Pr Kyprolis®
carfilzomib for injection

When multiple myeloma relapses, Consider KYPROLIS® (carfilzomib for injection) as a next option in the treatment journey

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

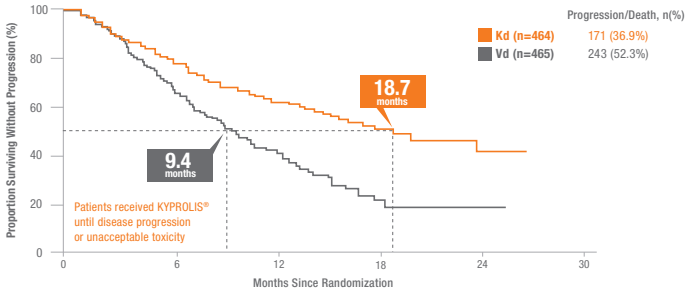
AMGEN

The ENDEAVOR* Study | A randomized, open-label, active-controlled, multicentre, phase 3 study

PRIMARY ENDPOINT

Kd (20/56 mg/m²) significantly improved Progression-free Survival (PFS) vs Vd in patients with relapsed or refractory multiple myeloma

Demonstrated 47% reduction in the risk of disease progression or death (HR=0.53 [95% CI: 0.44-0.65]; p<0.0001; one-sided)[1,2]



Adapted from Dimopoulos et al.[2] and the KYPROLIS® 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[2]	Median PFS (months)	**NE**	**11.2**
	Progression or death events, n/N	66/214	102/213
	HR=0.48 [95% CI: 0.36-0.66]		
Prior bortezomib[2]	Median PFS (months)	**15.6**	**8.1**
	Progression or death events, n/N	105/250	141/252
	HR=0.56 [95% CI: 0.44-0.73]		
1 prior line of therapy[3]	Median PFS (months)	**22.2**	**10.1**
	Progression or death events, n/N	70/232	109/232
	HR=0.45 [95% CI: 0.33-0.61]; p<0.0001; one-sided		
≥2 prior lines of therapy[3]	Median PFS (months)	**14.9**	**8.4**
	Progression or death events, n/N	101/232	134/233
	HR=0.60 [95% CI: 0.47-0.78]; p<0.0001; one-sided		
High cytogenetic risk[4†]	Median PFS (months)	**8.8**	**6.0**
	Progression or death events, n/N	56/97	71/113
	HR=0.65 [95% CI: 0.45-0.92]; p=0.0075; one-sided		
Standard cytogenetic risk[4†]	Median PFS (months)	**NE**	**10.2**
	Progression or death events, n/N	81/284	142/291
	HR=0.44 [95% CI: 0.33-0.58]; p<0.0001; one-sided		

Open-label trial; pre-planned subgroup analysis; results were not adjusted for multiplicity and should be interpreted descriptively[3,4]

CI = confidence interval; HR = hazard ratio; Kd = KYPROLIS + dexamethasone; NE = not evaluable; Vd = bortezomib + dexamethasone.

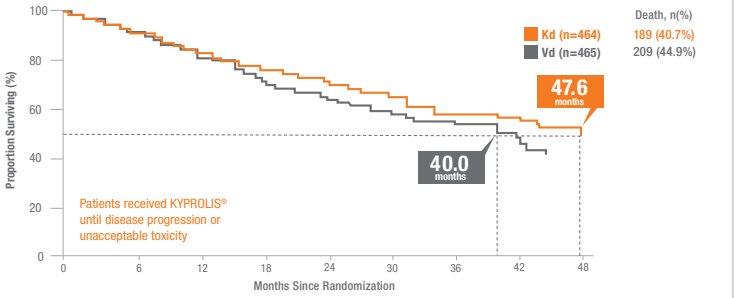
*ENDEAVOR: randomized, open-label, multicentre, phase 3 study conducted in 929 patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. Patients were randomized 1:1 to receive Kd (n=464) or Vd (n=465). Kd twice weekly: KYPROLIS (IV 30 min) 20/56 mg/m² in 28-day 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). PFS 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.[1,2,5]

†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.[4]

SECONDARY ENDPOINT

Kd significantly improved Overall Survival (OS) vs Vd in patients with relapsed or refractory multiple myeloma

Demonstrated 21% reduction in the risk of death (HR=0.79 [95% CI: 0.65-0.96]; p=0.01; one-sided)[1,5]



The median follow-up was approximately 37 months.[1,7] Adapted from Dimopoulos et al.[3] and the KYPROLIS® 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 Progression-free Survival of 11.3 months (95% CI: 8.6-13.2 months)[1§] The number of progression or death events in the once-weekly Kd arm was 126/240 (52.5%).[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; Vd = bortezomib + dexamethasone.

