KYPROLIS, in combination with either lenalidomide and dexamethasone (KRd) or dexamethasone alone (Kd), is indicated for the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy.[1]

Pr Kyprolis®
carfilzomib for injection

When multiple myeloma relapses

Push back with the power of KYPROLIS® (carfilzomib)

Overall response rate for KRd vs Rd was 87% vs 67% ($p<0.0001$; secondary endpoint)*[1,2]

*ASPIRE: randomized, open-label, multicentre, phase 3 study conducted in 792 patients with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy. Patients were randomized 1:1 to receive KRd (n=396) or Rd (n=396). KRd: KYPROLIS (IV 10 min) 20/27 mg/m^2 in 28-day cycles for up to 12 cycles then on days 1, 2, 15 and 16 in Cycles 13-18 for up to 18 cycles or until progressive disease or unacceptable toxicity; lenalidomide 25 mg on days 1-21; dexamethasone 40 mg on days 1, 8, 15 and 22 or Rd: lenalidomide 25 mg on days 1-21; dexamethasone 40 mg on days 1, 8, 15 and 22, until progressive disease or unacceptable toxicity. The primary endpoint, PFS, was determined by an Independent Review Committee using standard objective International Myeloma Working Group/European Blood and Marrow Transplantation response criteria. Important exclusion criteria included creatinine clearance <50 mL/min, disease progression on a bortezomib-containing regimen, progression during the first three months of Rd treatment, or progression at any time during Rd treatment if this was the most recent therapy. Progression-free survival was defined as the duration in months from randomization to documented progressive disease or death due to any cause, whichever was earlier. OS was defined as the time from randomization to the date of death from any cause.[1,2,3]

Kd = KYPROLIS + dexamethasone; KRd = KYPROLIS + lenalidomide + dexamethasone; PFS = progression-free survival; OS = overall survival; Rd = lenalidomide + dexamethasone.

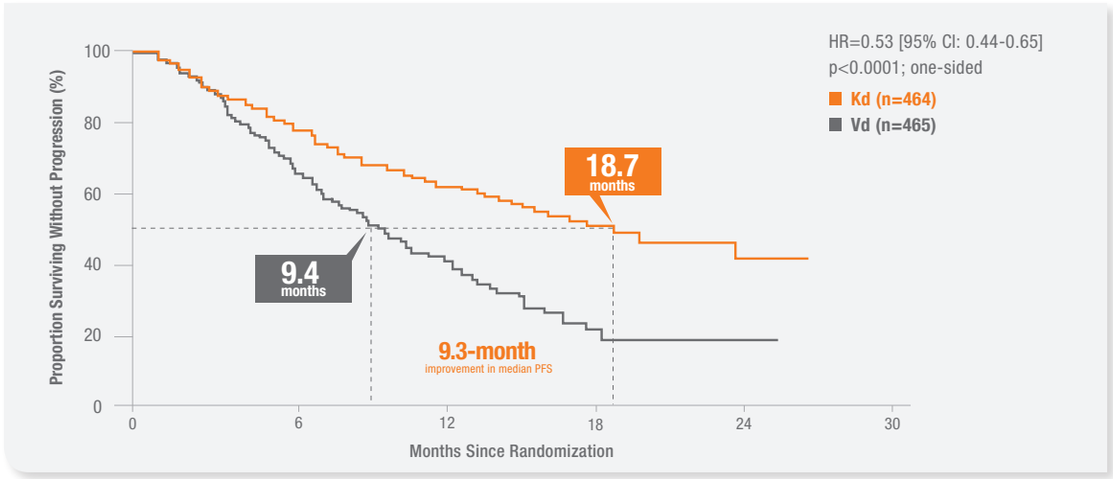
AMGEN®
Oncology

The ENDEAVOR* Study

Primary Endpoint

Progression-free Survival (PFS): Kd (20/56 mg/m²) doubled PFS vs Vd in patients with relapsed multiple myeloma (18.7 vs 9.4 months; p<0.0001; one-sided)[1,4]

Kd reduced the risk of disease progression or death vs Vd by 47% in patients with relapsed multiple myeloma (HR=0.53 [95% CI: 0.44-0.65]; p<0.0001; one-sided)†[1,4]



