

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

Chance for a powerful, deep, and durable response with DKd¹

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.

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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 \geq 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 Kd¹:
 - **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 Kd¹
 - 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).^{1,3,4,‡}

†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; \geq 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 \geq 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.

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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**^{5,6}

- 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 preferred⁷

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 2a 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.⁷

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.

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How to dose DKd^{1,2}

	2nd-generation PI + mAb + dex DKd once weekly*
	Infusion time 30 minutes
	KYPROLIS® priming dose 20 mg/m ² on Day 1 of Cycle 1 to evaluate tolerability
	Target KYPROLIS® therapeutic dose 70 mg/m ² starting Day 8 of Cycle 1
Treatment schedule <ul style="list-style-type: none"> • 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 mg¹



Calculating the priming & therapeutic dose¹

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 treatment¹

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.

*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.^{1,8}

[†]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.

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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.

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.

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.

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IMPORTANT SAFETY INFORMATION FOR KYPROLIS (cont'd)

Thrombocytopenia

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

Hepatic Toxicity and Hepatic Failure

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

Thrombotic Microangiopathy

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

Posterior Reversible Encephalopathy Syndrome (PRES)

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

Progressive Multifocal Leukoencephalopathy (PML)

- Cases of PML, including fatal cases, have occurred. In addition to KYPROLIS, other contributory 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 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.** 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. **4.** 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. **5.** 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. **6.** Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. *Haematologica*. 2016;101:396-406. **7.** 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. **8.** 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.

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