

HYPOTHETICAL CASE STUDY OF A STANDARD-RISK* PATIENT WITH MULTIPLE MYELOMA AT FIRST RELAPSE TIME FOR A DEEP AND DURABLE RESPONSE

ELIZABETH

66-YEAR-OLD AFRICAN-AMERICAN FEMALE

- Retired nurse with active, healthy lifestyle
- Hypertension well-controlled with medication
- M-protein levels monitored regularly
- Standard-risk cytogenetics*
- ECOG PS 1

*Standard-risk cytogenetics is defined as cytogenetics that are not considered high risk (trisomies, t(11;14), t(6;14)) and/or R-ISS stage I.^{1,2}

M-protein = monoclonal protein; ECOG PS = Eastern Cooperative Oncology Group Performance Status; R-ISS = Revised International Staging System.



Not an actual patient.

INDICATION

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of 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), restrictive 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 events until recovery, and consider whether to restart at 1 dose level reduction based on a benefit/risk assessment.

Please see full Important Safety Information below.



Elizabeth's multiple myeloma treatment history

FIRST LINE

- Diagnosed with multiple myeloma after complaining of severe back pain and fatigue
- Treated with bortezomib, lenalidomide, and dexamethasone (VRd) for 4 cycles

MAINTENANCE

- Followed by ASCT and 24 months of lenalidomide; remained in CR during maintenance

PROGRESSION

- 9 months after stopping maintenance:
 - M-protein levels began slowly rising
 - Patient started experiencing mild back pain and CT scan revealed L1 vertebral compression fracture

➤ Elizabeth wants a treatment with a **DEEP AND DURABLE** response so she can continue her lifestyle



For standard-risk patients, go for a deep and durable response at first relapse

IMPORTANT CONSIDERATIONS FOR ELIZABETH

- **PRIOR PI EXPOSURE:** 66% of patients had prior bortezomib use at baseline (KRd vs Rd Study)³
- **POST HOC ANALYSIS:** At first relapse, KRd demonstrated a 12-month increase in median PFS vs Rd alone (29.6 months KRd vs 17.6 months Rd)³
 - Post hoc analysis: Demonstration of PFS efficacy by prior lines of therapy was not a study objective. The study was not powered to evaluate PFS efficacy within this subgroup
 - Median PFS in ITT population: 26.3 months KRd vs 17.6 months Rd (HR = 0.69; 95% CI: 0.57-0.83; *P* = 0.0001, two-sided)⁴
- **POST HOC ANALYSIS:** Adding KYPROLIS® to Rd: 4x the patient's chance of achieving ≥ CR at first relapse vs Rd alone (33.7% KRd vs 7.0% Rd)³
 - ≥ CR in ITT population: 32% KRd vs 9% Rd⁴
 - **Post hoc analysis:** Demonstration of complete response by prior lines of therapy was not a study objective

VRd = bortezomib+lenalidomide plus dexamethasone; ASCT = autologous stem cell transplant; CR = complete response; M-protein = monoclonal protein; CT = computed tomography; PI = proteasome inhibitor; KRd = KYPROLIS®+lenalidomide and dexamethasone; Rd = lenalidomide+dexamethasone; PFS = Progression-free Survival; ITT = intent-to-treat; HR = hazard ratio; CI = confidence interval; ≥ CR = complete response or better.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Cardiac Toxicities (cont'd)

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

Please see full Important Safety Information below.



Biochemical relapse may require treatment

According to the International Myeloma Working Group (IMWG), A BIOCHEMICAL RELAPSE IS AN INCREASE IN THE LEVEL OF ANY OF THE FOLLOWING IN 2 CONSECUTIVE MEASUREMENTS⁵

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



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

ASK YOUR KYPROLIS[®] REPRESENTATIVE ABOUT PARTICIPATING IN A PROBLEM-BASED LEARNING PROGRAM

**KRd: NCCN
PREFERRED**

NCCN Guidelines[®]: Carfilzomib (KYPROLIS[®]) in combination with lenalidomide and dexamethasone (KRd) is a preferred regimen for relapsed multiple myeloma⁶

KRd has a Category 1 designation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Multiple Myeloma (Version 2.2020) for previously treated multiple myeloma⁶

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.

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 adverse events (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



How to dose KRd⁴

	IMiD-CONTAINING
	KRd TWICE WEEKLY
Infusion time	10 minutes
KYPROLIS[®] priming dose	20 mg/m ² Days 1 and 2 of Cycle 1 to evaluate tolerability
Target KYPROLIS[®] therapeutic dose	27 mg/m ² starting Day 8 of Cycle 1
Treatment schedule	<ul style="list-style-type: none"> • Administer 27 mg/m² 2 consecutive days each week for 3 weeks • Follow with 12-day rest period, as part of 28-day treatment cycle • From Cycle 13, omit Day 8 and 9 doses • Continue until disease progression or unacceptable toxicity occurs • Discontinue KYPROLIS[®] after Cycle 18

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



Calculating the priming & therapeutic dose⁴

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

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

EXAMPLES:

Calculate the correct KRd mg/m² dose for a patient with a BSA of 1.8 m²

Priming Dose: $1.8 \text{ m}^2 \times 20 \text{ mg/m}^2 = 36 \text{ mg}$

Therapeutic Dose: $1.8 \text{ m}^2 \times 27 \text{ mg/m}^2 = 49 \text{ mg}$



Manage hydration throughout treatment⁴

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

Refer to the full Prescribing Information and Dosing and Administration Guide for more information.

- The recommended hydration includes 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

KRd = KYPROLIS[®]+lenalidomide and dexamethasone; IMiD = immunomodulatory drug; IV = intravenous.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Tumor Lysis Syndrome

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

Please see full Important Safety Information below.
Click [here](#) for full Prescribing Information.

References: 1. The mSMART Clinical Practice Guidelines in relapsed myeloma. Mayo Stratification for Myeloma and Risk-adapted Therapy website. <https://nebula.wsimg.com/1c0adc8316c5947bb2b948ad5e9e2e55?AccessKeyId=A0994494BBBCBE4A0363&disposition=0&alloworigin=1>. Accessed October 14, 2019. 2. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33:2863-2869. 3. Dimopoulos MA, Stewart AK, Masszi T, et al. Carfilzomib-lenalidomide-dexamethasone vs lenalidomide-dexamethasone in relapsed multiple myeloma by previous treatment. *Blood Cancer J*. 2017;7:e554. 4. KYPROLIS[®] (carfilzomib) prescribing information, Onyx Pharmaceuticals Inc., an Amgen Inc. subsidiary. 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. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Multiple Myeloma V.2.2020. © National Comprehensive Cancer Network, Inc 2019. All rights reserved. Accessed October 14, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

INDICATION

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of 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), restrictive 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 events until recovery, and consider whether to restart at 1 dose level reduction based on a benefit/risk assessment.
- 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.

Acute Renal Failure

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

Tumor Lysis Syndrome

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

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. Thromboprophylaxis is recommended for patients being treated with the combination of KYPROLIS with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.
- Patients using hormonal contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment.

Infusion Reactions

- Infusion 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 reactions. Inform patients of the risk and of symptoms and seek immediate medical attention if they occur.

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.

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 events 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.
- Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS and for 6 months following the final dose. Males of reproductive potential should be advised to avoid fathering a child while being treated with KYPROLIS and for 3 months following the final dose. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Adverse Reactions

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

[Click here for full Prescribing Information.](#)

AMGEN[®]

Oncology