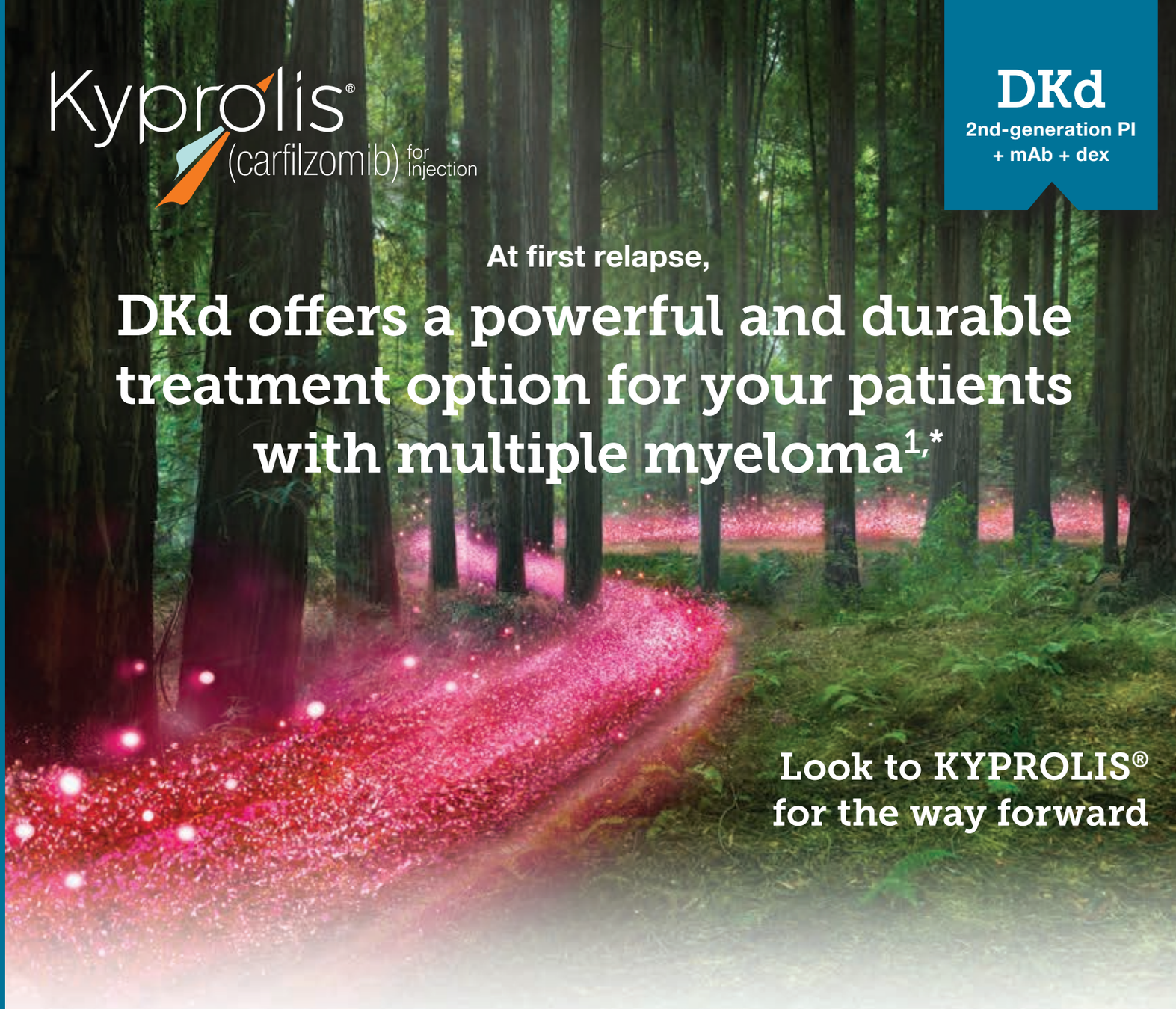


***Median PFS:** At a median follow-up of 16.9 months, median PFS has not yet been reached (DKd; n = 312) vs 15.8 months (Kd; n = 154); HR = 0.63; 95% CI: 0.46-0.85; *P* = 0.0014, one-sided.[1,2]

DKd vs Kd study design: Phase 3, randomized, open-label, multicenter trial that compared KYPROLIS® plus daratumumab and dexamethasone (DKd) to KYPROLIS® plus dexamethasone (Kd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. 466 patients were randomized 2:1 to receive DKd (n = 312) or Kd (n = 154) twice weekly for 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint was PFS. Select secondary endpoints included ORR, MRD-negative CR rate at 12 months, OS, and safety.[1,2]

DKd = KYPROLIS®+Darzalex® (daratumumab) and dexamethasone; PI = proteasome inhibitor; mAb = monoclonal antibody; dex = dexamethasone; PFS = progression-free survival; Kd = KYPROLIS®+dexamethasone; HR = hazard ratio; CI = confidence interval; IV = intravenous; ORR = overall response rate; MRD = minimal residual disease; CR = complete response; OS = overall survival.