*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 regimen has not been compared with the twice-weekly Kd 20/56 mg/m² regimen within a clinical trial.[1,6]

†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.[1]

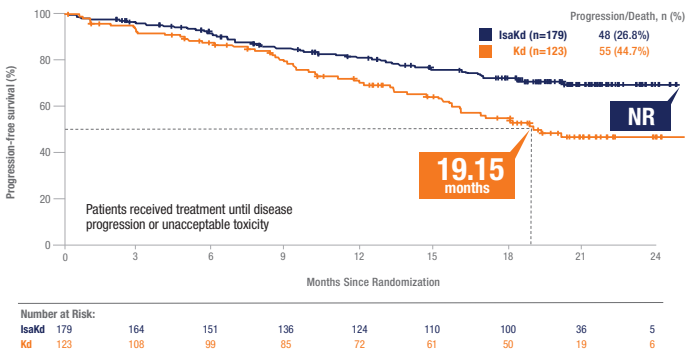
§The PFS analysis was performed after 126 events (disease progression or death) in the once-weekly Kd arm.[6]

The IKEMA* Study | A randomized, open-label, active-controlled, multicentre, phase 3 study

PRIMARY ENDPOINT

IsaKd significantly improved Progression-free Survival vs Kd in patients with relapsed and/or refractory multiple myeloma

Demonstrated 46.9% reduction in the risk of disease progression or death (HR=0.53 [99% CI: 0.318-0.889]; p=0.0013; stratified log-rank test)[1,11]



Adapted from KYPROLIS Product Monograph† and Moreau et al.[12]

Subgroup analyses based on PFS hazard ratio were consistent across the prespecified subgroups including patients with high-risk cytogenics, ≥65 years of age, with baseline eGFR (MDRD) <60 mL/min/1.73 m², with >1 prior line of therapy, or with ISS stage III at study entry[1,12]

Subgroup[12]		IsaKd	Kd
High cytogenetic risk†	Median PFS (months)	**NC**	**18.2**
	Progression or death events, n/N	17/42	15/31
	HR=0.72 [95% CI: 0.36-1.45]		
≥65 years of age	Median PFS (months)	NC	17.2
	Progression or death events, n/N	23/91	29/57
	HR=0.43 [95% CI: 0.25-0.74]		
Baseline eGFR (MDRD) <60 mL/min/1.73m²	Median PFS (months)	NC	13.4
	Progression or death events, n/N	10/43	10/18
	HR=0.27 [95% CI: 0.11-0.66]		
>1 prior line of therapy	Median PFS (months)	**NC**	**16.2**
	Progression or death events, n/N	30/99	36/68
	HR=0.48 [95% CI: 0.29-0.78]		
ISS Stage III at study entry[12]	Median PFS (months)	**12.88**	**9.36**
	Progression or death events, n/N	11/26	14/20
	HR=0.65 [95% CI: 0.30-1.43]		

Pre-planned subgroup analysis

CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; IsaKd = Isatuximab + KYPROLIS + dexamethasone; ISS = International Staging System; Kd = KYPROLIS + dexamethasone; MDRD = modification of diet in renal disease formula; NC = not calculated; NR = not reached; PFS = progression-free survival.

