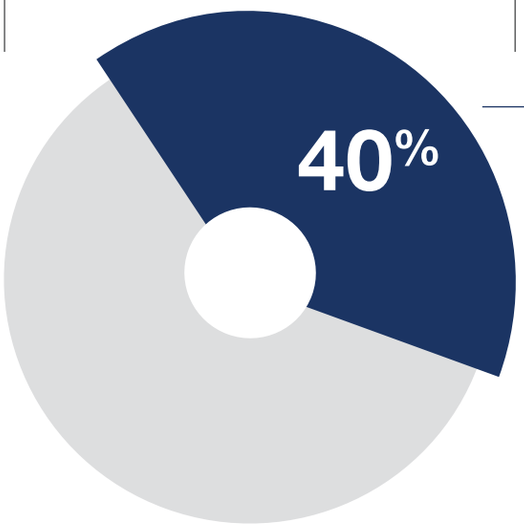
The proportion of patients achieving ≥VGPR decreased from 58% at first relapse to 43% at second relapse and to 32% at third relapse*



*Observational chart review performed during 2014 in the EU, including Belgium, France, Germany, Italy, Spain, Switzerland, and the UK. A total of 4,997 patient charts were reviewed. In the 6 months before inclusion in the study, 1,802 patients had been treated up to the end of first line, 1,380 up to the end of second line, and 1,815 up to the end of third line or later.

In 4 out of 10 patients, their treatment at first relapse may be their last[4]

Patients who start their first relapse treatment...



Of the 40% who do not receive subsequent treatment:

- 30% die
- 40% enter hospice
- 30% refuse further treatment

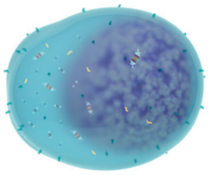
Based on real-world, patient-level data and modeling (data range, 2010-2016). Data analyzed from the US Census Bureau; National Program of Cancer Registries (NPCR); Surveillance, Epidemiology, and End Results (SEER); and additional primary and secondary research sources.

≥VGPR = very good partial response or better.

The proteasome is an important therapeutic target in multiple myeloma[6,7]

About multiple myeloma

Multiple myeloma is characterized by overproduction of monoclonal proteins within plasma cells.[6] These cells rely heavily on proteasomes to recycle excess proteins, preventing the cell from becoming overburdened and triggering apoptosis.[7]

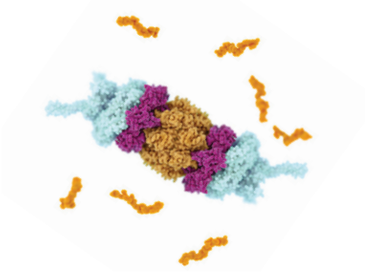


Proteasomes exist in every cell[7]
Proteasomes are important to myeloma cell survival, making them a logical target.[6]

Proteasome inhibitors (PIs) work inside the cell[7]
Proteasomes are found inside the cell cytoplasm and nucleus.[7]

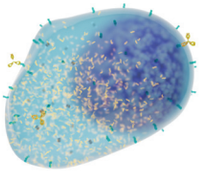
How PIs work

Proteasome



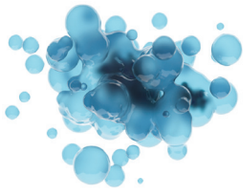
PIs inhibit proteasomal activity, preventing proteasomes from recycling excess proteins.[6,8]

Myeloma cell



This causes protein levels to build up inside the cell…[6,8]

Apoptosis



…resulting in myeloma cell apoptosis.[6,8]

KYPROLIS® is a second-generation PI with irreversible binding for the proteasome[1,8,9]

Hypothetical representation for illustrative purposes only.

Note: The clinical significance of in vitro studies is unknown. Mechanism of action statements are not meant to imply clinical efficacy.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Cardiac Toxicities (cont'd)

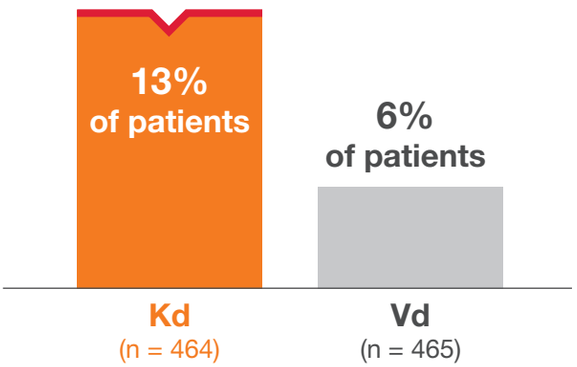
- While adequate hydration is required prior to each dose in Cycle 1, monitor all patients for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate.
- For patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment prior to starting treatment with KYPROLIS and remain under close follow-up with fluid management.

In a head-to-head study in RMM,

Kd 56 mg/m^2 DOUBLED the chance of patients achieving CR or better (Kd vs Vd)[1]

Deep

2x ≥CR with Kd vs Vd (Kd 13% vs Vd 6%)[1]



2x ≥CR
vs Vd[1]

Kd: National Comprehensive Cancer Network® (NCCN®) recommended doublet[10]

NCCN Guidelines®: Carfilzomib (KYPROLIS®) in combination with dexamethasone (Kd) is the only recommended doublet regimen for relapsed multiple myeloma

Carfilzomib (KYPROLIS®) in combination with dexamethasone (Kd twice weekly) has a category 1 designation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma (Version 2.2021) for previously treated multiple myeloma.

NCCN makes no warranties of any kind whatsoever regarding this content, use or application and disclaims any responsibility for their application or use in any way.[10]

RMM = relapsed multiple myeloma; ≥CR = complete response or better.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Acute Renal Failure

- Cases of acute renal failure, including some fatal renal failure events, and renal insufficiency (including renal failure) have occurred. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome

- Cases of Tumor Lysis Syndrome (TLS), including fatal outcomes, have occurred. Patients with a high tumor burden should be considered at greater risk for TLS. Adequate hydration is required prior to each dose in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, and withhold until resolved.

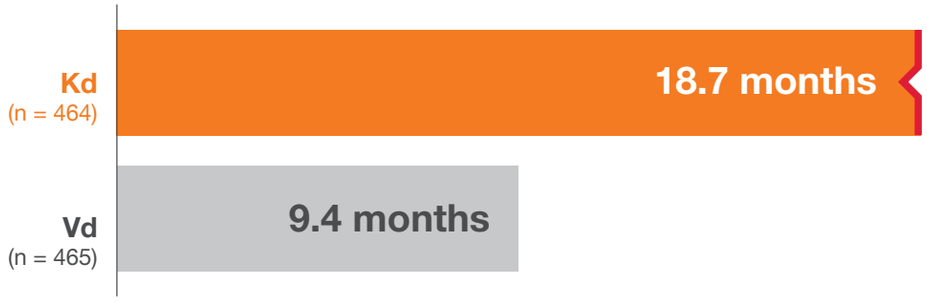
Kyprolis® (carfilzomib) for Injection

In a head-to-head study in RMM,

Kd 56 mg/m^2 nearly DOUBLED median PFS vs Vd[1,2]

Durable

Kd significantly increased time to disease progression or death[1,2]



~2x
the duration of PFS vs Vd[1,2]

