

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

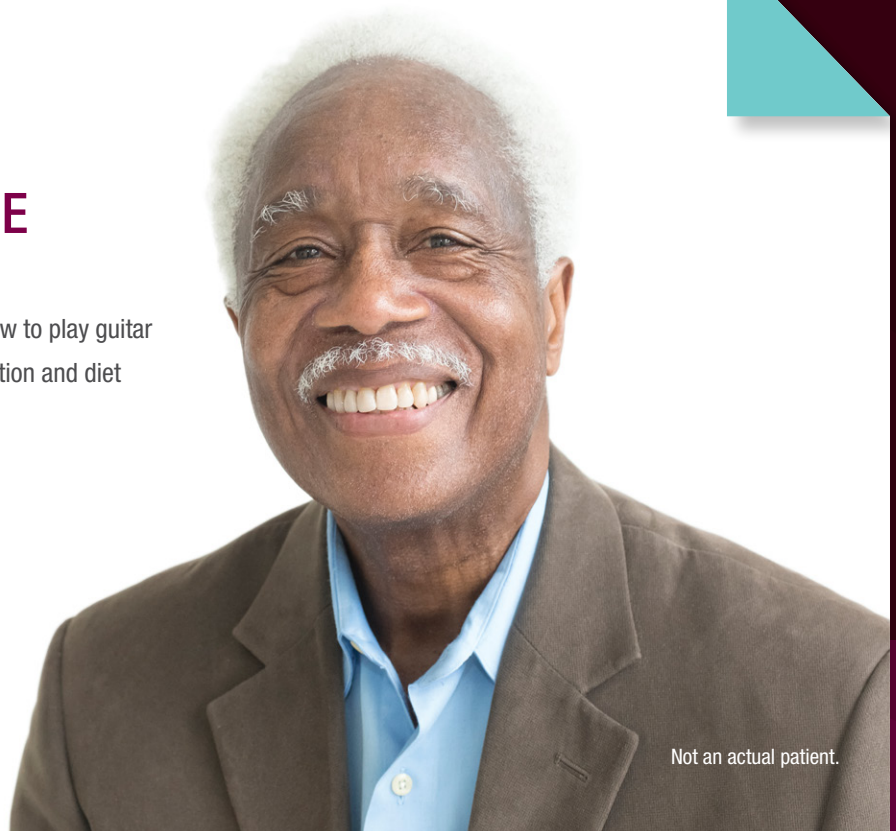
## JOSEPH

### 76-YEAR-OLD AFRICAN-AMERICAN MALE

- Retired high school history teacher, widowed
- Amateur musician, enjoys teaching his grandchildren how to play guitar
- Type 2 diabetes moderately well-controlled with medication and diet
- COPD limits his physical activity
- Traveling to and from visits can be challenging
- Standard-risk cytogenetics\*
- ECOG PS 2

\*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.<sup>1,2</sup>

COPD = chronic obstructive pulmonary disease; 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.



## Joseph's multiple myeloma treatment history

### FIRST LINE

- Diagnosed with multiple myeloma after complaining of fatigue and nonpainful tingling in fingers
- Treated with bortezomib, lenalidomide, and dexamethasone (VRd) for 4 cycles

### MAINTENANCE

- Followed by ASCT and maintenance with lenalidomide; remained in CR during maintenance

### PROGRESSION

- 36 months after starting maintenance, MRI revealed the presence of new bone lesions
- Patient is refractory to lenalidomide and might consider a lenalidomide-free regimen

➤ Joseph wants a treatment with a DEEP and DURABLE response



## Go for a deep and durable response at first relapse, regardless of cytogenetic risk

### IMPORTANT CONSIDERATIONS FOR JOSEPH

- **PRIOR PI EXPOSURE:** Kd twice weekly PFS results were consistent, independent of prior bortezomib exposure<sup>3</sup>
- **EXPLORATORY ANALYSIS:** At first relapse, Kd twice weekly demonstrated a 12-month increase in median PFS vs Vd (22 months Kd vs 10.1 months Vd)<sup>4</sup>
  - While this subgroup analysis was preplanned, demonstration of PFS efficacy within these subgroups was not a study objective. The study was not powered to evaluate PFS efficacy within this subgroup<sup>4</sup>
  - Median PFS in ITT population: 18.7 months Kd vs 9.4 months Vd (HR = 0.53; 95% CI: 0.44-0.65;  $P < 0.0001$ , one-sided<sup>5</sup>)
- **2X HIGHER ≥ CR:** Kd twice weekly delivered 2X the rate of ≥ CR vs Vd (13% Kd vs 6% Vd)<sup>5</sup>
- **5X LESS PERIPHERAL NEUROPATHY** with Kd twice weekly vs Vd (7% Kd vs 35% Vd)<sup>5</sup>