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

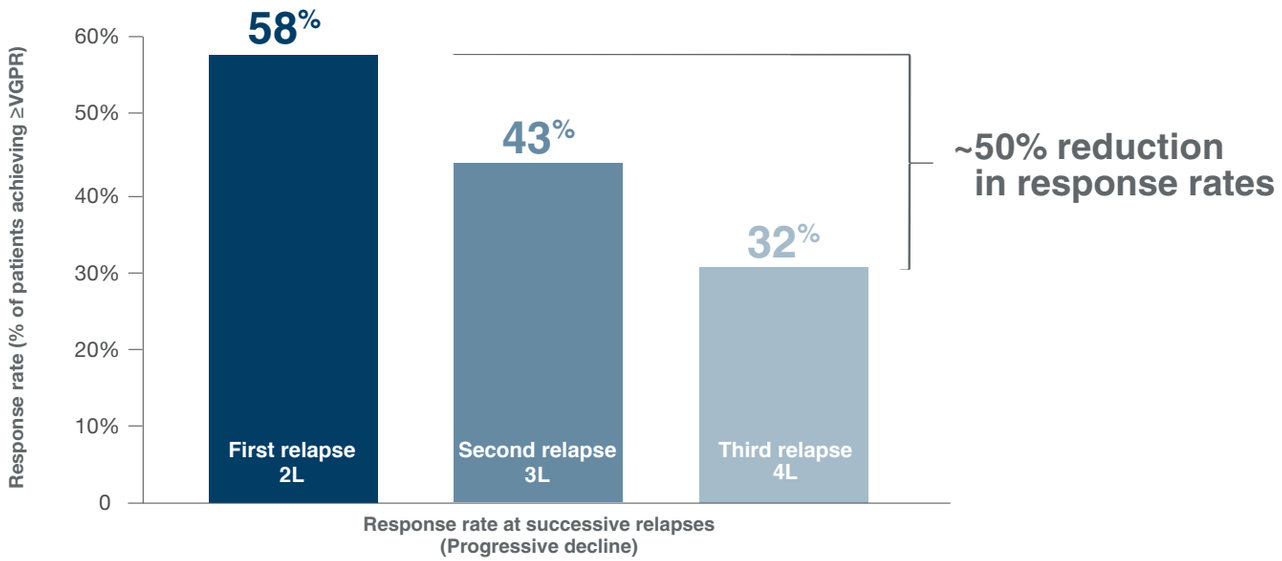
- New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients 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[3,4]

In patients who receive treatment for relapses, response rates decline by almost HALF by the third relapse[3]

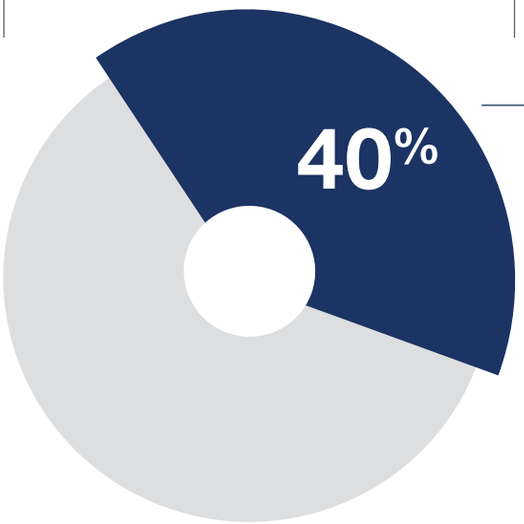
The proportion of patients achieving ≥VGPR decreased from 58% at first relapse to 43% at second relapse to 32% at third relapse*



*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.[3]

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.

At first relapse,

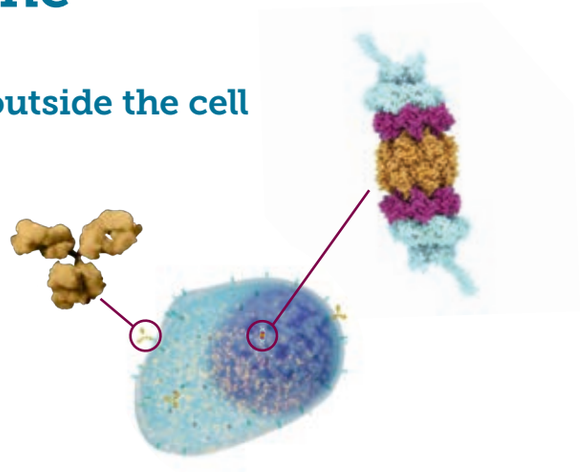
Choose the combination of a 2nd-generation PI, a CD38 mAb, and dexamethasone[2]

DKd delivers a dual-targeted approach inside and outside the cell

KYPROLIS® inhibits intracellular proteasomal activity, preventing cells from recycling excess proteins[2]

– Second-generation PI with irreversible binding to the proteasome

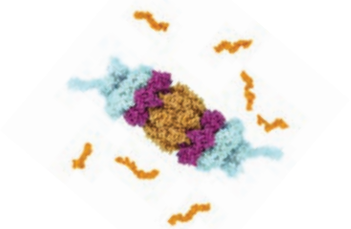
Daratumumab inhibits tumor cell growth by extracellular binding to the CD38 receptor on the myeloma cells, resulting in both direct and immune-mediated effects[2]



The proteasome is an important therapeutic target in multiple myeloma[5-7]

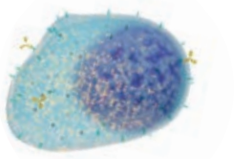
The evolution of clonal heterogeneity in multiple myeloma changes after exposure to certain therapies—but the existence of proteasomes within the myeloma cells remains

Proteasome



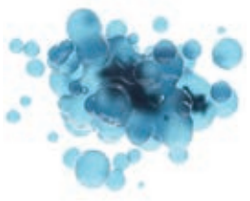
PIs inhibit proteasomal activity, preventing proteasomes from recycling excess proteins.[5,8]

Myeloma cell



This causes protein levels to build up inside the cell…[5,8]

Apoptosis



…resulting in myeloma cell apoptosis.[5,8]

Take action in targeting multiple myeloma with 2 distinct mechanisms of action[1,2]

For more information, see the video "Pathway to Proteasome Inhibition" at KYPROLIS-HCP.com/mechanism-of-action

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.