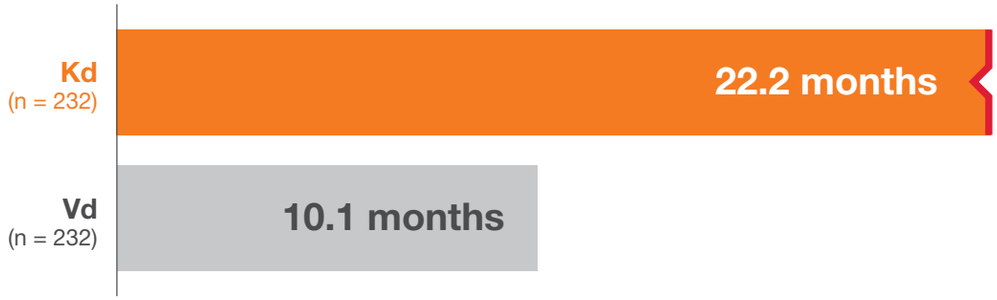
HR = 0.53; 95% CI: 0.44-0.65; *P* < 0.0001, one-sided.[1,2]

- **Overall, 47% reduction in the risk of disease progression or death vs Vd[1,2]**

Exploratory analysis:

At first relapse, Kd 56 mg/m^2 demonstrated a 1-year increase in median progression-free survival over Vd[11]

- At first relapse, 22.2 months with Kd (n = 232) vs 10.1 months with Vd (n = 232) (HR = 0.45; 95% CI: 0.33-0.61)
- **Exploratory analysis**: While this subgroup analysis was preplanned, demonstration of PFS efficacy within this subgroup was not a study objective. The study was not powered to evaluate PFS efficacy within this subgroup



1-year increase
in PFS over Vd[11]

Kd 56 mg/m^2 is the first and only doublet with a proven median overall survival advantage vs Vd (Kd 47.6 months vs Vd 40.0 months)[1,2,12]

HR = 0.79; 95% CI: 0.65-0.96; *P* = 0.01, one-sided.[1,2,12]

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Pulmonary Toxicity

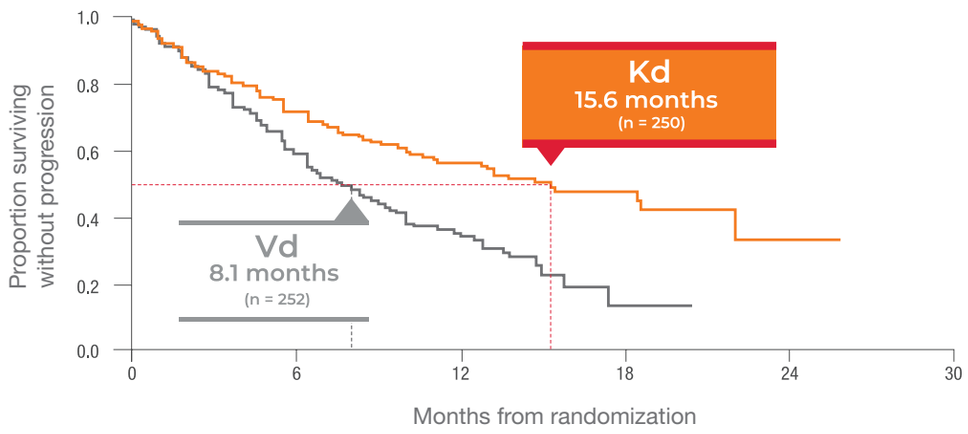
- Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue KYPROLIS.

Kyprolis® (carfilzomib) for Injection

Exploratory subgroup analysis:

Kd 56 mg/m² PFS results were consistent, independent of prior PI exposure²

Prior bortezomib exposure²

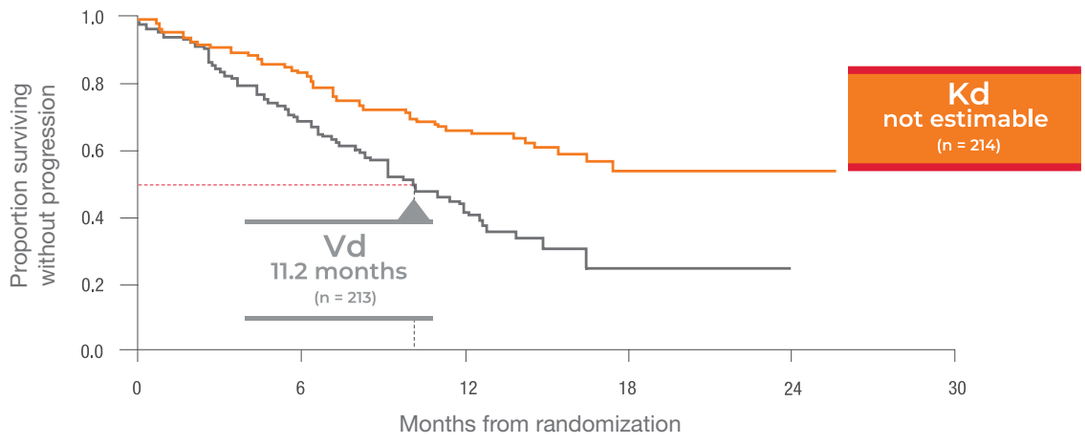


Number of patients at risk:

Kd	250	163	70	22	2	0
Vd	252	124	34	3	0	0

- HR = 0.56; 95% CI: 0.44-0.73²
- In an exploratory subgroup analysis of patients with prior exposure to bortezomib, results were consistent with overall PFS results. Study was not powered for PFS efficacy in these subgroups, and estimation of PFS was not a study objective²

Bortezomib naive²



Number of patients at risk:

Kd	214	168	74	19	2	0
Vd	213	128	47	9	1	0

- HR = 0.48; 95% CI: 0.36-0.66²

For patients with relapsed MM, choose Kd instead of Vd[1,2]

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Pulmonary Hypertension

- Pulmonary arterial hypertension (PAH) was reported. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for PAH until resolved or returned to baseline and consider whether to restart based on a benefit/risk assessment.

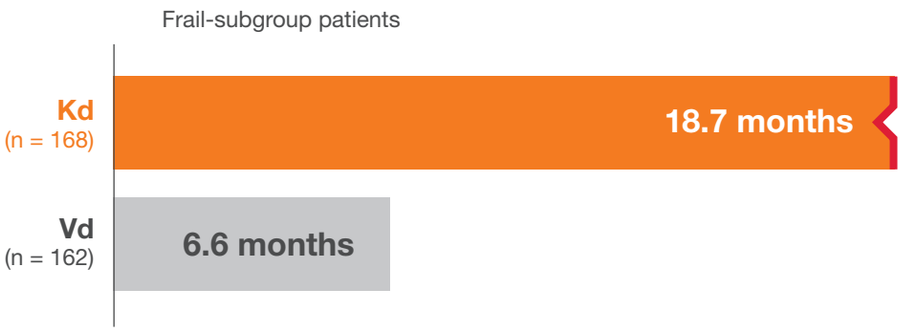
Kyprolis® (carfilzomib) for Injection

Post hoc analysis:

Frail-subgroup patients with Kd 56 mg/m^2 experienced mPFS 18.7 months vs 6.6 months with Vd[13,*,†]

Patient's age, ECOG PS, and medical history (comorbidities) were used to evaluate frailty status[13,*]

Median PFS[13,†]



- **Post hoc analysis:** Demonstration of PFS by frailty status was not a study objective. This study was not powered to evaluate PFS efficacy within this subgroup

*Patients who scored ≥ 2 by the proxy algorithm were categorized as frail-subgroup patients. Frail-subgroup patients represented 36% (168/464) and 35% (162/465) of patients in the Kd and Vd arms, respectively.[13]

