KRD: Previously Treated Multiple Myeloma; Primary Therapy for Newly Diagnosed, Transplant Eligible Multiple Myeloma Patients

Constituents of Regimen: Carfilzomib, lenalidomide, dexamethasone

Common Names or Abbreviations for Regimen: KRD

Other Names of Regimen Constituents and Unique Ingredient Identifier (UNII):

- Carfilzomib: PR-171, Kyprolis®, CFZ, UNII code: 72X6E3J5AR
- Lenalidomide: CC5013, CDC-501, IMID3, 191732-72-6, Revlimid®, UNII: F0P408N6V4
- Dexamethasone: Dex, DM, DXM, Decadron®, UNII: 7S5I7G3JQL

Mechanism(s) of Action:

Carfilzomib is a novel epoxyketone-based selective proteasome inhibitor that targets and irreversibly binds to the β5 subunit of the constitutive 26S proteasome and LMP7 immunoproteasome, resulting in sustained inhibition of chymotrypsin-like activity and apoptosis of myeloma cells.[1-5] Lenalidomide is an immunomodulatory drug (IMiD) that exerts its effects through multiple pathways both directly on multiple myeloma (MM) tumor cells and indirectly through activation of T-cells as well as lowering the threshold of natural killer (NK) cell activation and augmenting stimulated NK cell responses as described below.[6,7] The mechanism by which the glucocorticoid dexamethasone induces apoptosis in MM cells has not been fully elucidated, although studies suggests that either transactivation through the glucocorticoid response element (GRE) resulting in activation of proapoptotic genes,[8-11] transrepression of NF-κB, phosphorylation of RAFTK (Pyk2), or induction of Bim is important in exerting its therapeutic activity.[12-19]

The rationale for combining carfilzomib with an IMiD, such as lenalidomide, and the glucocorticoid dexamethasone is essentially the same as that provided for combining bortezomib with lenalidomide and dexamethasone. Supporting the combination is that these drugs have different but overlapping mechanisms of anti-MM activity in preclinical studies.[20-22] Proteasome inhibitor-induced tumor cell death has been associated with activation of both the mitochondrial, caspase-9–mediated and Fas/caspase-8–mediated apoptotic pathways, as well as the induction of endoplasmic reticulum stress and inhibition of nuclear factor κ-B signaling.[20,21] Lenalidomide primarily triggers the caspase-8–mediated apoptotic pathway and also down-regulates nuclear factor κ-B activity via a mechanism distinct from that of the proteasome inhibitor bortezomib.[22] Lenalidomide binding to cereblon has been show to result in the interaction of Ikaros and Aiolos to CRL4(CRBN), leading to their ubiquitination, subsequent proteasomal degradation and T-cell activation.[6] Lenalidomide has also been recently shown to lower the threshold for NK-cell activation, allowing NK cells to respond to lower doses of ligand. In addition, lenalidomide augments NK-cell

responses, but does not trigger IFN-γ production in unstimulated NK cells.[7] Both bortezomib[20] and the immunomodulatory drugs enhance the activity of dexamethasone, and synergy has been demonstrated between bortezomib and lenalidomide.[22] Clinical evidence of the efficacy and safety of carfilzomib in combination with an IMiD was first established in a multicenter phase I dose escalation study of carfilzomib plus lenalidomide plus low-dose dexamethasone in relapsed and refractory MM.[23]

National Comprehensive Cancer Network (NCCN) Recommendations with Level of Evidence: *(Category 1 implies a preferred regimen based on a high level of evidence and uniform NCCN consensus; category 2A implies a lower level of evidence, but uniform NCCN consensus that the intervention is appropriate).*

Therapy for Previously Treated Multiple Myeloma – Category 1 – preferred

Primary (induction) Therapy for Newly Diagnosed, Transplant Eligible Multiple Myeloma – Category 2a – Other [NCCN notes that the optimal dosing of this regimen has not been defined]

NCCN Evidence Blocks™ (see EB-1 for explanation of Evidence Blocks Categories)[24]:

Evidence Blocks for KRD: Previously Treated Multiple Myeloma

Efficacy: 5/5

Safety of Regimen/Agent: 3/5

Quality of Evidence: 4/5

Consistency of Evidence: 4/5

Affordability of Regimen/Agent: 1/5

Evidence Blocks for KRD Primary (induction) Therapy for Newly Diagnosed, Transplant Eligible Multiple Myeloma

Efficacy: 5/5

Safety of Regimen/Agent: 3/5

Quality of Evidence: 3/5

Consistency of Evidence: 4/5

Affordability of Regimen/Agent: 1/5

Dose Schedule:

KRD Therapy for Previously Treated Multiple Myeloma; the ASPIRE Phase III Trial[25]

- **Carfilzomib:** Carfilzomib was administered as a 10-minute infusion on days 1, 2, 8, 9, 15, and 16 (starting dose, 20 mg/m^2 on days 1 and 2 of cycle 1; target dose, 27 mg/m^2 thereafter) during cycles 1 through 12 and on days 1, 2, 15, and 16 during cycles 13 through 18, after which carfilzomib was discontinued.
- **Lenalidomide:** 25 mg PO on days 1 through 21.
- **Dexamethasone:** 40 mg PO days 1, 8, 15, 22.

Note: Pretreatment and post-treatment intravenous hydration (250 to 500 mL) was required during cycle 1. Pretreatment hydration could be continued in subsequent cycles at the investigator's discretion.

Post-KRD Maintenance: *Patients received only lenalidomide and dexamethasone beyond cycle 18 until disease progression.*

KRD Primary Treatment, for Newly Diagnosed, Transplant-Eligible MM[26,27]

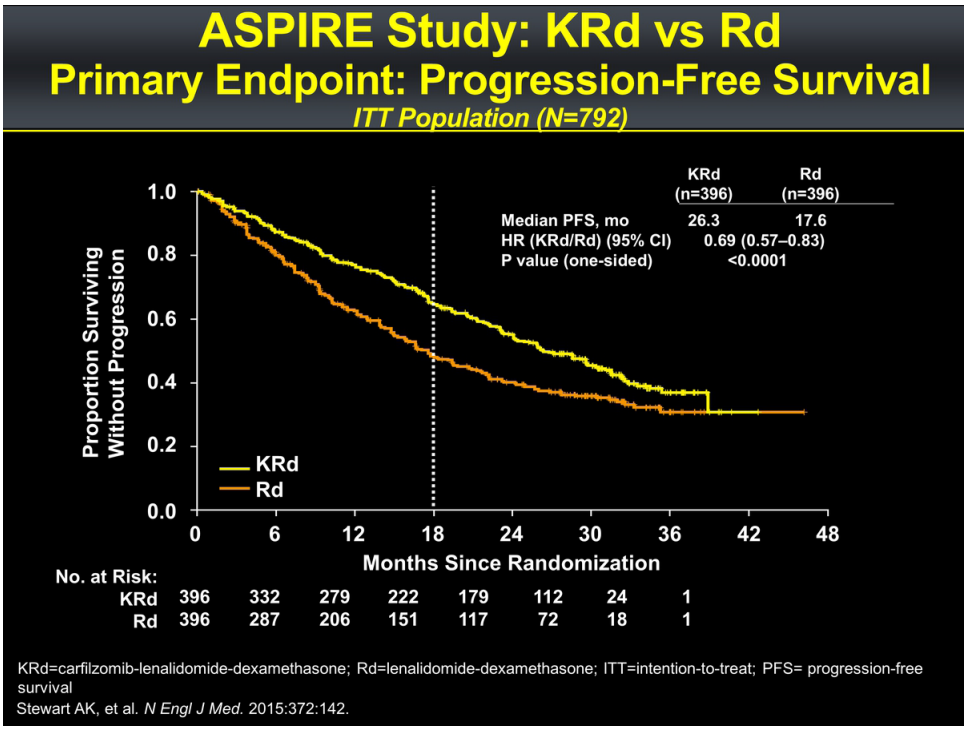
- **Carfilzomib:** Carfilzomib was administered intravenously 20/36 mg/m^2 on days 1, 2, 8, 9, 15 and 16 of a 28-day cycle.
- **Lenalidomide:** 25 mg PO on days 1 through 21.
- **Dexamethasone:** 40/20 mg PO weekly (cycles 1-4 induction/5-8 consolidation).