The pre-planned PFS analysis was performed after 171 events (disease progression or death) in the Kd arm and 243 events in the Vd arm[4]

Adapted from Dimopoulos et al[4] and the KYPROLIS® (carfilzomib) Product Monograph[1]

The PFS benefit of Kd over Vd was consistently observed in all subgroups including those defined according to prior bortezomib therapy, number of prior lines of therapy, cytogenic risk and age.[1]

Subgroup		Kd	Vd
No prior bortezomib[4]	Median PFS (months)	**NE**	**11.2**
	n	214	213
	HR=0.48 [95% CI: 0.36-0.66]		
Prior bortezomib[4]	Median PFS (months)	**15.6**	**8.1**
	n	250	252
	HR=0.56 [95% CI: 0.44-0.73]		
1 prior line of therapy[5]	Median PFS (months)	**22.2**	**10.1**
	n	232	232
	HR=0.45 [95% CI: 0.33-0.61] p<0.0001; one-sided		
≥2 prior lines of therapy[5]	Median PFS (months)	**14.9**	**8.4**
	n	232	233
	HR=0.60 [95% CI: 0.47-0.78] p<0.0001; one-sided		
High cytogenetic risk[6‡]	Median PFS (months)	**8.8**	**6.0**
	n	97	113
	HR=0.65 [95% CI: 0.45-0.92] p=0.0075; one-sided		
Standard cytogenetic risk[6‡]	Median PFS (months)	**NE**	**10.2**
	n	284	291
	HR=0.44 [95% CI: 0.33-0.58] p<0.0001; one-sided		

Open label trial; preplanned subgroup analysis; results were not adjusted for multiplicity and should be interpreted descriptively[5,6]

CI = confidence interval; HR = hazard ratio; Kd = KYPROLIS + dexamethasone; NE = not evaluable; PFS = progression-free survival; Vd = bortezomib + dexamethasone.

*ENDEAVOR: randomized, open-label, multicentre, phase 3 study conducted in 929 patients with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy. Patients were randomized 1:1 to receive Kd (n=464) or Vd (n=465). Kd twice weekly: KYPROLIS (IV 30 min) 20/56 mg/m² in 28-day cycles on days 1, 2, 8, 9, 15 and 16; dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22 and 23 or Vd: bortezomib 1.3 mg/m² on days 1, 4, 5 and 11 and dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. Cycles were repeated until disease progression or unacceptable toxicity. The primary endpoint, PFS, was determined by an Independent Review Committee using standard objective International Myeloma Working Group/European Blood and Marrow Transplantation response criteria. Patients were required to have a documented partial response to at least one line of prior therapy (including prior therapy with bortezomib or KYPROLIS). Progression-free survival was defined as the time from randomization until disease progression or death due to any cause, whichever occurred first. Overall survival was defined as the time from randomization to the date of death from any cause.[1,4,7]

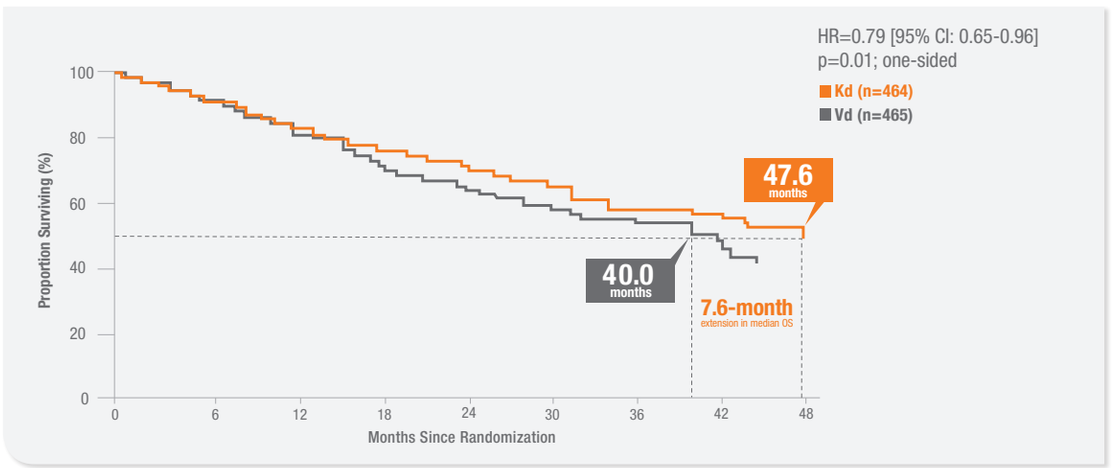
†Patients received KYPROLIS until disease progression or unacceptable toxicity.[1]