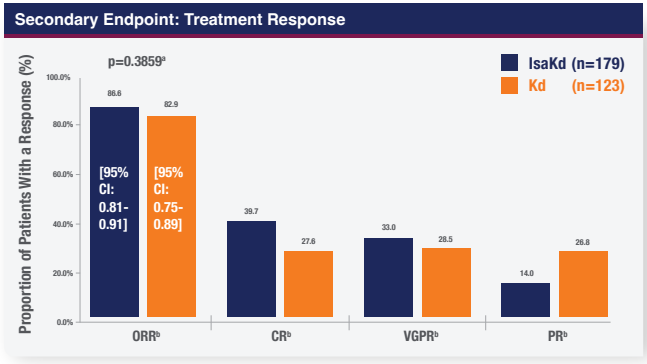
*IKEMA: randomized, open-label, multicentre, phase 3 study conducted in 302 patients with relapsed and/or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. Patients were randomized 3:2 to receive IsaKd (n=179) or Kd (n=123) in 28-day cycles. Cycles were continued until disease progression or unacceptable toxicity. KYPROLIS (IV) was administered at a dose of 20 mg/m² on days 1 and 2; 56 mg/m² on days 8, 9, 15, and 16 of Cycle 1; and at a dose of 56 mg/m² on days 1, 2, 8, 9, 15, and 16 for subsequent cycles. Dexamethasone 20 mg was given on days 1, 2, 8, 9, 15, 16, 22, and 23 for each 28-day cycle (IV on the days of isatuximab and/or KYPROLIS infusions, and orally on the other days). Isatuximab 10 mg/kg IV was administered weekly in the first cycle and every two weeks thereafter. The primary endpoint, PFS, was determined by an Independent Response Committee based on central laboratory data for M-protein and central radiologic imaging review using International Myeloma Working Group criteria. Exclusion criteria included patients with primary refractory disease or were refractory to previous anti-CD38 monoclonal antibody treatment.[1,12]

†High-risk cytogenetic status is defined as the presence of at least one: del(17p) or translocation t(4;14) or translocation t(14;16).

SECONDARY ENDPOINT

IKEMA: Overall Response Rate (ORR) shown in patients treated with IsaKd vs Kd

IsaKd achieved a higher ORR compared with Kd in patients with relapsed and/or refractory multiple myeloma. ORR was 86.6% with IsaKd vs 82.9% with Kd (95% CI: 0.81-0.91, 0.75-0.89, respectively; p=0.3859[a]; stratified Cochran-Mantel-Haenszel)



In the IKEMA study, the most common adverse reactions (>20%) in the IsaKd arm (n=179) included: respiratory tract infection (66.7%), infusion reactions (45.8%), fatigue (41.8%), hypertension (37.3%), pneumonia (36.2%), diarrhea (36.2%), dyspnea (28.8%), insomnia (23.7%), bronchitis (23.7%), and back pain (22.0%).[1]

CR = complete response; IRC= Independent Response Committee; IMWG = International Myeloma Working Group; IsaKd = Isatuximab + KYPROLIS + dexamethasone; Kd = KYPROLIS + dexamethasone; ORR = overall response rate; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

[a]Stratified on number of previous lines of therapy (1 versus >1) and R-ISS (I or II versus III versus not classified) according to IRT.

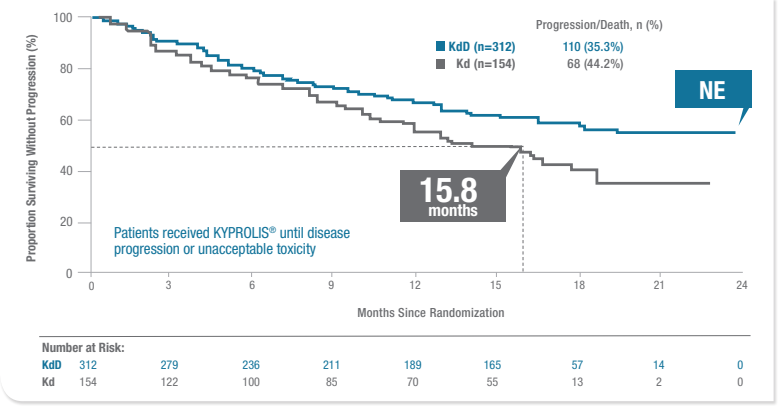
[b]sCR, CR, VGPR, and PR were evaluated by the IRC using the IMWG response criteria.