Select frail-subgroup safety profile (Kd 56 mg/m^2 vs Vd)[13]

- Grade ≥ 3 adverse events of interest Kd (n = 168) vs Vd (n = 159):
  - peripheral neuropathy: **2% Kd vs 9% Vd**
  - acute renal failure: **9% Kd vs 4% Vd**
  - cardiac failure: **9% Kd vs 4% Vd**
  - ischemic heart disease: **5% Kd vs 4% Vd**
  - pulmonary hypertension: **0% Kd vs 1% Vd**
- Discontinuation rates due to adverse events: **33% Kd vs 30% Vd**

Post hoc subgroup design

In a post hoc analysis, patients were categorized into 3 groups according to frailty status using a proxy algorithm based on the IMWG frailty index. Scores derived separately for patient age, a modified Charlson Comorbidity Index (CCI) derived from medical history, and ECOG PS as follows: age: score = 0 if < 75 years, score = 1 if 75-80 years, score = 2 if > 80 years; modified CCI: score = 0 if modified CCI ≤ 1, score = 1 if modified CCI > 1; ECOG PS: score = 0 if ECOG PS = 0, score = 1 if ECOG PS = 1, score = 2 if ECOG PS ≥ 2. Patients with frailty-score sums of 0, 1, or ≥ 2 were classified as fit, intermediate, or frail, respectively.[13]

†Overall median follow-up for patients in the Kd vs Vd study was approximately 37 months.[1]

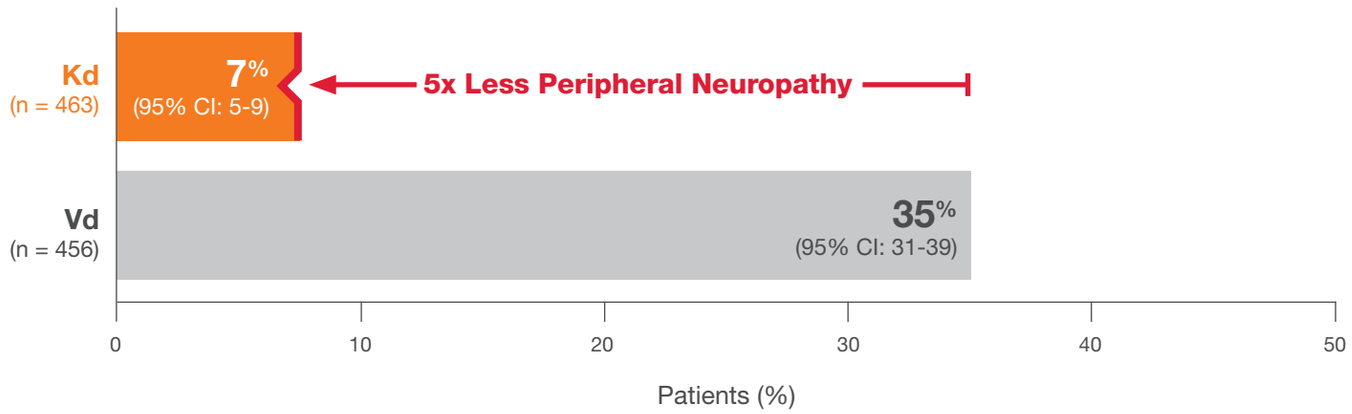
mPFS = median progression-free survival; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IMWG = International Myeloma Working Group.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Dyspnea

- Dyspnea was reported in patients treated with KYPROLIS. 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 based on a benefit/risk assessment.

Kd 56 mg/m^2 patients experienced 5x less peripheral neuropathy (Grade ≥ 2) vs Vd patients[1]



Among patients in the Vd group, 82% received subcutaneous bortezomib throughout their treatment.[1]

Select cardiac ARs in Kd 56 mg/m^2 and Vd arms[1,2]

	Kd (n = 463)		Vd (n = 456)	
Preferred term	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Cardiac failure*	11%	5%	3%	2%
Ischemic heart disease†	3%	2%	2%	2%
Pulmonary hypertension‡	1%	1%	0.2%	0.2%
Hypertension§	18%	7%	7%	3%

Cardiac-related inclusion and exclusion criteria: Eligible patients were required to have a left ventricular ejection fraction of at least 40%. Patients were excluded if they had myocardial infarction within 4 months before randomization, or New York Heart Association Class III or IV heart failure.[1,12]

*Cardiac failure included (in descending order of frequency): cardiac failure, ejection fraction decreased, pulmonary edema, acute cardiac failure, congestive cardiac failure, acute pulmonary edema, acute left ventricular failure, chronic cardiac failure, cardiopulmonary failure, hepatojugular reflux, right ventricular failure, and left ventricular failure.[2]

†Ischemic heart disease included (in descending order of frequency): angina pectoris, acute coronary syndrome, myocardial infarction, increased troponin T, coronary artery disease, increased troponin I, acute myocardial infarction, myocardial ischemia, and cardiomyopathy stress.[2]

‡Pulmonary hypertension included (in decreasing order of frequency): pulmonary hypertension, right ventricular failure, and pulmonary arterial hypertension.[2]

§Hypertension includes hypertension, hypertensive crisis, and hypertensive emergency.[1]

ARs = adverse reactions.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

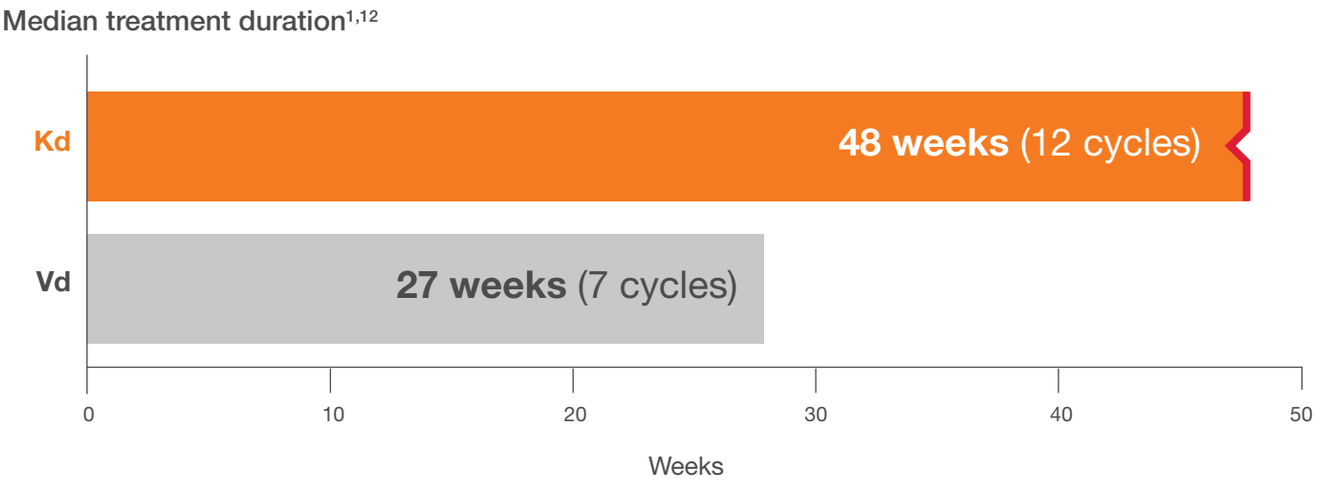
Hypertension

- Hypertension, including hypertensive crisis and hypertensive emergency, has been observed, some fatal. Control hypertension prior to starting KYPROLIS. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold KYPROLIS and evaluate. Consider whether to restart based on a benefit/risk assessment.