Kyprolis® (carfilzomib) for Injection

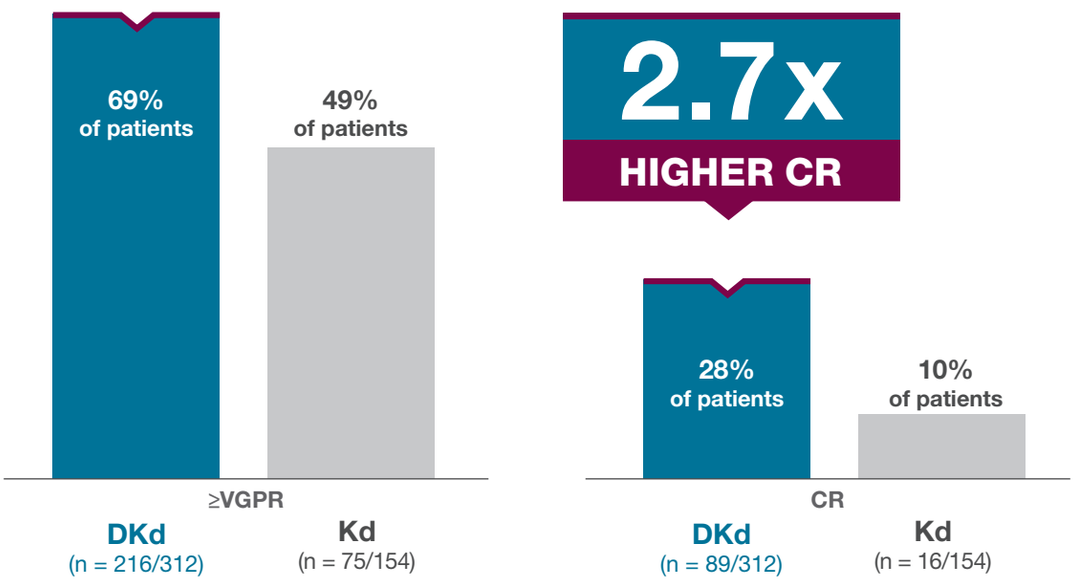
DKd more than DOUBLED the chance of achieving a complete response vs Kd[1]

Deep and deeper

DKd delivered higher ORR, ≥VGPR, CR, and MRD-negative CR than Kd, beginning at first relapse[1]

- ORR: Patients in the DKd arm achieved an ORR of 84% vs 75% for the Kd arm (P = 0.0040, one-sided)[1,*]

Responses by category[1]



~4 out of 10 patients with a CR achieved an even deeper response of MRD negativity[1,†]

- 12% of patients achieved MRD-negative CR at 12 months with DKd vs 1.3% with Kd (P < 0.0001, one-sided)[1,†]
- MRD tests detect residual tumor cells in the bone marrow at **100x-10,000x lower concentration** than conventional methods for assessing CR[9,10,‡]

*ORR was defined as proportion of patients with PR or better.[2]
†MRD-negative CR (at the 10^{-5} level) is defined as achievement of CR per the IMWG-URC and MRD-negative status assessed by the next generation sequencing assay (ClonoSEQ) at the 12-month landmark (from 8 months to 13 months window).[1]
‡Based on sensitivity limits of < 1 in 10^4 to 10^6 for MRD-negative CR vs < 5% for CR.[9,10]

IMWG-URC = International Myeloma Working Group-Uniform Response Criteria.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Acute Renal Failure

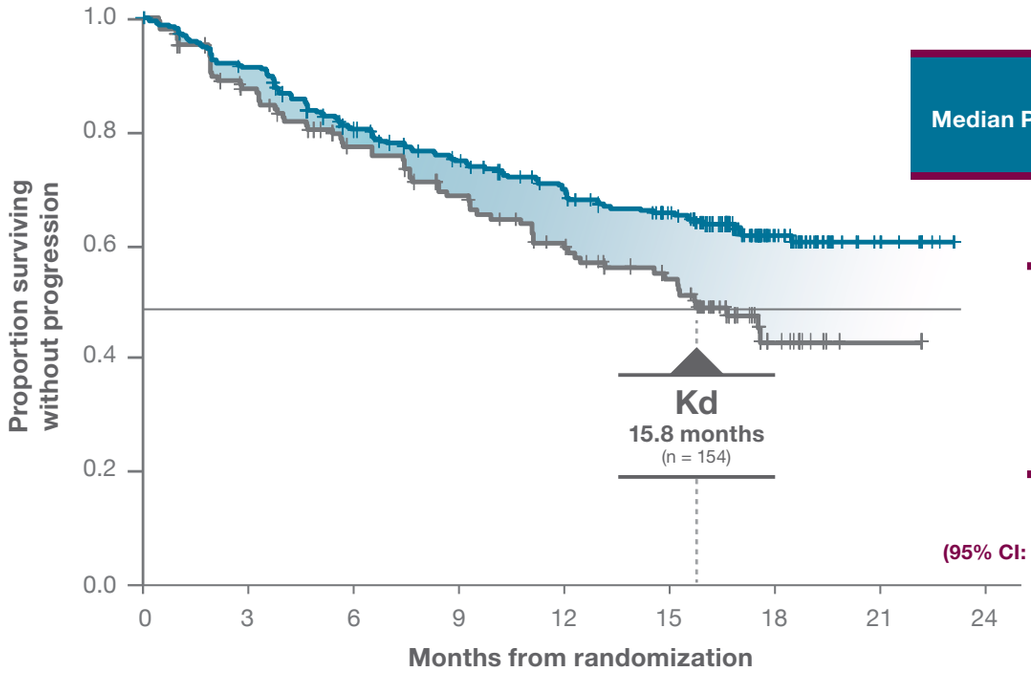
- Cases of acute renal failure, including some fatal renal failure events, and renal insufficiency (including renal failure) have occurred. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal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

Kyprolis® (carfilzomib) for Injection

DKd significantly reduced the risk of disease progression or death by 37% vs Kd[1]

Durable

With a median follow-up of nearly 17 months, the majority of patients on DKd had not progressed, so median PFS has not yet been reached[1,2]



DKd
Median PFS has not yet been reached
(n = 312)

37%
reduced risk
of disease progression or death with DKd vs Kd

HR = 0.63
(95% CI: 0.46-0.85; *P* = 0.0014, one-sided)

Number at risk:

DKd	**312**	**279**	**236**	**211**	**189**	**165**	**57**	**14**	**0**
Kd	**154**	**122**	**100**	**85**	**70**	**55**	**13**	**2**	**0**

DKd: National Comprehensive Cancer Network® (NCCN®) preferred[11]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Carfilzomib (KYPROLIS®) in combination with daratumumab (Darzalex®) and dexamethasone (DKd) is included under "preferred regimens" as a treatment option for previously treated multiple myeloma

Carfilzomib (KYPROLIS®) in combination with daratumumab (Darzalex®) and dexamethasone (DKd) has a category 1 designation in the 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.[11]

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.