‡The high-risk group consisted of patients with the genetic subtype t(4;14) or t(14;16) in 10% of screened plasma cells or with del(17p) in 20% of screened plasma cells. The standard-risk group consisted of all other patients with available and known baseline cytogenetics.[6]

Secondary Endpoint

Overall Survival (OS): Kd (20/27 mg/m²) significantly improved OS vs Vd (47.6 vs 40.0 months; p=0.01; one-sided)[1,7]

Kd reduced the risk of death vs Vd by 21% in patients with relapsed multiple myeloma (HR=0.79 [95% CI: 0.65-0.96]; p=0.01; one-sided)*[1,7]



The pre-planned OS analysis was performed after 189 deaths in the Kd arm and 209 deaths in the Vd arm[1,7]

The median follow-up was approximately 37 months[1,7]

Adapted from Dimopoulos et al[5] and the KYPROLIS® (carfilzomib) Product Monograph[1]

In the ENDEAVOR study, the most common adverse reactions (>20%) in the Kd arm (n=463) included: anemia (42.5%), diarrhea (36.3%), respiratory tract infection (35.9%), pyrexia (32.4%), dyspnea (32.2%), fatigue (32.2%), hypertension (32.2%), thrombocytopenia (31.7%), cough (30.9%), insomnia (27.0%), peripheral edema (25.1%), nausea (23.5%), bronchitis (23.3%), asthenia (23.1%), back pain (23.1%), and headache (20.5%).[1]

The ARROW† study

Primary Endpoint

In the open-label ARROW study‡ evaluating once weekly Kd (20/70 mg/m²) vs twice weekly Kd (20/27 mg/m²)§, patients treated with once-weekly Kd (20/70 mg/m²) had a median PFS of 11.3 months (95% CI [8.6-13.2 months])[1¶]

In the ARROW study, the most common adverse reactions (>20%) in the Kd once-weekly arm (n=238) included: respiratory tract infection (29.4%), anemia (26.9%), pyrexia (23.1%), thrombocytopenia (22.3%), hypertension (21.4%), and fatigue (20.2%).[1]

CI = confidence interval; HR = hazard ratio; Kd = KYPROLIS + dexamethasone; OS = overall survival; Vd = bortezomib + dexamethasone.

*Patients received KYPROLIS until disease progression or unacceptable toxicity.[1]

†ARROW: randomized, open-label, multicentre, phase 3 study conducted in 478 patients with relapsed and refractory multiple myeloma who had received 2 to 3 prior lines of therapy. Patients were randomized 1:1 to receive Kd (n=240) once weekly or Kd (n=238) twice weekly. Kd once weekly: KYPROLIS (IV 30 min) 20/70 mg/m² in 28-day cycles on days 1, 8, and 15; dexamethasone 40 mg on days 1, 8, 15 and 22 for Cycles 1-9 and on days 1, 8, and 15 for Cycles 10 and later or Kd twice weekly: KYPROLIS (IV 10 min) 20/27 mg/m² in 28-day cycles on days 1, 2, 8, 9, 15 and 16; dexamethasone 40 mg on days 1, 8, 15 and 22 for Cycles 1-9 and on days 1, 8 and 15 for Cycles 10 and later. Cycles were repeated until disease progression or unacceptable toxicity. The primary endpoint was PFS. Patients were required to have a documented partial response to at least one line of prior therapy (including prior therapy with a proteasome inhibitor and an immunomodulatory agent). The once-weekly Kd 20/70 mg/m² regiment has not been compared with the twice-weekly Kd 20/56 mg/m² regimen within a clinical trial.[1,8]

‡The safety and efficacy of once-weekly Kd (20/70 mg/m²) was evaluated in patients with relapsed AND refractory multiple myeloma who had received 2 to 3 prior lines of therapy.[1] The safety and efficacy of twice-weekly Kd (20/56 mg/m²) was evaluated in patients with relapsed OR refractory multiple myeloma who had received 1 to 3 prior lines of therapy.[1]

§The twice weekly Kd 20/27 mg/m² regimen is not an authorized therapy.