Kyprolis® (carfilzomib) for Injection

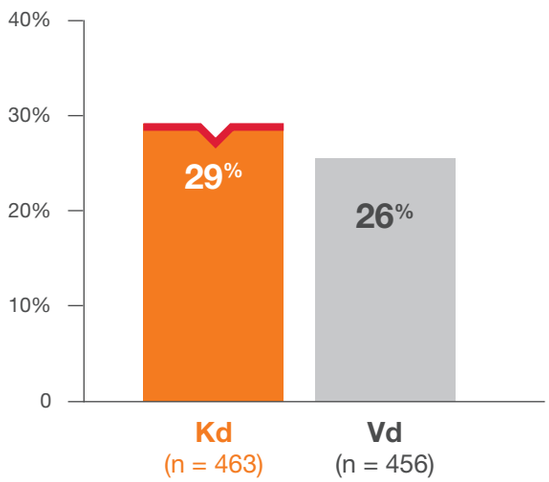
Kd 56 mg/m^2 led to a longer time on therapy and comparable discontinuation rates[1,12]

Median treatment duration[1,12]



Kd 56 mg/m^2 had comparable discontinuation rates vs Vd[1]

Discontinuation due to any ARs[1]



- The most common reaction leading to discontinuation was cardiac failure in the Kd arm (n = 8, 2%) and peripheral neuropathy in the Vd arm (n = 22, 5%)[1]

- Deaths due to ARs within 30 days of last study treatment occurred in 7% of patients (n = 32) in the Kd arm and 5% of patients (n = 21) in the Vd arm[1]
- Death due to cardiac ARs occurred in 1% of patients (n = 4) in the Kd arm and 1% of patients (n = 5) in the Vd arm[1]

Click here for information on managing cardiac ARs, as well as on managing hydration before and throughout treatment.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Venous Thrombosis

- Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed. Provide thromboprophylaxis for patients being treated with the combination of KYPROLIS with dexamethasone or with lenalidomide plus dexamethasone or with daratumumab and dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

Kyprolis® (carfilzomib) for Injection

Kd 70 mg/m² once weekly provides superior PFS and ORR vs Kd 27 mg/m² twice weekly

Extended PFS by 47%[1]

- **11.2 months in the once-weekly arm vs** 7.6 months in the twice-weekly arm*

*HR = 0.69; 95% CI: 0.54-0.88; *P* = 0.0014, one-sided.

54% higher ORR[1]

- **62.9% in the once-weekly arm vs** 40.8% in the twice-weekly arm†

†*P* < 0.0001, one-sided.

Deeper response[1]

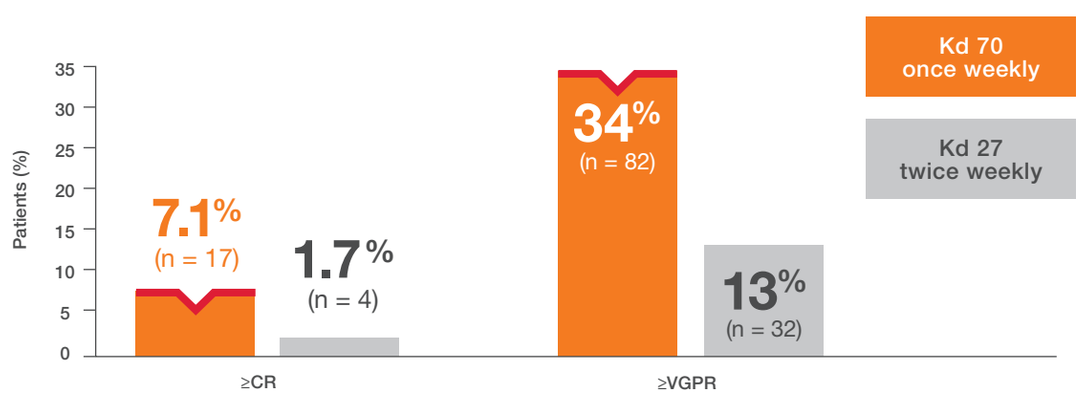
- **4x as many patients achieved ≥CR:** 7.1% in the once-weekly arm vs 1.7% in the twice-weekly arm‡
- **Nearly 3x as many patients achieved ≥VGPR:** 34% in the once-weekly arm vs 13% in the twice-weekly arm‡

‡A subgroup analysis of ORR.

31% reduction

in the risk of disease progression or death with Kd 70 mg/m² once weekly vs Kd 27 mg/m² twice weekly[1]

NOTE: Kd 27 mg/m² IS NOT AN FDA-APPROVED DOSE FOR KYPROLIS®.[1]



THE FDA GRANTED PRIORITY REVIEW

KYPROLIS® (carfilzomib) is the first hematology product approved under the FDA Oncology Center of Excellence Real-Time Oncology Review Pilot Program.[14,15]

Kd 70 = Kd 70 mg/m²; Kd 27 = Kd 27 mg/m² twice weekly.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Venous Thrombosis (cont'd)

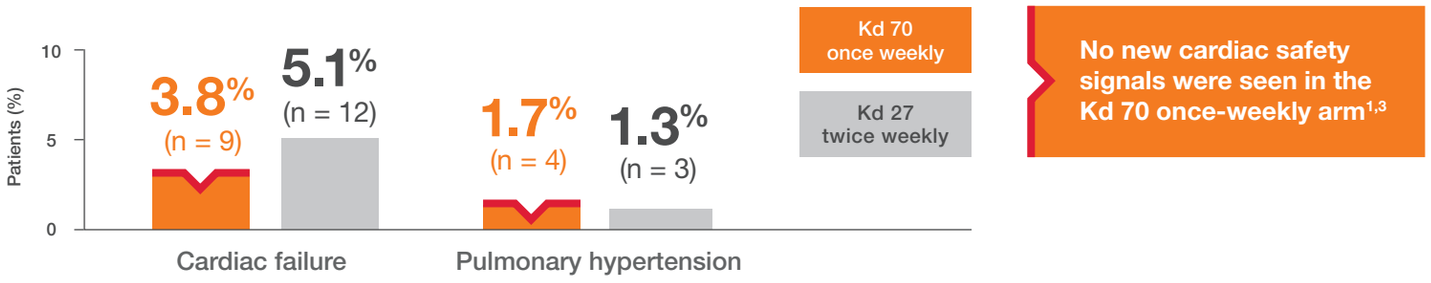
- For patients using hormonal contraception associated with a risk of thrombosis, consider an alternative method of effective contraception during treatment.