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

Adverse reactions (≥ 15%) in patients who received either DKd or Kd[1]

Adverse reactions		DKd (n = 308)		Kd (n = 153)	
		All grades	Grade 3 or Grade 4	All grades	Grade 3 or Grade 4
General disorders and administration site conditions	Infusion-related reactions[a]	41%	12%	28%	5%
	Fatigue[b]	32%	11%	28%	8%
	Pyrexia	20%	1.9%	15%	0.7%
Infections	Respiratory tract infection[c]	40%[g]	7%	29%	3.3%
	Pneumonia	18%[g]	13%	12%	9%
	Bronchitis	17%	2.6%	12%	1.3%
Blood and lymphatic system disorders	Thrombocytopenia[d]	37%	25%	30%	16%
	Anemia[e]	33%	17%	31%	14%
Gastrointestinal disorders	Diarrhea	32%	3.9%	14%	0.7%
	Nausea	18%	0%	13%	0.7%
Vascular disorders	Hypertension	31%	18%	28%	13%
Respiratory, thoracic, and mediastinal disorders	Cough[f]	21%	0%	21%	0%
	Dyspnea	20%	3.9%	22%	2.6%
Psychiatric disorders	Insomnia	18%	3.9%	11%	2.0%
Musculoskeletal and connective tissue disorders	Back pain	16%	1.9%	10%	1.3%

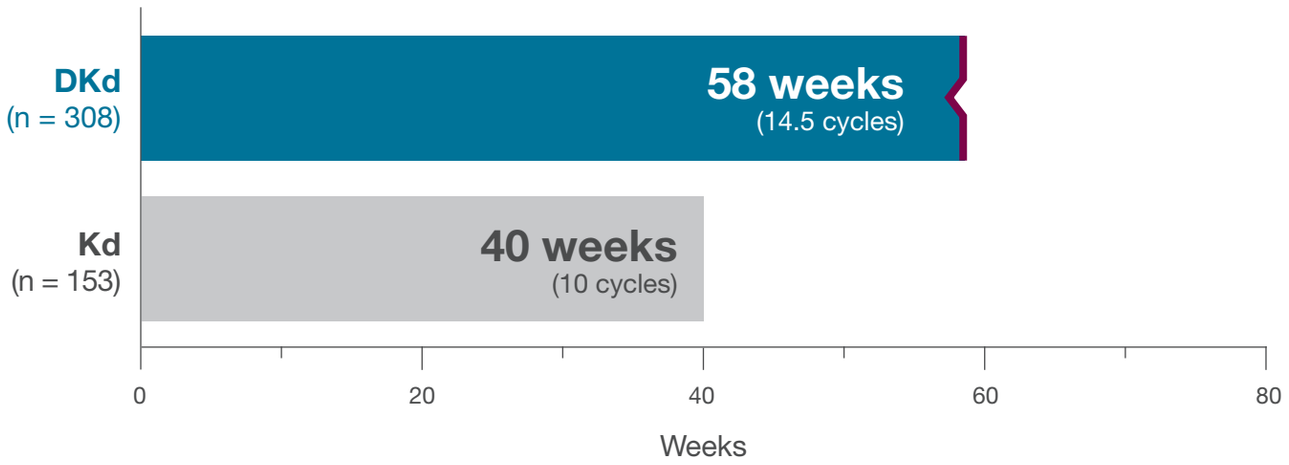
[a]The incidence of infusion related reactions is based on a group of symptoms (including hypertension, pyrexia, rash, myalgia, hypotension, blood pressure increased, urticaria, acute kidney injury, bronchospasm, face edema, hypersensitivity, rash, syncope, wheezing, eye pruritus, eyelid edema, renal failure, swelling face) related to infusion reactions which occurred within 1 day after DKd or Kd administration.
[b]Fatigue includes fatigue and asthenia.
[c]Respiratory tract infection includes respiratory tract infection, lower respiratory tract infection, upper respiratory tract infection and viral upper respiratory tract infection.
[d]Thrombocytopenia includes platelet count decreased and thrombocytopenia.
[e]Anemia includes anemia, hematocrit decreased and hemoglobin decreased.
[f]Cough includes productive cough and cough.
[g]Includes fatal adverse reactions.

Adverse reactions were consistent with the known safety profiles of each medication[9]