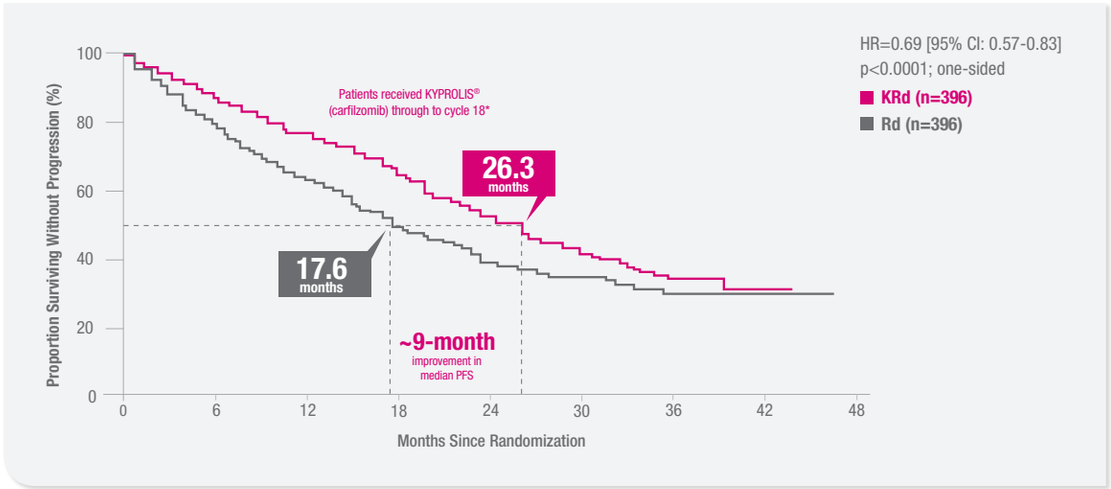
¶The PFS analysis was performed after 126 events (disease progression or death) in the once weekly Kd arm.[1]

The ASPIRE Study

Primary Endpoint

Progression-free Survival (PFS): KRd (20/27 mg/m²) significantly extended PFS vs Rd in patients with relapsed multiple myeloma (26.3 vs 17.6 months; p<0.0001; one-sided)[1,2]

KRd reduced the risk of disease progression or death vs Rd by 31% in patients with relapsed multiple myeloma (HR=0.69 [95% CI: 0.57-0.83]; p<0.0001; one-sided)*[1,2]



The pre-planned PFS analysis was performed after 207 events (disease progression or death) in the KRd arm and 224 events in the Rd arm[2]

Adapted from Stewart et al[2] and the KYPROLIS Product Monograph[1]

The PFS benefit was consistently observed in all subgroups including those defined according to number of prior lines of therapy, cytogenic risk and age.[1]

Subgroup		KRd	Rd
1 prior line of therapy[9]	Median PFS (months)	**29.6**	**17.6**
	n	184	157
	HR=0.71 [95% CI: 0.53-0.96] p=0.0118; one-sided		
≥2 prior lines of therapy[9]	Median PFS (months)	**25.8**	**16.7**
	n	212	239
	HR=0.72 [95% CI: 0.56-0.92] p=0.0046; one-sided		
High cytogenetic risk[10†]	Median PFS (months)	**23.1**	**13.9**
	n	48	52
	HR=0.70 [95% CI: 0.43-1.16] p=0.0829; one-sided		
Standard cytogenetic risk[10†]	Median PFS (months)	**29.6**	**19.5**
	n	147	170
	HR=0.66 [95% CI: 0.48-0.90] p=0.0039; one-sided		

Open label trial; preplanned subgroup analysis; results were not adjusted for multiplicity and should be interpreted descriptively[9,10]

CI = confidence interval; HR = hazard ratio; KRd = KYPROLIS + lenalidomide + dexamethasone; PFS = progression-free survival; Rd = lenalidomide + dexamethasone.