Kyprolis® (carfilzomib) for Injection

Kd 70 mg/m^2 once weekly has a comparable safety profile to Kd 27 mg/m^2 twice weekly[1,3]

Comparable safety profiles[1,3]

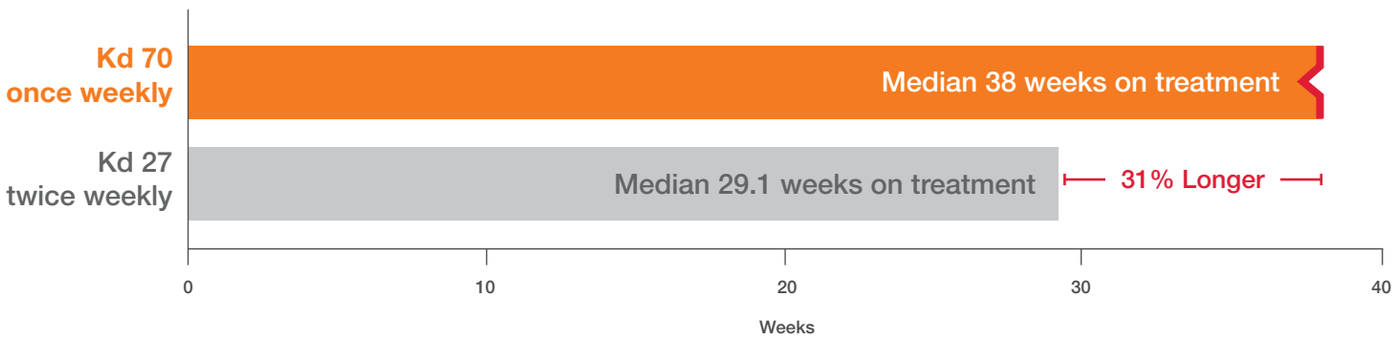
Select adverse events of interest



No new cardiac safety signals were seen in the Kd 70 once-weekly arm[1,3]

Patients were able to stay on treatment longer[1]

- **Patients stayed on treatment 31% longer in the once-weekly arm vs the twice-weekly arm**



Grade ≥ 3 adverse reactions of interest, Kd 70 mg/m^2 once weekly (n = 80) vs Kd 27 mg/m^2 twice weekly (n = 61): peripheral neuropathy, 0 vs 1; acute renal failure, 9 vs 13; cardiac failure, 7 vs 10; ischemic heart disease, 2 vs 2; pulmonary hypertension, 0 vs 1.[3]

- Discontinuation rates due to any AR: 13% Kd 70 mg/m^2 once weekly vs 12% Kd 27 mg/m^2 twice weekly[1]

Note: Kd 27 mg/m^2 is not an FDA-approved dose for KYPROLIS®.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Infusion-Related Reactions

- Infusion-related reactions, including life-threatening reactions, have occurred. 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. Premedicate with dexamethasone to reduce the incidence and severity of infusion-related reactions.

Kyprolis® (carfilzomib) for Injection

Once-weekly and twice-weekly dosing options[1]

Once-weekly dosing means 50% fewer KYPROLIS® infusions for appropriate patients

IMiD-FREE Kd | 70 mg/m² ONCE WEEKLY

Infusion time
30 minutes

KYPROLIS® priming dose
20 mg/m² Day 1 of Cycle 1 to evaluate tolerability

Target KYPROLIS® therapeutic dose
70 mg/m² starting Day 8 of Cycle 1

Treatment schedule
- Administer 70 mg/m² 1 day each week for 3 weeks
- Follow with 13-day rest period, as part of 28-day treatment cycle
- For Cycles 10 and beyond, dexamethasone is not given on Day 22
- Continue until disease progression or unacceptable toxicity occurs

IMiD-FREE Kd | 56 mg/m² TWICE WEEKLY

Infusion time
30 minutes

KYPROLIS® priming dose
20 mg/m² Days 1 and 2 of Cycle 1 to evaluate tolerability

Target KYPROLIS® therapeutic dose
56 mg/m² starting Day 8 of Cycle 1

Treatment schedule
- Administer 56 mg/m² 2 consecutive days each week for 3 weeks
- Follow with 12-day rest period, as part of 28-day treatment cycle
- Continue until disease progression or unacceptable toxicity occurs

KYPROLIS® is offered in 3 single-dose vial sizes: 10 mg, 30 mg, and 60 mg[1]

Refer to dexamethasone Prescribing Information for additional dosage information.

Manage hydration throughout treatment[1]

Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity.

IMiD = immunomodulatory drug.

Please see the full Prescribing Information for KYPROLIS® for dosing and administration.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Hemorrhage
- Fatal or serious cases of hemorrhage have been reported. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.

Kyprolis® (carfilzomib) for Injection

IMPORTANT SAFETY INFORMATION FOR KYPROLIS (cont'd)

Thrombocytopenia

- KYPROLIS causes thrombocytopenia with recovery to baseline platelet count usually by the start of the next cycle. Monitor platelet counts frequently during treatment. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure

- Cases of hepatic failure, including fatal cases, have occurred. KYPROLIS can cause increased serum transaminases. Monitor liver enzymes regularly regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy

- Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal outcome have occurred. Monitor for signs and symptoms of TTP/HUS. Discontinue if diagnosis is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS is not known.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Cases of PRES have occurred in patients receiving KYPROLIS. If PRES is suspected, discontinue and evaluate with appropriate imaging. The safety of reinitiating KYPROLIS is not known.

Progressive Multifocal Leukoencephalopathy (PML)

- Cases of PML, including fatal cases, have occurred. In addition to KYPROLIS, other contributary factors may include prior or concurrent use of immunosuppressive therapy. Consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms. If PML is suspected, discontinue and initiate evaluation for PML including neurology consultation.

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

- In a clinical trial of transplant-ineligible patients with newly diagnosed multiple myeloma comparing KYPROLIS, melphalan, and prednisone (KMP) vs bortezomib, melphalan, and prednisone (VMP), a higher incidence of serious and fatal adverse reactions was observed in patients in the KMP arm. KMP is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

Embryo-fetal Toxicity

- KYPROLIS can cause fetal harm when administered to a pregnant woman.
- Advise pregnant women of the potential risk to a fetus. Females of reproductive potential should use effective contraception during treatment with KYPROLIS and for 6 months following the final dose. Males of reproductive potential should use effective contraception during treatment with KYPROLIS and for 3 months following the final dose.

Adverse Reactions

- The most common adverse reactions in the combination therapy trials: anemia, diarrhea, fatigue, hypertension, pyrexia, upper respiratory tract infection, thrombocytopenia, cough, dyspnea, and insomnia.

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information.