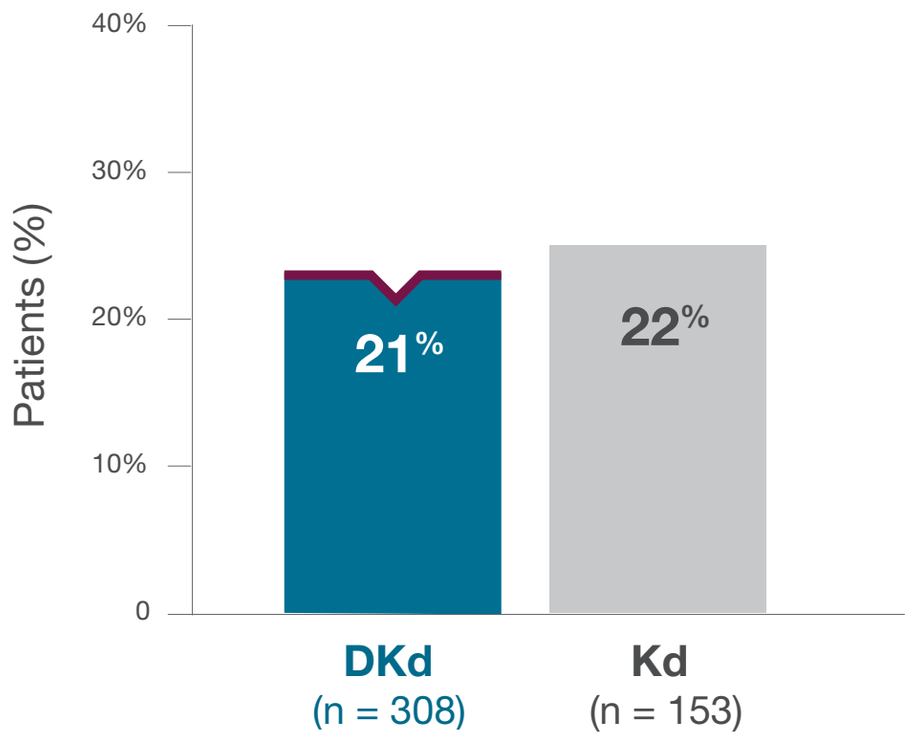
Kyprolis® (carfilzomib) for Injection

DKd led to longer time on therapy and had comparable discontinuation rates vs Kd[1]

Median treatment duration of KYPROLIS®[1]



Permanent discontinuation of KYPROLIS® due to ARs[1]



ARs = adverse reactions.

Please see additional Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

A once-weekly dosing option for your patients[1,2,*]

DKd

70 mg/m²

ONCE WEEKLY

2nd-generation PI + mAb + dex
DKd once weekly

Infusion time
30 minutes

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

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

Treatment schedule
- Administer KYPROLIS® 70 mg/m² 1 day each week for 3 weeks
- Follow with a 13-day rest period, as part of a 28-day treatment cycle
- Continue until disease progression or unacceptable toxicity occurs

- DKd also offers a twice-weekly, 56-mg/m² dosing option with a 20-mg/m² priming dose[1,†]

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

Refer to Darzalex® (daratumumab) and dexamethasone Prescribing Information for additional dosage information on that product.

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. Hydration should be monitored throughout treatment and adjusted according 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.

*Once-weekly dosing was demonstrated in the EQUULEUS study, a phase 1b, open-label, multi-cohort study (N = 85) which evaluated the combination of once-weekly KYPROLIS® with IV daratumumab and dexamethasone in patients with relapsed or refractory multiple myeloma who received 1 to 3 prior lines of therapy. KYPROLIS® was administered weekly on Days 1, 8, and 15 of each 28-day cycle at a dose of 70 mg/m² with a priming dose of 20 mg/m² on Day 1 of Cycle 1. Safety and tolerability of DKd were evaluated as primary endpoints. Results from the EQUULEUS study set a precedent of DKd regimen safety and efficacy for the phase 3 CANDOR study and provided the rationale for the once weekly dosing of DKd.[1,12]

†Demonstrated in the phase 3 CANDOR study.[1]

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.

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.

Kyprolis® (carfilzomib) for Injection

IMPORTANT SAFETY INFORMATION FOR KYPROLIS (cont'd)

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.

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

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.

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.

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, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2020;396:186-197. **3.** Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol*. 2016;175:252-264. **4.** Data on file. Amgen, Inc. 2016. **5.** 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. **6.** Crawford LJ, Walker B, Irvine AE. Proteasome inhibitors in cancer therapy. *J Cell Commun Signal*. 2011;5:101-110. **7.** Keats J, Chesi M, Egan, J, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012;120:1067-1076. **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.** Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study [supplementary appendix]. *Lancet*. 2020;396:186-197. **10.** Kumar S, Paiva B, Anderson K, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17:e328-346. **11.** 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. **12.** Chari A, Martinez-Lopez J, Mateos MV, et al. Daratumumab plus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. *Blood*. 2019;134:421-431. **13.** 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. **14.** Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. *Haematologica*. 2016;101:396-406.

Kyprolis® (carfilzomib) for injection

DKd delivers a powerful and durable approach for your patients with multiple myeloma at first relapse[1]

Deep[1]

DKd delivered higher ORR, ≥VGPR, CR, and MRD-negative CR than Kd, beginning at first relapse

- ORR: 84% vs 75%; *P* = 0.0040, one-sided*
- ≥VGPR: 69% vs 49%
- CR: 28% vs 10%
- MRD-negative CR at 12 months: 12% vs 1.3%; *P* < 0.0001, one-sided†

Durable[1]

DKd significantly reduced the risk of disease progression or death by 37% vs Kd (HR = 0.63; 95% CI: 0.46-0.85; *P* = 0.0014, one-sided)‡

Adverse reactions consistent with the known safety profiles of each medication[9]

- The most common adverse reactions in the DKd vs Kd study: Infusion reactions, respiratory tract infections, thrombocytopenia, anemia, diarrhea, hypertension, fatigue, and cough[1]

DKd: NCCN preferred[11]

NCCN Guidelines:

Carfilzomib (KYPROLIS®) in combination with daratumumab (Darzalex®) and dexamethasone (DKd) has a category 1 designation in the 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.

*ORR was defined as proportion of patients with PR or better.[2]

†MRD-negative CR (at the 10^{-5} level) is defined as achievement of CR per the IMWG-URC and MRD-negative status assessed by the next generation sequencing assay (ClonoSEQ) at the 12-month landmark (from 8 months to 13 months window).[1]

‡With a median follow-up of nearly 17 months, the majority of patients on DKd had not progressed, so median PFS has not yet been reached.[1,2]