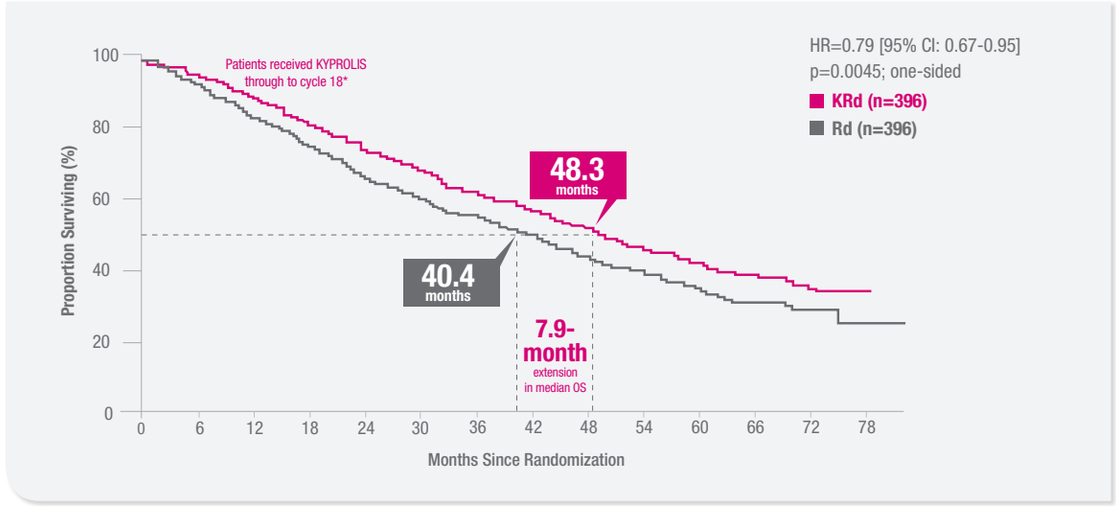
*KYPROLIS treatment was administered for a maximum of 18 cycles unless discontinued early for disease progression or unacceptable toxicity. Lenalidomide and dexamethasone administration could continue until progression or unacceptable toxicity.[1]

†The high-risk subgroup consisted of patients with genetic subtypes t(4;14) or t(14;16), or with del(17p) as determined by the central laboratories. The stringent cutoff value of 60% for the proportion of plasma cells with del(17p) was used to be consistent with the recommendations from the International Myeloma Workshop Consensus Panel. The standard-risk subgroup consisted of all other patients with known baseline cytogenetic status.[10]

Secondary Endpoint

Overall Survival (OS): KRd (20/27 mg/m²) significantly improved OS vs Rd (48.3 vs 40.4 months; p=0.0045; one-sided)[1,11]

KRd reduced the risk of death vs Rd by 21% in patients with relapsed multiple myeloma (HR=0.79 [95% CI: 0.67-0.95]; p=0.0045; one-sided)*[1,11]



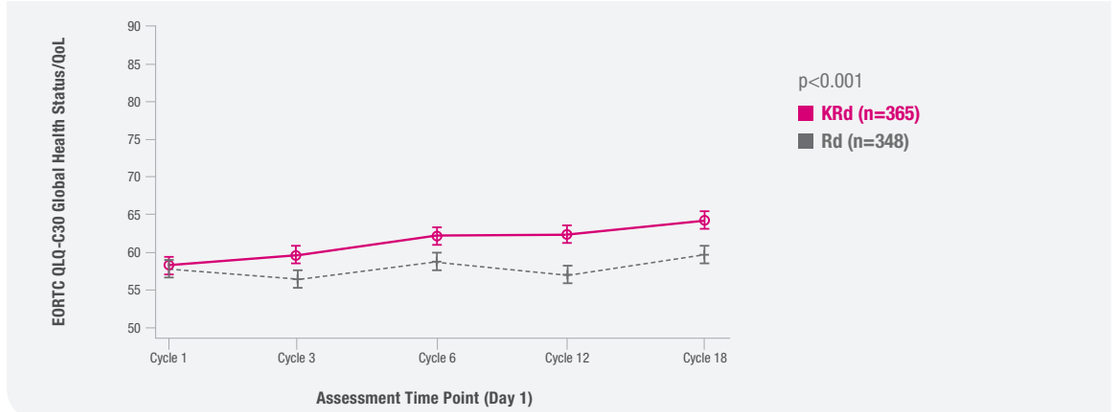
The pre-planned OS analysis was performed after 246 deaths in the KRd arm and 267 deaths in the Rd arm[1,11]