References: 1. KYPROLIS® (carfilzomib) prescribing information, Onyx Pharmaceuticals Inc., an Amgen Inc. subsidiary. **2.** Dimopoulos M, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicenter study. *Lancet Oncol*. 2016;17:27-38. **3.** Moreau P, Mateos MV, Berenson JR, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. *Lancet Oncol*. 2018;19:953-964. **4.** Data on file, Amgen; 2016. **5.** Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol*. 2016;175:252-264. **6.** Kubiczkova L, Pour L, Sedlarikova L, Hajek R, Sevcikova S. Proteasome inhibitors—molecular basis and current perspectives in multiple myeloma. *J Cell Mol Med*. 2014;18:947-961. **7.** Crawford LJ, Walker B, Irvine AE. Proteasome inhibitors in cancer therapy. *J Cell Commun Signal.* 2011;5:101-110. **8.** Kuhn DJ, Chen Q, Voorhees PM, et al. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. *Blood.* 2007;110:3281-3290. **9.** Orlowski RZ, Kuhn DJ. Proteasome inhibitors in cancer therapy: lessons from the first decade. *Clin Cancer Res*. 2008;14:1649-1657. **10.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.2.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed September 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. **11.** Moreau P, Joshua D, Chng W-J, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. *Leukemia.* 2017;31:155-122. **12.** Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18:1327-1337. **13.** Facon T, Niesvizky R, Weisel K, et al. Carfilzomib in relapsed or refractory multiple myeloma: frailty subgroup analysis from phase 3 ASPIRE and ENDEAVOR. Poster presented at: 17th International Myeloma Workshop; September 12-15, 2019; Boston, MA. **14.** Amgen Inc. "FDA approves KYPROLIS® (carfilzomib) once-weekly 70 mg/m^2 in combination with dexamethasone (Kd70) for patients with relapsed or refractory multiple myeloma." News release; October 1, 2018. **15.** Prevision Policy: Real-time oncology review: pilot on fast track to expand – but sponsors may need time to catch up. November 19, 2018. **16.** The mSMART Clinical Practice Guidelines in relapsed myeloma. Mayo Stratification for Myeloma and Risk-adapted Therapy website. https://static1.squarespace.com/static/5b44f08ac258b493a25098a3/t/5ebc6d766a179e3b0e30c8d0/1589407097177/Treatment-of-Relapsed-Myeloma+rev7_May2020.pdf. Accessed September 2020. **17.** Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol.* 2015;33:2863-2869. **18.** Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol.* 2014;32:587-600. **19.** Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. *Haematologica*. 2016;101:396-406. **20.** Mikhael J. Management of carfilzomib-associated cardiac adverse events. *Clin Lymphoma Myeloma Leuk.* 2016;16:241-245. **21.** Moreau P, Stewart K, Dimopoulos M, et al. Once weekly (70 mg/m^2) vs twice-weekly (56 mg/m^2) dosing of carfilzomib in patients with relapsed or refractory multiple myeloma: A post hoc analysis of the ENDEAVOR, A.R.R.O.W., and CHAMPION-1 trials. *Cancer Medicine.* 2020;00:1-8.

Kyprolis® (carfilzomib) for Injection

Choose the proteasome inhibitor with superior progression-free survival for your patients with RMM[1]

Deep

Improved rates of complete response or better: 13% Kd vs 6% Vd[1]

Durable

- **Significantly extended median progression-free survival vs Vd: 18.7 months Kd vs 9.4 months Vd[1,*]**
- **First and only doublet with a proven median overall survival advantage vs Vd[1,2,12,*]**

5x less peripheral neuropathy (Grade ≥ 2)

with Kd twice weekly (7%) vs Vd (35%)[1]

Kd: Only NCCN-recommended doublet[10]

Carfilzomib (KYPROLIS®) in combination with dexamethasone (Kd twice weekly) has a category 1 designation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma (Version 2.2021) for previously treated multiple myeloma.

NCCN makes no warranties of any kind whatsoever regarding this content, use or application and disclaims any responsibility for their application or use in any way.[10]

Kd 70 mg/m^2 once weekly demonstrated superior PFS vs Kd 27 mg/m^2 twice weekly[1]

- **Median PFS 11.2 months (Kd 70 mg/m^2 once weekly) vs 7.6 months (Kd 27 mg/m^2 twice weekly)[1,†]**

*Kd vs Vd. Median PFS: 18.7 months (Kd) vs 9.4 months (Vd); HR = 0.53; 95% CI: 0.44-0.65; $P < 0.0001$, one-sided. Median OS: 47.6 months (Kd) vs 40.0 months (Vd); HR = 0.79; 95% CI: 0.65-0.96; $P = 0.01$, one-sided.[1,2,12]

†Kd 70 mg/m^2 once weekly vs Kd 27 mg/m^2 twice weekly. Median PFS: 11.2 month (Kd 70 mg/m^2 once weekly) vs 7.6 months (Kd 27 mg/m^2 twice weekly); HR = 0.69; 95% CI: 0.54–0.88; $P = 0.0014$, one-sided.[1]

Note: Kd 27 mg/m^2 is not an FDA-approved dose for KYPROLIS®.[1]

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Adverse Reactions

- The most common adverse reactions in the combination therapy trials: anemia, diarrhea, fatigue, hypertension, pyrexia, upper respiratory tract infection, thrombocytopenia, cough, dyspnea, and insomnia.

Please see additional Important Safety Information throughout.

AMGEN® Oncology

USA-171-81242 09/20

Patient Profile

Kyprolis™ (carfilzomib) for Injection

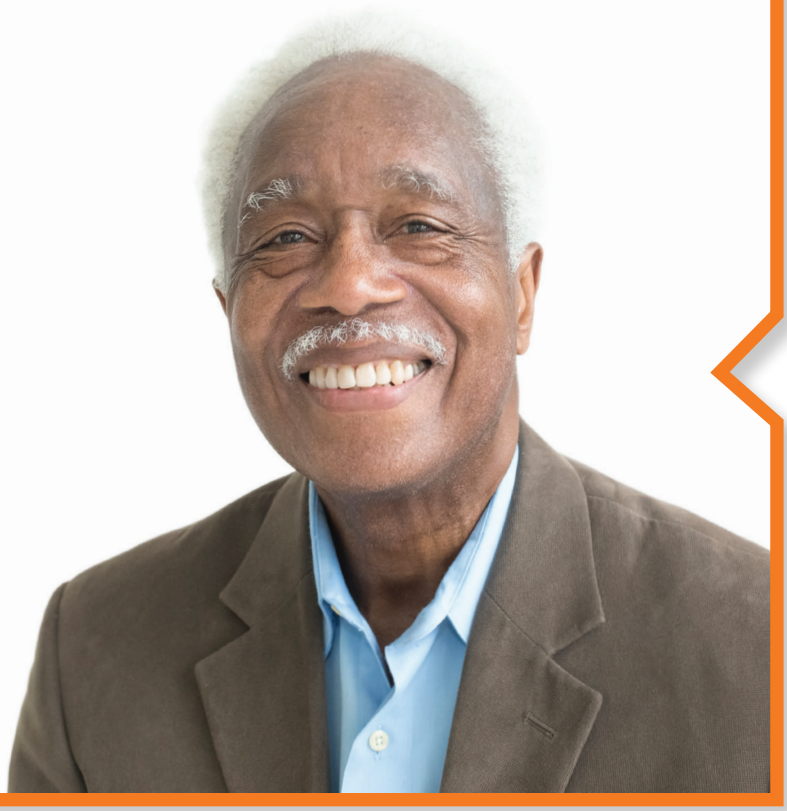
Hypothetical case study of a standard-risk* patient with multiple myeloma at first relapse

Time for a deep and durable response

JOSEPH

76-YEAR-OLD MALE

- Retired high school history teacher
- Amateur musician, enjoys teaching his grandchildren how to play guitar
- Type 2 diabetes moderately well controlled with medication and diet
- COPD limits his physical activity
- Standard-risk cytogenetics*
- ECOG PS 2



*Standard-risk cytogenetics is defined as cytogenetics that are not considered high risk (trisomies, t(11;14), t(6;14), and/or R-ISS stage I.[16,17]

COPD = chronic obstructive pulmonary disease; ECOG PS = Eastern Cooperative Oncology Group Performance Status; R-ISS = Revised International Staging System.

Not an actual patient.

INDICATION

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone or with daratumumab and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

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. Death due to cardiac arrest has occurred within one day of administration.
- Monitor patients for signs or symptoms of cardiac failure or 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 at 1 dose level reduction based on a benefit/risk assessment.

Please see full Important Safety Information throughout.