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-171-81386 09/20

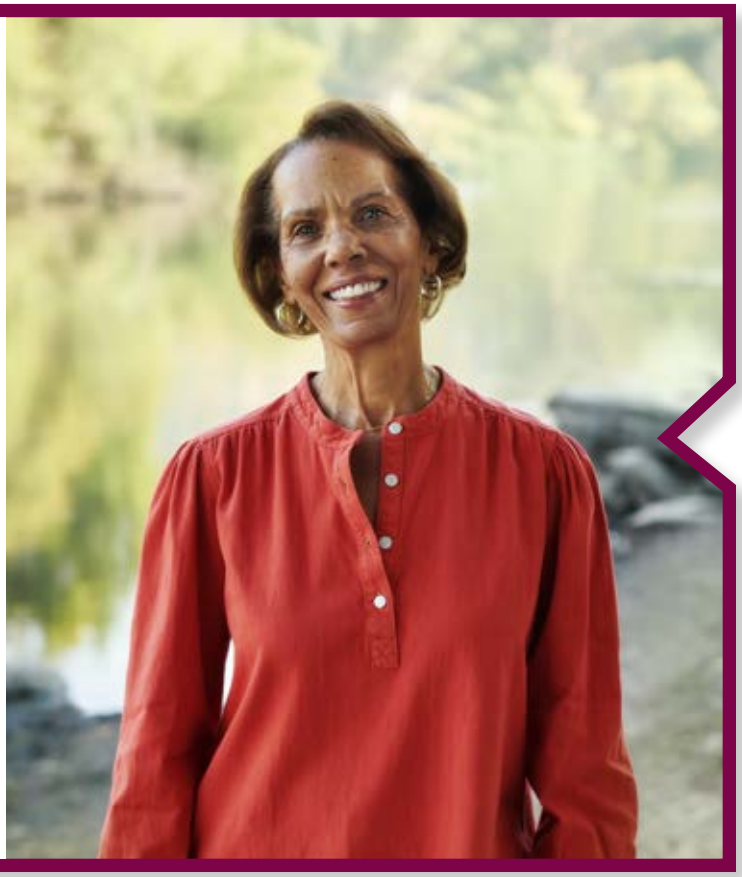
Hypothetical case study of a high-risk* patient with multiple myeloma at first relapse

Chance for a powerful, deep, and durable response with DKd[1]

DIANE

65-YEAR-OLD ACTIVE FEMALE

- Recently retired and moved with her husband to be closer to their children
- Enjoys long walks and playing with her grandchildren
- Diagnosed with multiple myeloma after presenting with fatigue and bone pain
- High-risk cytogenetics with LDH greater than the upper limit of normal (275 IU/L)
- Transplant eligible
- ECOG PS 0



*High-risk defined as a patient with cytogenetic abnormalities that are considered high-risk, including t(4; 14), t(14; 16), or del17p.[2]

DKd = KYPROLIS®+Darzalex® (daratumumab) and dexamethasone; LDH = lactate dehydrogenase; ECOG PS = Eastern Cooperative Oncology Group Performance Status.

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 additional Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

Diane's multiple myeloma treatment history

FIRST LINE
- Treated with VRd for 4 cycles (induction), followed by ASCT, and then 2 cycles of VRd consolidation

MAINTENANCE
- Achieved ≥VGPR after ASCT, which was maintained post-VRd consolidation
- Patient moved to a maintenance regimen with lenalidomide (10 mg)

PROGRESSION
- 10 months after starting maintenance therapy, MRI revealed the presence of new bone lesions
- Patient may be refractory to lenalidomide and might benefit from a 2nd-generation PI + mAb + dex triplet regimen

Diane's doctor may suggest a 2nd-generation PI + mAb + dex triplet regimen with a powerful, deep, and durable response[1,2]

For patients at first relapse, choose a unique, dual-targeted approach with DKd[1,2]

Important considerations from the CANDOR trial:

- **2.7x CR:** DKd more than DOUBLED the chance of achieving a complete response vs Kd[1]:
  - **Complete response (CR):** 28% of patients (n = 89) experienced CR with DKd vs 10% (n = 16) with Kd
  - **1.4x higher rate of VGPR or better:** 69% of patients (n = 216) on DKd achieved VGPR or better vs 49% (n = 75) on Kd
- **HIGHER RATES OF MRD-NEGATIVE CR:** DKd delivered higher MRD-negative CR than Kd[1]
  - 28% of patients reached CR, of which ~4 out of 10 patients achieved an even deeper response of MRD negativity[1,*]
- **MEDIAN PFS:** DKd significantly reduced the risk of disease progression or death by 37% vs Kd (HR = 0.63; 95% CI: 0.46-0.85; *P* = 0.0014, one-sided)[1,2,†]
- **MEDIAN TREATMENT DURATION (KYPROLIS®):** DKd 58 weeks (14.5 cycles) vs Kd 40 weeks (10 cycles)[1]
- **COMPARABLE PERMANENT DISCONTINUATION RATES OF KYPROLIS®:** 21% DKd (n = 308) vs 22% Kd (n = 153)[1]

*12% of patients achieved MRD-negative CR at 12 months with DKd vs 1.3% with Kd ($P < 0.0001$, one-sided).[1,9,10,‡]
†With a median follow-up of nearly 17 months, the majority of patients on DKd had not progressed, so median PFS has not yet been reached.[1,2]
‡MRD-negative CR (at the 10^{-5} level) is defined as achievement of CR per the IMWG-URC and MRD-negative status assessed by the next generation sequencing assay (ClonoSEQ) at the 12-month landmark (from 8 months to 13 months window).[1]

VRd = Velcade® (bortezomib)+lenalidomide and dexamethasone; ASCT = autologous stem cell transplant; ≥VGPR = very good partial response or better; MRI = magnetic resonance imaging; PI = proteasome inhibitor; mAb = monoclonal antibody; dex = dexamethasone; Kd = KYPROLIS®+dexamethasone; MRD = minimal residual disease; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; IMWG-URC = International Myeloma Working Group-Uniform Response Criteria.

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 additional Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

Biochemical relapse is also an indicator for evaluating a treatment change

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[13,14]

- 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 high-risk hypothetical case like Diane's with a multiple myeloma expert?

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

DKd: NCCN preferred[11]

NCCN Guidelines: Carfilzomib (KYPROLIS®) in combination with daratumumab (Darzalex®) and dexamethasone (DKd) is included under "preferred regimens" as a treatment option for previously treated multiple myeloma

Carfilzomib (KYPROLIS®) in combination with daratumumab (Darzalex®) and dexamethasone has a category 1 designation in the 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.[11]

M-proteins = monoclonal proteins; FLC = free light chain.