High-dose therapy with autologous stem cell transplantation (HDT/ASCT) was performed after cycle 4. For cycles 8-18, KRd was given with a modified carfilzomib schedule on days 1, 2, 15, and 16 and then lenalidomide alone after cycle 18.

Primary and Secondary Efficacy Outcomes:

KRD for Patients Who Have Been Previously Treated; Phase 3 ASPIRE Trial[25]

- ClinicalTrials.gov number, NCT01080391: Study design:
    - 792 patients with relapsed MM were randomly assigned to carfilzomib with lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group).
- Primary endpoints: Progression-free survival (PFS):
    - PFS significantly improved with the addition of carfilzomib: median, 26.3 months, vs. 17.6 months in the control group; hazard ratio for progression or death, 0.69; 95% confidence interval [CI], 0.57 to 0.83; *P*=.0001.



KRd=carfilzomib-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; ITT=intention-to-treat; PFS= progression-free survival

Stewart AK, et al. *N Engl J Med.* 2015:372:142.

- Secondary endpoints: Overall survival (OS), rate of overall response rate (ORR) (partial response (PR) or better), duration of response (DOR), health-related quality of life (HRQOL):
    - Median OS not reached in either group at the interim analysis. 24-month overall survival rates were 73.3% and 65.0% in the carfilzomib and control groups, respectively (hazard ratio for death, 0.79; 95% CI, 0.63 to 0.99; *P*=.04).
    - ORR was 87.1% and 66.7% in the carfilzomib and control groups, respectively (*P*<.001; 31.8% and 9.3% of patients in the respective groups had a complete response or better; 14.1% and 4.3% had a stringent complete response).
    - The median duration of treatment was 88.0 weeks (range, 1.0 to 185.0) in the carfilzomib group and 57.0 weeks (range, 1.0 to 201.0) in the control group.
    - Patients in the carfilzomib group reported superior health-related quality of life.

KRD Primary Therapy for Newly Diagnosed, Transplant Eligible MM (Phase II)[26]

- At time of report, study accrual goal of 53 patients had been met; median age 62 years (range 40-76), International Staging System (ISS) stage II/III 53%, high-risk cytogenetics 27%, as per International Myeloma Working Group (IMWG).
- At time of report, 49 patients completed induction, 41 transplant, 23 consolidation, and 7 completed 18 cycles of KRd.
- A median 9.79x106/kg CD34+ cells were collected (range 3.89-16.79).
- After a median follow-up of 9.7 months (range 1.6-23), all patients were alive and 52 of 53 progression free.

Response to Carfilzomib/Lenalidomide/Dexamethasone Treatment in Newly Diagnosed MM Patients[26,27]

	Post-Induction %	Post-Transplant %	Post-Consolidation %	Post-KRd %
Overall Response (≥ PR)	98	100	100	100
≥ VGPR	78	97	100	100
≥ nCR	14	44	91	100
sCR	10	25	70	86

VGPR=very good partial response; nCR=near complete response; sCR=stringent complete response

Safety:

KRD for Previously Treated MM[25]

- Adverse events (AEs) of grade 3 or higher were reported in 83.7% and 80.7% of patients in the carfilzomib and control groups, respectively; 15.3% and 17.7% of patients discontinued treatment owing to adverse events.
    - o AE ≥ grade 3: dyspnea (2.8% in the carfilzomib group and 1.8% in the control group (LD)), cardiac failure (grouped term; 3.8% and 1.8%), ischemic heart disease (grouped term; 3.3% and 2.1%), hypertension (4.3% and 1.8%), and acute renal failure (grouped term; 3.3% and 3.1%), diarrhea (3.8 % in the carfilzomib group, 4.1% in the control group), fatigue 7.7% in the carfilzomib group, 6.4% in the control).
    - o No meaningful differences in incidence of peripheral neuropathy (17.1% in carfilzomib group, 17.0% in the control group).