ASCT = autologous stem cell transplant; CR = complete response; MRI = magnetic resonance imaging; PI = proteasome inhibitor; Kd = KYPROLIS®+dexamethasone; PFS = Progression-free Survival; Vd = bortezomib+dexamethasone; 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 MEASUREMENTS<sup>6</sup>**

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



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

**ASK YOUR KYPROLIS<sup>®</sup> REPRESENTATIVE ABOUT PARTICIPATING IN A PROBLEM-BASED LEARNING PROGRAM**

**Kd: ONLY  
NCCN-  
PREFERRED  
DOUBLET**

NCCN Guidelines<sup>®</sup>: Carfilzomib (KYPROLIS<sup>®</sup>) in combination with dexamethasone (Kd) is the only preferred doublet regimen for relapsed multiple myeloma

Kd twice weekly has a Category 1 designation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Multiple Myeloma (Version 2.2020) for previously treated multiple myeloma.<sup>7</sup>

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<sup>™</sup>**  
(carfilzomib) for Injection



## How to dose Kd<sup>5</sup>

	IMI <sup>d</sup> -FREE	
	Kd TWICE WEEKLY	Kd ONCE WEEKLY
<b>Infusion time</b>	30 minutes	30 minutes
<b>KYPROLIS<sup>®</sup> priming dose</b>	20 mg/m <sup>2</sup> Days 1 and 2 of Cycle 1 to evaluate tolerability	20 mg/m <sup>2</sup> Day 1 of Cycle 1 to evaluate tolerability
<b>Target KYPROLIS<sup>®</sup> therapeutic dose</b>	56 mg/m <sup>2</sup> starting Day 8 of Cycle 1	70 mg/m <sup>2</sup> starting Day 8 of Cycle 1
<b>Treatment schedule</b>	<ul style="list-style-type: none"> <li>Administer 56 mg/m<sup>2</sup> 2 consecutive days each week for 3 weeks</li> <li>Follow with 12-day rest period, as part of 28-day treatment cycle</li> <li>Continue until disease progression or unacceptable toxicity occurs</li> </ul>	<ul style="list-style-type: none"> <li>Administer 70 mg/m<sup>2</sup> 1 day each week for 3 weeks</li> <li>Follow with 13-day rest period, as part of 28-day treatment cycle</li> <li>For Cycles 10 and beyond, dexamethasone is not given on Day 22</li> <li>Continue until disease progression or unacceptable toxicity occurs</li> </ul>

Refer to dexamethasone Prescribing Information.

- KYPROLIS<sup>®</sup> is offered in 3 single-dose vial sizes: 10 mg, 30 mg, and 60 mg.<sup>5</sup>



## Calculating the priming & therapeutic dose<sup>5</sup>

Patient's body surface area (BSA; m<sup>2</sup>) x dose (mg/m<sup>2</sup>)

### EXAMPLES: Kd 56 mg/m<sup>2</sup> TWICE WEEKLY:

Calculate the correct Kd twice weekly mg/m<sup>2</sup> dose for a patient with a BSA of 1.8 m<sup>2</sup>

Priming Dose: 1.8 m<sup>2</sup> x 20 mg/m<sup>2</sup> = 36 mg

Therapeutic Dose: 1.8 m<sup>2</sup> x 56 mg/m<sup>2</sup> = 101 mg

### Kd 70 mg/m<sup>2</sup> ONCE WEEKLY:

Calculate the correct Kd once weekly mg/m<sup>2</sup> dose for a patient with a BSA of 1.8 m<sup>2</sup>

Priming Dose: 1.8 m<sup>2</sup> x 20 mg/m<sup>2</sup> = 36 mg

Therapeutic Dose: 1.8 m<sup>2</sup> x 70 mg/m<sup>2</sup> = 126 mg



## Manage hydration throughout treatment<sup>5</sup>

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<sup>®</sup> 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

Kd = KYPROLIS<sup>®</sup>+dexamethasone; IMI<sup>d</sup> = 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.**

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. Mateos MV, Goldschmidt H, San Miguel JF, et al. Relapsed or refractory multiple myeloma patients treated with second-line carfilzomib and categorized by prior exposure to bortezomib: A subgroup analysis of the randomized phase 3 ASPIRE and ENDEAVOR trials. *Blood*. 2017;130:1840. 4. Moreau P, Joshua D, Chng W-J, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. *Leukemia*. 2017;31:115-122. 5. KYPROLIS<sup>®</sup> (carfilzomib) prescribing information, Onyx Pharmaceuticals, an Amgen, Inc. subsidiary. 6. 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. 7. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) 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.

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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. 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.](#)

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