The median follow-up was approximately 67 months[1,11]

Adapted from Siegel et al[11] and the KYPROLIS Product Monograph[1]

Secondary Endpoint

Quality of Life (QoL): Patients tr mpared with Rd over 18 cycles of treatment[1,2]



Adapted from supplement to Stewart et al.[3]

The minimal clinically important difference for between-groups differences on the QLQ-C30 Global Health Status/QoL scale is 5.0 points[3]

In the ASPIRE study, the most common adverse reactions (>20%) in the KRd arm (n=392) included: respiratory tract infection (49.7%), diarrhea (44.4%), anemia (44.1%), neutropenia (43.4%), fatigue (33.4%), thrombocytopenia (32.7%), cough (32.7%), pyrexia (29.8%), hypokalemia (29.6%), muscle spasms (27.0%), pneumonia (23.2%), nausea (20.9%), insomnia (20.7%), constipation (20.7%), and bronchitis (20.2%).[1]

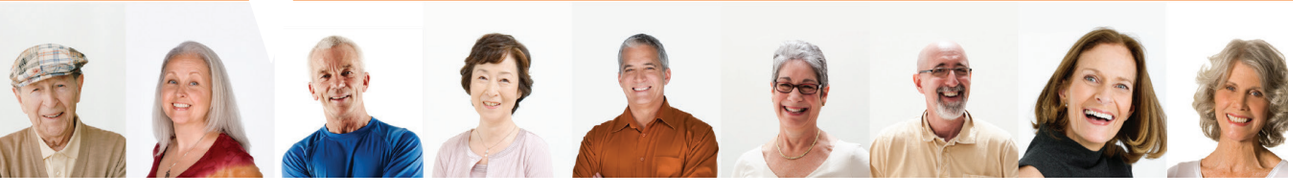
CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire-core 30; HR = hazard ratio; KRd = KYPROLIS + lenalidomide + dexamethasone; OS = overall survival; QoL = quality of life; Rd = lenalidomide + dexamethasone.

*KYPROLIS treatment was administered for a maximum of 18 cycles unless discontinued early for disease progression or unacceptable toxicity. Lenalidomide and dexamethasone administration could continue until progression or unacceptable toxicity.[1]

VICTORY® Program

Patient Assistance Program

KYPROLIS® (carfilzomib) Dosing Options



VICTORY® Program Services for patients taking KYPROLIS® (carfilzomib)

Designed to offer support services for patients with relapsed multiple myeloma who have been prescribed KYPROLIS.

Services offered by the VICTORY® Program include:

- Transportation
- Lodging
- Private infusion support

The VICTORY® program may also be able to provide drug assistance to patients who do not have private and public access to KYPROLIS.

For more information, encourage your patient to call the VICTORY® Care Coordinator at 1-888-706-4717, ext. 32 or visit https://www.victoryassist.ca