Kyprolis™ (carfilzomib) for Injection

Joseph's multiple myeloma treatment history

FIRST LINE

- Diagnosed with multiple myeloma after complaining of fatigue and nonpainful tingling in fingers
- Treated with bortezomib, lenalidomide, and dexamethasone (VRd) for 4 cycles

MAINTENANCE

- Followed by ASCT and maintenance with lenalidomide; remained in CR during maintenance

PROGRESSION

- 36 months after starting maintenance, MRI revealed the presence of new bone lesions

Joseph wants a treatment with a DEEP and DURABLE response

Go for a deep and durable response at first relapse, regardless of cytogenetic risk

Important considerations for Joseph

- **PRIOR PI EXPOSURE:** Kd twice weekly PFS results were consistent, independent of prior bortezomib exposure[2]
- **EXPLORATORY ANALYSIS:** At first relapse, Kd twice weekly demonstrated a 12-month increase in median PFS vs Vd (22.0 months Kd vs 10.1 months Vd)[11]
  - While this subgroup analysis was preplanned, demonstration of PFS efficacy within these subgroups was not a study objective. The study was not powered to evaluate PFS efficacy within this subgroup[1]
  - Median PFS in ITT population: 18.7 months Kd vs 9.4 months Vd (HR = 0.53; 95% CI: 0.44-0.65; $P < 0.0001$, one-sided)[1]
- **2X HIGHER ≥CR:** Kd twice weekly delivered 2x the rate of ≥CR vs Vd (13% Kd vs 6% Vd)[1]
- **5X LESS PERIPHERAL NEUROPATHY** with Kd twice weekly vs Vd (7% Kd vs 35% Vd)[1]

ASCT = autologous stem cell transplant; CR = complete response; MRI = magnetic resonance imaging; PI = proteasome inhibitor; Kd = KYPROLIS®+dexamethasone; PFS = progression-free survival; Vd = Velcade® (bortezomib)+dexamethasone; ITT = intent-to-treat; HR = hazard ratio; CI = confidence interval; ≥CR = complete response or better.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Cardiac Toxicities (cont'd)

- 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.
- For patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment prior to starting treatment with KYPROLIS and remain under close follow-up with fluid management.

Please see full Important Safety Information throughout.

Kyprolis™ (carfilzomib) for Injection

Biochemical relapse may require treatment

According to the International Myeloma Working Group (IMWG), a biochemical relapse is an INCREASE IN THE LEVEL OF ANY OF THE FOLLOWING IN 2 CONSECUTIVE MEASUREMENTS[18,19]

- Serum M-proteins (doubling or ≥ 10 g/L)
- Urine M-proteins (≥ 500 mg/24 hours)
- Serum FLC levels (≥ 200 mg/L or 25% increase)

Interested in further reviewing a standard-risk hypothetical case like Joseph's with a multiple myeloma expert?

Ask your KYPROLIS® representative about participating in a Problem-based Learning Program

Kd: NCCN recommended doublet[10]

NCCN Guidelines®: Carfilzomib (KYPROLIS®) in combination with dexamethasone (Kd) is the only recommended doublet regimen for relapsed multiple myeloma

Carfilzomib (KYPROLIS®) in combination with dexamethasone (Kd twice weekly) has a category 1 designation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma (Version 2.2021) for previously treated multiple myeloma.

NCCN makes no warranties of any kind whatsoever regarding this content, use or application and disclaims any responsibility for their application or use in any way.[10]

M-proteins = monoclonal proteins; FLC = free light chain; NCCN = National Comprehensive Cancer Network.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Acute Renal Failure

- Cases of acute renal failure, including some fatal renal failure events, and renal insufficiency (including renal failure) have occurred. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Kyprolis™ (carfilzomib) for Injection

Please see full Important Safety Information throughout.

Kyprolis™ (carfilzomib) for Injection

How to dose Kd[1]

IMiD-FREE

Kd 70 mg/m² ONCE WEEKLY

Infusion time
30 minutes

KYPROLIS® priming dose
20 mg/m² Day 1 of Cycle 1 to evaluate tolerability

Target KYPROLIS® therapeutic dose
70 mg/m² starting Day 8 of Cycle 1

Treatment schedule
- Administer 70 mg/m² 1 day each week for 3 weeks
- Follow with 13-day rest period, as part of 28-day treatment cycle
- For Cycles 10 and beyond, dexamethasone is not given on Day 22
- Continue until disease progression or unacceptable toxicity occurs

IMiD-FREE

Kd 56 mg/m² TWICE WEEKLY

Infusion time
30 minutes

KYPROLIS® priming dose
20 mg/m² Days 1 and 2 of Cycle 1 to evaluate tolerability

Target KYPROLIS® therapeutic dose
56 mg/m² starting Day 8 of Cycle 1

Treatment schedule
- Administer 56 mg/m² 2 consecutive days each week for 3 weeks
- Follow with 12-day rest period, as part of 28-day treatment cycle
- Continue until disease progression or unacceptable toxicity occurs

Refer to dexamethasone Prescribing Information.

- **KYPROLIS® is offered in 3 single-dose vial sizes: 10 mg, 30 mg, and 60 mg[1]**

Calculating the priming & therapeutic dose[1]

Patient's body surface area (BSA; m²) **x dose** (mg/m²)

In patients with a BSA > 2.2 m², calculate the dose based upon a BSA of 2.2 m²

EXAMPLES:

Kd 70 mg/m² ONCE WEEKLY:
Calculate the correct Kd once weekly mg/m² dose for a patient with a BSA of 1.8 m²
Priming Dose: **1.8 m² x 20 mg/m² = 36 mg**
Therapeutic Dose: **1.8 m² x 70 mg/m² = 126 mg**

Kd 56 mg/m² TWICE WEEKLY:
Calculate the correct Kd twice weekly mg/m² dose for a patient with a BSA of 1.8 m²
Priming Dose: **1.8 m² x 20 mg/m² = 36 mg**
Therapeutic Dose: **1.8 m² x 56 mg/m² = 101 mg**

Manage hydration throughout treatment[1]

Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity.

- Consider hydration with both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and IV fluids (250 mL to 500 mL of appropriate IV fluid prior to each dose in Cycle 1)
- If needed, give an additional 250 mL to 500 mL of IV fluids following KYPROLIS® administration
- Continue oral and/or IV 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

Please see the full Prescribing Information for KYPROLIS® for dosing and administration.

IMiD = immunomodulatory drug; IV = intravenous.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Tumor Lysis Syndrome

- Cases of Tumor Lysis Syndrome (TLS), including fatal outcomes, have occurred. Patients with a high tumor burden should be considered at greater risk for TLS. Adequate hydration is required prior to each dose in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, and withhold until resolved.

Please see full Important Safety Information throughout.

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Kyprolis® (carfilzomib) for Injection

Cardiac adverse reaction (AR) considerations and management strategies

A large myeloma practice treating **several hundred patients** with KYPROLIS® shared its experience in the considerations and strategies for the prevention and management of certain cardiac ARs (cardiac failure and hypertension).

Cardiac ARs (cardiac failure and hypertension)[20]

1 PRIOR TO KYPROLIS® INITIATION[20]

- Ensure patients with cardiac risk factors have been assessed by a hematologist/oncologist and a cardiologist (if required)
- Patients with baseline hypertension or coronary disease do not need to be excluded from KYPROLIS® treatment
- Ensure underlying cardiac conditions are managed
- Plan hydration needs for individual patients

2 DURING TREATMENT[20]

- Monitor for signs and symptoms of cardiac ARs (including dyspnea)
- Monitor for volume overload, and adjust hydration as necessary

3 IF A CARDIAC AR OCCURS[20]

- Withhold KYPROLIS® while patient is being evaluated
- Assess for fluid overload and involve cardiologist to address clinical issues as needed
- Consider reinstitution only if cardiac issue has been settled, and upon benefit/risk assessment
- Consider dose reduction and/or fluid restrictions upon therapy reinstitution

INDICATION

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone or with daratumumab and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

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. Death due to cardiac arrest has occurred within one day of administration.
- Monitor patients for signs or symptoms of cardiac failure or 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 at 1 dose level reduction based on a benefit/risk assessment.