The CANDOR* Study | A randomized, open-label, multicentre, phase 3 study

PRIMARY ENDPOINT

KdD significantly improved Progression-free Survival vs Kd in patients with relapsed or refractory multiple myeloma

Demonstrated 37% reduction in the risk of disease progression or death (HR=0.63 [95% CI: 0.46-0.85]; p=0.0014; one-sided)[1,11]

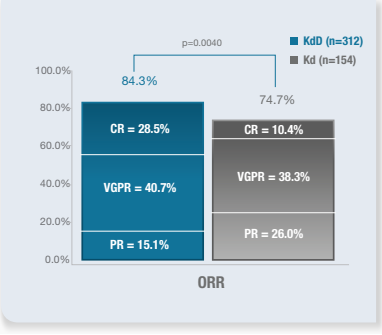


Adapted from KYPROLIS Product Monograph[1] and Dimopoulos et al.[11]

SECONDARY ENDPOINT

KdD achieved a higher ORR compared with Kd in patients with relapsed and refractory multiple myeloma

ORR was 84.3% with KdD vs 74.7% with Kd; odds ratio (95% CI) 1.925 (1.18-3.13); one-sided p=0.0040.[1,11]



In the CANDOR study, the most common adverse reactions (>20%) in the KdD arm (n=308) included: respiratory tract infection (40.3%), thrombocytopenia (37.3%), anemia (32.8%), diarrhea (31.5%), hypertension (30.5%), fatigue (24.4%), and cough (20.5%).[1,11]

KdD achieved a higher rate of minimal residual disease-negative complete response [MRD (-) CR] at 12 months compared with Kd:

MRD (-) CR rate at 12 months was 12.5% in the KdD group vs 1.3% in Kd group; odds ratio (95% CI) 11.329 (2.70, 47.48); one-sided p<0.0001.[1,11]

CI = confidence interval; CR = complete response; Kd = KYPROLIS + dexamethasone; KdD = KYPROLIS + dexamethasone + daratumumab; MRD (-) CR = minimal residual disease negative complete response; NE = not estimable; ORR = overall response rate; PR = partial response; VGPR = very good partial response.

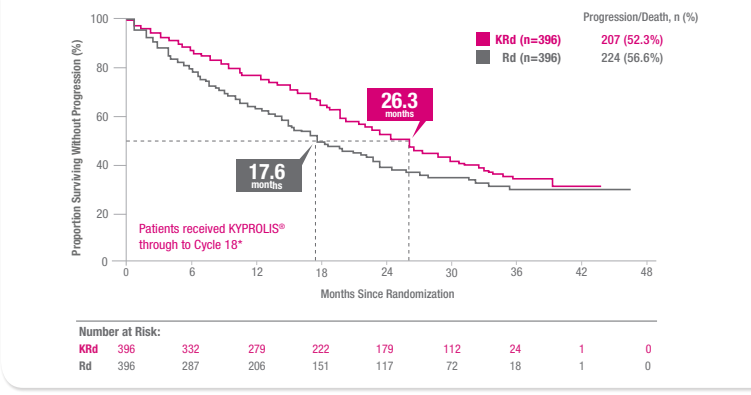
*CANDOR: randomized, open-label, phase 3 study conducted in 466 patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. Patients were randomized 2:1 to receive KdD twice weekly (20/56 mg/m^2; n=312) or Kd twice weekly (20/56 mg/m^2; n=154) in 28-day cycles. Dexamethasone is administered 20/40 mg weekly and daratumumab is 8/16 mg/kg weekly. All patients continued receiving treatment until progressive disease or unacceptable toxicity. The primary endpoint, PFS, was determined by a Blinded Independent Review Committee using IMWG Uniform Response Criteria. Exclusion criteria included known moderate or severe persistent asthma within the past 2 years, known chronic obstructive pulmonary disease (COPD) with FEV1 <50% of predicted normal, and active congestive heart failure.[1,11]

The ASPIRE* Study | A randomized, open-label, multicentre, phase 3 study

PRIMARY ENDPOINT

KRd (20/27 mg/m^2) significantly extended Progression-free Survival vs Rd in patients with relapsed multiple myeloma

Demonstrated 31% reduction in the risk of disease progression or death (HR=0.69 [95% CI: 0.57-0.83]; p<0.0001; one-sided)[1,7]