	NEW once-weekly dosing option[1]	Twice-weekly dosing options[1]	
	Kd 20/70 mg/m²	**Kd 20/56 mg/m²**	**KRd 20/27 mg/m²**
	(KYPROLIS + dexamethasone)	(KYPROLIS + dexamethasone)	(KYPROLIS + lenalidomide + dexamethasone)
Starting dose of KYPROLIS	20 mg/m² on Day 1 of Cycle 1 If tolerated, proceed with "target dose"	20 mg/m² on Days 1 and 2 of Cycle 1 If tolerated, proceed with "target dose"	20 mg/m² on Days 1and 2 of Cycle 1 If tolerated, proceed with "target dose"
Target dose of KYPROLIS	70 mg/m² starting on Day 8 of Cycle 1	56 mg/m² starting on Day 8 of Cycle 1	27 mg/m² starting on Day 8 of Cycle 1
KYPROLIS infusion time	30 minutes	30 minutes	10 minutes
KYPROLIS treatment schedule *Note: Continue treatment until disease progression or unacceptable toxicity*	Infuse KYPROLIS on Days 1, 8, and 15, as part of a 28-day treatment cycle	Infuse KYPROLIS on Days 1, 2, 8, 9, 15, and 16, as part of a 28-day treatment cycle	Infuse KYPROLIS on Days 1, 2, 8, 9, 15, and 16, as part of a 28-day cycle (Cycles 1-12) From Cycle 13 onward, omit KYPROLIS infusions on Days 8 and 9
Concurrent therapy (lenalidomide and/or dexamethasone) dosing†	Dexamethasone (40 mg orally or IV should be administered 30 minutes to 4 hours before KYPROLIS on Days 1, 8, 15 and 22 Dexamethasone is omitted on Day 22 of Cycles 10 and higher	Dexamethasone (20 mg orally or IV) should be administered 30 minutes to 4 hours before KYPROLIS on Days 1, 2, 8, 9, 15, 16, 22 and 23	Lenalidomide (25 mg orally) should be administered on Days 1-21‡ Dexamethasone (40 mg orally or IV) should be administered 30 minutes to 4 hours before KYPROLIS on Days 1, 8, 15 and 22

*Refer to the lenalidomide and/or dexamethasone product monographs for additional dosing considerations when using these agents in combination with KYPROLIS.

†Appropriate dose reduction for the starting dose of lenalidomide should be considered according to the recommendations in the lenalidomide product monograph.[1]

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire-core 30; Kd = KYPROLIS + dexamethasone; KRd = KYPROLIS + lenalidomide + dexamethasone; QoL = Quality of life; Rd = lenalidomide + dexamethasone.

Kd once-weekly dosing (20/70 mg/m²) is available as an option for patients who cannot adhere to the twice-weekly Kd (20/56 mg/m²) regimen due to the burden of dosing frequency[1]

The once-weekly Kd 20/70 mg/m² regimen has not been compared with the twice-weekly Kd 20/56 mg/m² regimen within a clinical trial.[1]

References:

1. KYPROLIS Product Monograph. Amgen Canada Inc. February 2020.
2. Stewart AK, et al. *N Engl J Med.* 2015;372:142-152.
3. Supplementary Appendix to Stewart AK, et al. *N Engl J Med.* 2015; 372:142-152.
4. Dimopoulos MA, et al. *Lancet Oncol.* 2016; 17:27-38.
5. Moreau, et al. *Leukemia.* 2017;31:115-122.
6. Chng W-J, et al. *Leukemia.* 2017;31:1368-1374.
7. Dimopoulos MA, et al. *Lancet Oncol.* 2017; 18:1327-37.
8. Dimopoulos MA, et al. *Blood Cancer J.* 2017;7:e554.
9. Avet-Loiseau H, et al. *Blood.* 2016;138:1174-1180.
10. Siegel DS, et al. *J Clin Oncol.* 2018; 36:728-734.

KYP03220E

Pr Kyprolis®
carfilzomib for injection

AMGEN Oncology

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

Safety Information

Clinical use

Clinical effectiveness of KRd has not been established in patients with renal impairment (CrCL <50 mL/min). Clinical effectiveness of KRd or Kd has not been established in patients who progressed during prior bortezomib therapy.

The incidence of certain adverse events (including cardiac failure) in clinical trials was higher for patients who were ≥65 years (vs <65 years).

The safety and effectiveness of KYPROLIS® (carfilzomib) in pediatric patients have not been established.

Most serious warnings and precautions

Duration of infusion: KYPROLIS dosed at 56 mg/m^2 and 70 mg/m^2 must be infused over 30 minutes; KYPROLIS dosed at 27 mg/m^2 must be infused over ≥10 minutes. KYPROLIS administered with a short infusion time, without pre-medication with dexamethasone and adequate hydration, or without stepped up dosing, may not be well tolerated.