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.

Please see additional Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

How to dose DKd[1,2]

DKd

70 mg/m²

ONCE WEEKLY

2nd-generation PI + mAb + dex
DKd once weekly*

Infusion time
30 minutes

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

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

Treatment schedule
- Administer KYPROLIS® 70 mg/m² 1 day each week for 3 weeks
- Follow with a 13-day rest period, as part of a 28-day treatment cycle
- Continue until disease progression or unacceptable toxicity occurs

- DKd also offers a twice-weekly, 56-mg/m² dosing option with a 20-mg/m² priming dose[1,†]

  Refer to Darzalex® (daratumumab) and dexamethasone Prescribing Information for additional dosage information on that product.
- 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) **= Priming or therapeutic dose** (mg)
In patients with a BSA > 2.2 m², calculate the dose based upon a BSA of 2.2 m²

EXAMPLES: *Calculate the correct DKd 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**

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.

*Demonstrated in the EQUULEUS study. Refer to page 8 of the brochure or the CANDOR subgroup analysis and EQUULEUS study design insert.[1]
†Demonstrated in the phase 3 CANDOR study.[1]
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 additional Important Safety Information throughout.

AMGEN®
Oncology

Kyprolis® (carfilzomib) for Injection

DKd: Study designs and subgroup analysis

DKd = KYPROLIS®+Darzalex® (daratumumab) and dexamethasone.

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.

DKd vs Kd study (CANDOR)

DKd vs Kd study design: Phase 3, randomized, open-label, multicenter trial that compared KYPROLIS® plus daratumumab and dexamethasone (DKd) to KYPROLIS® plus dexamethasone (Kd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. 466 patients were randomized 2:1 to receive DKd (n = 312) or Kd (n = 154) twice weekly for 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint was PFS. Select secondary endpoints included ORR, MRD-negative CR rate at 12 months, OS, and safety.[1,2]

Baseline characteristics of the intent-to-treat population[1,2]

	DKd (n = 312)	Kd (n = 154)	Total (N = 466)
Age—number of patients (%)			
18-64 years	163 (52)	77 (50)	240 (52)
65-74 years	121 (39)	55 (36)	176 (38)
75 years and older	28 (9.0)	22 (14)	50 (11)
ECOG PS—number of patients (%)			
0 or 1	295 (95)	147 (95)	442 (95)
2	15 (4.8)	7 (4.5)	22 (4.7)
Missing	2 (0.6)	0 (0.0)	2 (0.4)
Cytogenetic risk group determined by FISH—number of patients (%)*			
High risk	48 (15)	26 (17)	74 (16)
Standard risk	104 (33)	52 (34)	156 (34)
Unknown	160 (51)	76 (49)	236 (51)
Prior lines of therapy—number of patients (%)			
1	144 (46)	70 (45)	214 (46)
2	99 (32)	46 (30)	145 (31)
3	69 (22)	37 (24)	106 (23)
Prior therapy—number of patients (%)			
Prior bortezomib	287 (92.0)	134 (87.0)	421 (90)
Prior lenalidomide	123 (39)	74 (48)	197 (42)
Refractory to lenalidomide†	99 (32)	55 (36)	154 (33)

Key eligibility criteria (N = 466)[1,2]:

- 1 to 3 prior lines of therapy with ≥PR to ≥ 1 prior therapy
- ECOG PS 0-2
- CrCl ≥ 20 mL/min
- LVEF ≥ 40%

Key exclusion criteria[1,2,9]:

- Known moderate or severe persistent asthma within the past 2 years
- Known COPD with a FEV1 < 50% of predicted normal
- Active congestive heart failure (defined as NYHA Class III to IV)
- Symptomatic ischemia

*FISH analysis was conducted by the central lab. The high-risk group consisted of patients with the genetic subtypes t(4;14), t(14;16), or deletion 17p. The standard-risk group consisted of patients without cytogenetic abnormalities that are considered high risk. The unknown risk group consisted of patients with FISH results that failed or were canceled.[2]

†Patients were considered refractory to a drug received in previous regimens if any of the following criteria were met: (1) best response to any regimen containing the drug was stable disease or progressive disease; (2) reason the drug was stopped was progression in any regimen; (3) date of relapse/progression was after start date and within 60 days after stop date of the drug in any regimen.[2]

Kd = KYPROLIS®+dexamethasone; IV = intravenous; PFS = progression-free survival; ORR = overall response rate; MRD = minimal residual disease; CR = complete response; OS = overall survival; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ISS = International Staging System; IxRS = interactive voice–web response system; FISH = fluorescence in situ hybridization; ≥PR = partial response or better; CrCl = creatinine clearance; LVEF = left ventricular ejection fraction; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume; NYHA = New York Heart Association.

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.