Please see full Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

Manage hydration throughout treatment[1]

Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity.

- Consider hydration with both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and IV fluids (250 mL to 500 mL of appropriate IV fluid prior to each dose in Cycle 1)
- If needed, give an additional 250 mL to 500 mL of IV fluids following KYPROLIS® administration
- Continue oral and/or IV 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

Please see the full Prescribing Information for KYPROLIS® for dosing and administration.

IV = intravenous.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Cardiac Toxicities (cont'd)

- 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.
- For patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment prior to starting treatment with KYPROLIS and remain under close follow-up with fluid management.

Please see full Important Safety Information throughout.

AMGEN®

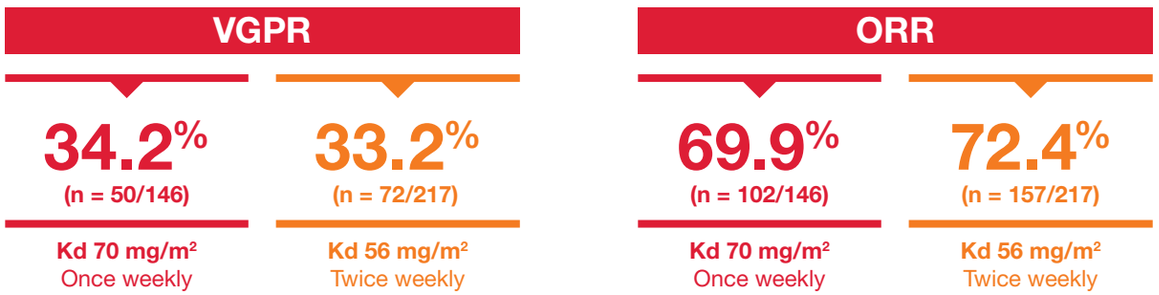
Oncology

Kyprolis® (carfilzomib) for Injection

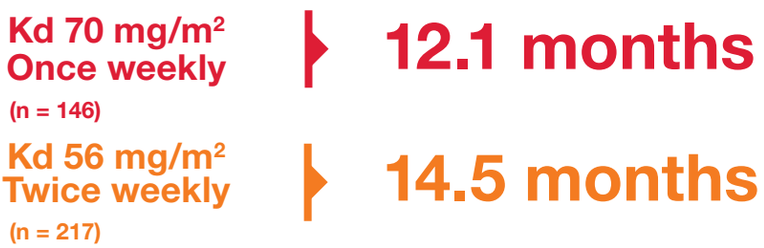
Comparable efficacy between Kd 70 mg/m² once weekly and Kd 56 mg/m² twice weekly[21]

Response rates and PFS were similar between the regimens in the post hoc analysis

Response rates[21]



Median progression-free survival[21]



- **Post hoc analysis:**
  Comparison of PFS, ORR, and VGPR between Kd 70 and Kd 56 were not the objectives of these studies. The studies used were not powered to evaluate PFS, ORR, and VGPR within this subgroup

- After adjusting for prognostic covariates, there were no significant differences in efficacy outcomes between the Kd 70 mg/m² once weekly and Kd 56 mg/m² twice weekly dosing schedules[21]

Post hoc subgroup design

In this post hoc analysis, data from the CHAMPION-1,* A.R.R.O.W., and ENDEAVOR trials were used to compare the safety and efficacy of Kd 70 mg/m² once weekly (n = 146) and Kd 56 mg/m² twice weekly (n = 217). Patients on Kd 70 in the CHAMPION-1 and A.R.R.O.W. studies were compared to patients on Kd 56 in the ENDEAVOR trial. To account for variations in the studies' respective patient populations, side-by-side efficacy and safety comparisons were performed in subgroups of **patients with 2 to 3 prior lines of therapy who were not refractory to bortezomib**. After adjusting for prognostic covariates (age, ISS stage, number of prior lines of therapy, and bortezomib- or lenalidomide-refractory status), the results of regression modeling further supported the side-by-side findings; there were no significant differences in efficacy outcomes between the Kd 70 mg/m² once weekly and Kd 56 mg/m² twice weekly dosing schedules after adjusting for prognostic covariates. The efficacy endpoints of this post hoc analysis were PFS and ORR.[21]

*CHAMPION-1 was a phase 1/2 dose-finding study of once-weekly KYPROLIS® in patients with RRMM with 1 to 3 prior lines of therapy.[21]
Kd = KYPROLIS®+dexamethasone; PFS = progression-free survival; VGPR = very good partial response; ORR = overall response rate; Kd 70 = Kd 70 mg/m² once weekly; Kd 56 = Kd 56 mg/m² twice weekly; ISS = International Staging System; RRMM = relapsed or refractory multiple myeloma.

INDICATION

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone or with daratumumab and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

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. Death due to cardiac arrest has occurred within one day of administration.
- Monitor patients for signs or symptoms of cardiac failure or 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 at 1 dose level reduction based on a benefit/risk assessment.

Please see full Important Safety Information throughout.

Post hoc analysis:

Comparable safety between Kd 70 mg/m² once weekly and Kd 56 mg/m² twice weekly[21]

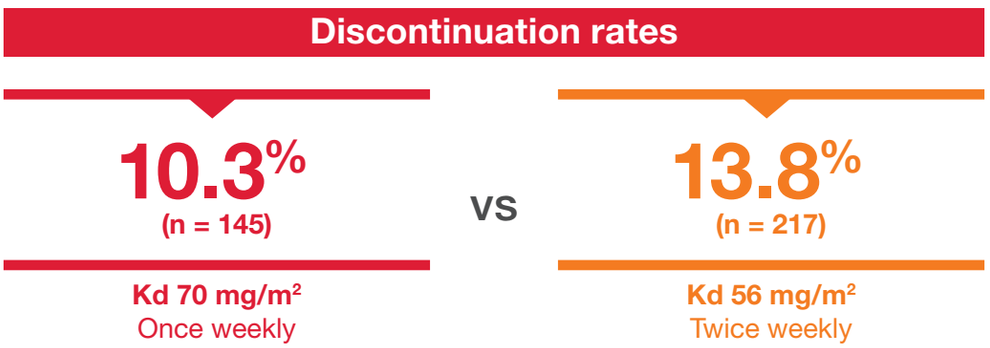
Kyprolis® (carfilzomib) for Injection

Safety profile

Select treatment-emergent adverse reactions of interest (Grade ≥ 3)[21]

	Kd 70 mg/m² once weekly (n = 145)	Kd 56 mg/m² twice weekly (n = 217)
Cardiac failure	1.4%	5.1%
Acute renal failure	3.4%	6.0%
Hypertension	5.5%	15.7%
Venous embolism and thrombotic events	2.1%	2.3%

Discontinuation due to any ARs[21]



ARs = adverse reactions.

Please see the full Prescribing Information for KYPROLIS® for dosing and administration.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Cardiac Toxicities (cont'd)

- 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.
- For patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment prior to starting treatment with KYPROLIS and remain under close follow-up with fluid management.

Please see full Important Safety Information throughout.

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