Cardiac toxicities: New or worsening cardiac failure and myocardial ischemia and infarction; increased risk of cardiovascular events (eg., cardiac failure) in elderly (≥75 years) and in Asian patients; fatal outcomes reported. Monitor and adjust fluid volume as clinically indicated. Withhold KYPROLIS until grade 3 or 4 cardiac events resolve.

Venous thrombosis: Including deep vein thrombosis and pulmonary embolism; fatal outcomes reported. Monitor for signs and symptoms. Thromboprophylaxis is recommended.

Hemorrhage: Including gastrointestinal, intracranial, and pulmonary hemorrhage; fatal outcomes reported.

Thrombotic microangiopathy: Including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS); fatal outcomes reported. Monitor for signs and symptoms. Withhold KYPROLIS if TTP/HUS is suspected; discontinue if confirmed.

Hepatic failure: Fatal cases reported. Monitor liver enzymes (ALT, AST) and bilirubin and reduce or withhold therapy as appropriate.

Posterior reversible encephalopathy syndrome (PRES): Cases reported. Withhold KYPROLIS if PRES is suspected; evaluate by imaging.
Discontinue if confirmed.

Pulmonary toxicities: Acute respiratory distress syndrome (ARDS), acute respiratory failure, acute diffuse infiltrative pulmonary disease, and pulmonary hypertension; fatal outcomes reported. Withhold KYPROLIS until these effects resolve or return to baseline.

Other relevant warnings and precautions

- Not indicated as monotherapy for relapsed and refractory multiple myeloma
- Dose reduction by 25% required in patients with mild or moderate hepatic impairment
- Not evaluated in patients with cardiac impairment (NYHA class III and IV heart failure); patients with LVEF <40% were not eligible for the ENDEAVOR study
- Infusion reactions, including life-threatening reactions, immediately or within 24 hours of dose; ensure appropriate hydration and dexamethasone administration prior to treatment
- Tumour lysis syndrome; fatal outcomes reported. Ensure appropriate hydration. Monitor serum electrolytes; consider uric acid lowering drugs for patients at high risk
- QT interval prolongation
- Hypertension, including hypertensive crisis and hypertensive emergency; fatal outcomes reported. Hypertension should be well-controlled prior to treatment initiation and evaluated throughout treatment; withhold KYPROLIS for hypertensive crisis and hypertensive emergency, and consider dose reductions when resuming treatment
- Thrombocytopenia; monitor platelet counts frequently and reduce or withhold KYPROLIS as appropriate
- Hepatitis B virus (HBV) reactivation; test prior to initiating treatment; for carriers of HBV, monitor for signs and symptoms of active infection and consider prophylactic antivirals before and throughout treatment and for at least six months after treatment
- Progressive multifocal leukoencephalopathy (PML) in patients on prior or concomitant immunosuppressive therapy; monitor for new or worsening signs/symptoms suggestive of PML as part of the differential diagnosis of CNS disorders; refer suspected cases to a specialist for diagnostic testing and discontinue KYPROLIS in confirmed cases
- Acute renal failure; fatal outcomes reported. Monitor renal function; reduce, withhold or discontinue KYPROLIS as appropriate
- Limited data in patients with renal impairment (CrCL <50 mL/min). KYPROLIS should be administered after dialysis procedure, if applicable
- Dyspnea; withhold KYPROLIS until grade 3 or 4 dyspnea resolves or returns to baseline
- Monitor blood pressure, complete blood cell counts (CBC), blood chemistry, and electrolytes at baseline and throughout treatment and liver enzymes regularly, regardless of baseline values, and modify based on toxicity
- Females of reproductive potential should use contraception during and for 30 days after therapy
- KYPROLIS should not be used during pregnancy unless the potential benefits outweigh the potential risks to the fetus
- Males should use contraception during and for 90 days after therapy
- KYPROLIS should not be administered while breastfeeding

For more information

Consult the Product Monograph at www.amgen.ca/Kyprolis_PM.pdf for important information relating to adverse reactions, drug interactions, and dosing and administration which has not been discussed in this piece. The Product Monograph is also available by calling 1-866-502-6436.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCL = creatinine clearance; Kd = KYPROLIS + dexamethasone; KRd = KYPROLIS + lenalidomide + dexamethasone; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.