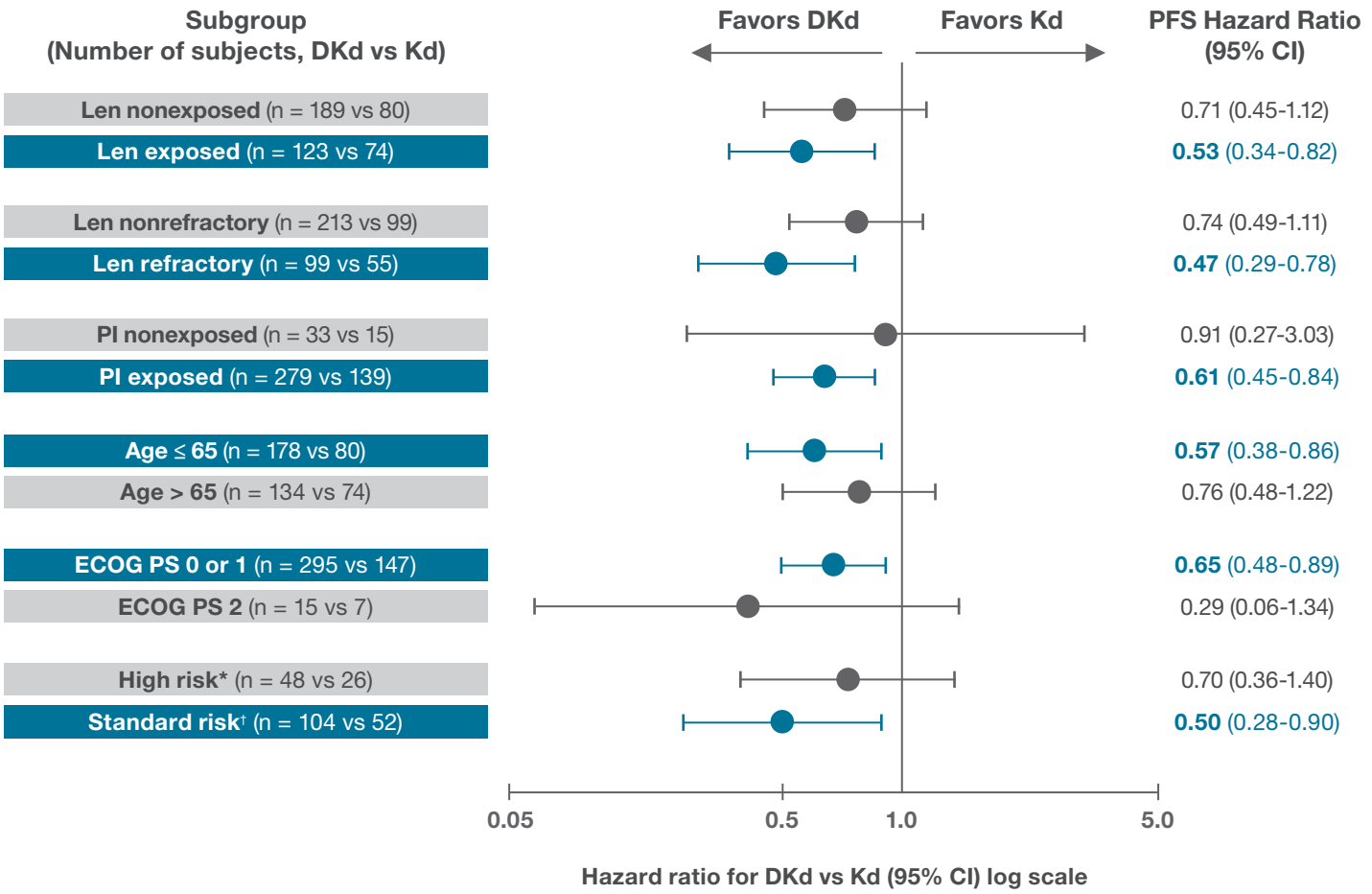
Please see additional Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

Exploratory analysis:

PFS was consistent across clinically important subgroups[2]

PFS in predefined subgroups, including prior lenalidomide-exposed, lenalidomide-refractory, and prior PI-exposed[2]



These results represent prespecified subgroup analyses of the CANDOR study; however, these analyses were not study objectives and the study was therefore not powered or adjusted for multiplicity to assess efficacy in these subgroups.[2]

*High-risk defined as a patient with cytogenetic abnormalities that are considered high-risk, including t(4; 14), t(14; 16), or del17p.[2]
†Standard-risk defined as a patient without cytogenetic abnormalities that are considered high risk.[2]

PI = proteasome inhibitor; CI = confidence interval; Len = lenalidomide.

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.

Please see additional Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

DKd once-weekly study (EQUULEUS)

DKd once-weekly study design: Phase 1b, open-label, multi-cohort study (N = 85) which evaluated the combination of once-weekly KYPROLIS® with IV daratumumab and dexamethasone in patients with relapsed or refractory multiple myeloma who received 1 to 3 prior lines of therapy. KYPROLIS® was administered weekly. Safety and tolerability of DKd were evaluated as primary endpoints. Key secondary endpoints included ORR and OS. PFS and MRD response were exploratory endpoints.[1,12]

Baseline characteristics in the DKd once-weekly arm[1,12]

	DKd (N = 85)
Age, number of patients (%)	
< 65 years	36 (42)
65 - < 75 years	41 (48)
≥ 75 years	8 (9)
ECOG PS—number of patients (%)	
0	32 (38)
1	46 (54)
2	7 (8)
Cytogenetic risk group determined by FISH—number of patients (%)*	
n	67
Standard risk	54 (81)
High risk	13 (19)
Prior lines of therapy—number of patients (%)	
1	20 (23)
2	40 (47)
3	23 (27)
> 3	2 (2)
Prior therapies—number of patients (%)	
Bortezomib	85 (100)
Lenalidomide	81 (95)
Refractory to lenalidomide†	50 (59)
Refractory to bortezomib‡	26 (31)

DoR = duration of response; IMiD = immunomodulatory drug.

Key eligibility criteria (N = 85)[1,12]:

- 1 to 3 prior lines of therapy, including bortezomib and IMiD, with ≥PR to ≥ 1 prior line
- Absolute neutrophil count ≥ 1.0 x 10^9/L and platelet count ≥ 75 x 10^9/L (> 50 x 10^9/L for patients with ≥ 50% bone marrow plasma cells)
- CrCl ≥ 20 mL/min/1.73 m^2
- LVEF ≥ 40%

Key exclusion criteria[1]:

- Known moderate or severe persistent asthma within the past 2 years
- Known COPD with a FEV1 < 50% of predicted normal
- Active congestive heart failure (defined as NYHA Class III or IV)

*Or karyotype testing.[12]
†Patients were considered refractory to lenalidomide if they experienced disease progression while on or within 60 days of completion of any dose of lenalidomide.[12]
‡Patients were considered refractory to bortezomib if they experienced disease progression while on or within 6 months of bortezomib therapy, unless bortezomib was given in the last line of therapy.[12]

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 additional Important Safety Information throughout.

AMGEN® Oncology

Kyprolis® (carfilzomib) for Injection