Adapted from Stewart et al.[7] 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[8]	Median PFS (months)	**29.6**	**17.6**
	Progression or death events, n/N	91/184	88/157
	HR=0.71 [95% CI: 0.53-0.96]; p=0.0118; one-sided		
≥2 prior lines of therapy[8]	Median PFS (months)	**25.8**	**16.7**
	Progression or death events, n/N	116/212	136/239
	HR=0.72 [95% CI: 0.56-0.92]; p=0.0046; one-sided		
High cytogenetic risk[9†]	Median PFS (months)	**23.1**	**13.9**
	Progression or death events, n/N	31/48	32/52
	HR=0.70 [95% CI: 0.43-1.16]; p=0.0829; one-sided		
Standard cytogenetic risk[9†]	Median PFS (months)	**29.6**	**19.5**
	Progression or death events, n/N	68/147	94/170
	HR=0.66 [95% CI: 0.48-0.90]; p=0.0039; one-sided		

Open-label trial; pre-planned subgroup analysis; results were not adjusted for multiplicity and should be interpreted descriptively[8,9]

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

*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. PFS 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.[1,7,10]

†The high-risk cytogenic group consisted of the genetic subtypes t(4;14), t(14;16), or del17p in ≥60% of plasma cells. The standard risk group consisted of all other patients with known baseline cytogenic status.[9]

‡Respiratory tract infection includes respiratory tract infection per term (PT), lower respiratory tract infection, upper respiratory tract infection PT, and viral upper respiratory tract infection.[1]

KYPROLIS® (carfilzomib for injection) Dosing Options (Kd)

	Once-weekly dosing option[1]	Twice-weekly dosing option[1]
	Kd 20/70 mg/m²	**Kd 20/56 mg/m²**
	KYPROLIS + dexamethasone	KYPROLIS + 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"
Target dose of KYPROLIS	70 mg/m² starting on Day 8 of Cycle 1	56 mg/m² starting on Day 8 of Cycle 1
KYPROLIS infusion time	30 minutes	30 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
Concurrent therapy 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 later	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

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]

Kd = KYPROLIS + dexamethasone.

*Refer to the dexamethasone product monograph for additional dosing considerations when using in combination with KYPROLIS.

KYPROLIS® (carfilzomib for injection) Dosing Options (IsaKd, KdD, KRd)

	Twice-weekly dosing option[1]	Twice-weekly dosing option[1]
	IsaKd 20/56 mg/m²	**KdD 20/56 mg/m²**
	Isatuximab + KYPROLIS + dexamethasone	KYPROLIS + dexamethasone + daratumumab
Starting dose of KYPROLIS	20 mg/m² on Days 1 and 2 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"
Target dose of KYPROLIS	56 mg/m² starting on Day 8 of Cycle 1	56 mg/m² starting on Day 8 of Cycle 1
KYPROLIS infusion time	30 minutes	30 minutes
KYPROLIS treatment schedule *Note: Continue treatment until disease progression or unacceptable toxicity*	Infuse KYPROLIS on Days 1, 2, 8, 9, 15, and 16, as part of a 28-day cycle	Infuse KYPROLIS on Days 1, 2, 8, 9, 15, and 16, as part of a 28-day cycle
Concurrent therapy dosing*†	Isatuximab (10 mg/kg IV) should be administered on Days 1, 8, 15, and 22 of Cycle 1. For Cycles 2 and later, administer Days 1 and 15. Dexamethasone (20 mg orally or IV) should be administered Days 1, 2, 8, 9, 15, 16, 22, and 23. On the days where both isatuximab and KYPROLIS are administered, administer dexamethasone first, followed by isatuximab infusion, then followed by KYPROLIS infusion	Daratumumab (16 mg/kg body weight intravenously) should be administered as a split dose of 8 mg/kg on Days 1 and 2 of Cycle 1, and as a full dose of 16 mg/kg on Days 8, 15, and 22 of Cycle 1 and Days 1, 8, 15, and 22 of Cycle 2, then every 2 weeks for Cycle 3 to 6 and every 4 weeks for the remaining cycles or until disease progression. Dexamethasone (20 mg orally or IV) should be administered at least 30 minutes to 4 hours before KYPROLIS on Days 1, 2, 8, 9, 15, and 16 and 40 mg on Day 22 of each 28-day cycle

	Twice-weekly dosing option[1]
	KRd 20/27 mg/m²
	KYPROLIS + lenalidomide + dexamethasone
Starting dose of KYPROLIS	20 mg/m² on Days 1 and 2 of Cycle 1 If tolerated, proceed with "target dose"
Target dose of KYPROLIS	27 mg/m² starting on Day 8 of Cycle 1
KYPROLIS infusion time	10 minutes
KYPROLIS treatment schedule *Note: Continue treatment until disease progression or unacceptable toxicity*	Infuse KYPROLIS on Days 1, 2, 8, 9, 15, and 16, as part of a 28-day cycle (Cycles 1 to 12). From Cycle 13 and later‡, omit KYPROLIS infusions on Days 8 and 9
Concurrent therapy dosing*†	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

*Premedicate with the recommended dose of dexamethasone PO or IV at least 30 minutes but no more than 4 hours prior to all doses of KYPROLIS to reduce the incidence and severity of infusion reactions.

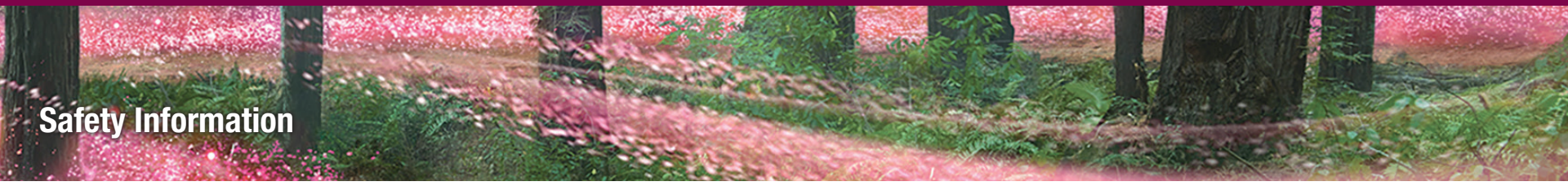
IsaKd = Isatuximab + KYPROLIS + dexamethasone; KdD = KYPROLIS + daratumumab + dexamethasone; KRd = KYPROLIS + lenalidomide + dexamethasone.

When given in combination with daratumumab or isatuximab, more premedication options should be considered.

†Refer to the respective Product Monographs for details. Refer to the lenalidomide, daratumumab, isatuximab, and/or dexamethasone product monographs for additional dosing considerations when using these agents in combination with KYPROLIS.

‡KYPROLIS is administered through Cycle 18; lenalidomide and dexamethasone continue thereafter.[1]

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



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, cardiomyopathy and myocardial ischemia and infarction; increased risk of cardiovascular events (e.g., 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.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCL = creatinine clearance; Kd = KYPROLIS + dexamethasone; KRd = KYPROLIS + lenalidomide + dexamethasone.

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
- Infections, including serious and fatal events have been reported. Monitor for sign and symptoms of infection and treat promptly
- QT interval prolongation
- Secondary primary malignancies: increased in patients treated with isatuximab-containing regimens
- 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), which can be fatal, has been reported 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; withhold KYPROLIS and refer suspected cases to a specialist for diagnostic testing; 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; test for HBV at baseline and monitor carriers throughout and following treatment
- 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 have not been discussed in this piece. The Product Monograph is also available by calling 1-866-502-6436.

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

Patient Support Services for patients taking KYPROLIS

For patients being treated with KYPROLIS, the VICTORY® Program offers the following additional services:

- Private infusion support
- Transportation support up to $200 per cycle with proof of receipts
- Lodging support up to $200 per cycle with proof of receipts for patients living 100 km from the treatment centre
- Prescribed blood pressure monitor reimbursement

VICTORY® helps your patients make the most of their coverage with public and/or private coverage navigation, appeal management, and/or co-pay support assessment.

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

Tens of thousands of patients enrolled
More than 20 years of patient support
ONLY 1 number to call: 1-888-706-4717

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Kyprolis® carfilzomib for injection

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