Adverse Events in the Safety Population[25]*

Event	Carfilzomib Group (N = 392)		Control Group (N = 389)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
	number of patients (percent)			
Most common nonhematologic adverse events				
Diarrhea	166 (42.3)	15 (3.8)	131 (33.7)	16 (4.1)
Fatigue	129 (32.9)	30 (7.7)	119 (30.6)	25 (6.4)
Cough	113 (28.8)	1 (0.3)	67 (17.2)	0
Pyrexia	112 (28.6)	7 (1.8)	81 (20.8)	2 (0.5)
Upper respiratory tract infection	112 (28.6)	7 (1.8)	75 (19.3)	4 (1.0)
Hypokalemia	108 (27.6)	37 (9.4)	52 (13.4)	19 (4.9)
Muscle spasms	104 (26.5)	4 (1.0)	82 (21.1)	3 (0.8)
Other adverse events of interest				
Dyspnea	76 (19.4)	11 (2.8)	58 (14.9)	7 (1.8)
Hypertension	56 (14.3)	17 (4.3)	27 (6.9)	7 (1.8)
Acute renal failure†	33 (8.4)	13 (3.3)	28 (7.2)	12 (3.1)
Cardiac failure‡	25 (6.4)	15 (3.8)	16 (4.1)	7 (1.8)
Ischemic heart disease§	23 (5.9)	13 (3.3)	18 (4.6)	8 (2.1)

* Adverse events reported in at least 25% of patients in either treatment group are listed. Other adverse events of particular clinical relevance are also listed. The safety population included all patients who received at least one dose of a study drug.

† The category of acute renal failure included (in descending order of frequency) acute renal failure, renal failure, renal impairment, azotemia, oliguria, anuria, toxic nephropathy, and prerenal failure.

‡ The category of cardiac failure included (in descending order of frequency) cardiac failure, congestive cardiac failure, pulmonary edema, hepatic congestion, cardiopulmonary failure, acute pulmonary edema, acute cardiac failure, and right ventricular failure.

§ The category of ischemic heart disease included (in descending order of frequency) angina pectoris, myocardial infarction, acute myocardial infarction, an increased serum creatine kinase level, coronary artery disease, myocardial ischemia, coronary artery occlusion, an increased troponin level, an increased level of troponin T, an acute coronary syndrome, abnormal results on a cardiac stress test, cardiomyopathy stress, unstable angina, coronary-artery stenosis, an abnormal ST-T segment on electrocardiography, and an abnormal T wave on electrocardiography.

- Drug discontinuation:
  - Most commonly due to disease progression (39.8% in the carfilzomib arm; 50.1% in the control arm).

KRD Primary Therapy for Newly Diagnosed, Transplant-eligible MM[26]

- KRd was well tolerated during induction with no new or unexpected events.
- After ASCT, KRd-related AEs were mostly Grade (G) 1/2; the, most common G3/4 AEs were lymphopenia (50%), leukopenia (14%), and neutropenia (21%).

Drug-specific Safety:

Black Box Warnings: Lenalidomide

- Embryofetal toxicity:
  - Lenalidomide is an analogue of thalidomide, a known human teratogen that causes life-threatening human birth defects or embryo-fetal death.
  - In females of reproductive potential, obtain two negative pregnancy tests before starting lenalidomide treatment.
  - Females of reproductive potential must use two forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after lenalidomide treatment.
  - To avoid embryo-fetal exposure to lenalidomide, lenalidomide is only available through a restricted distribution program, the REVLIMID REMS™ program (formerly known as the "RevAssist®" program).
- Hematological toxicity: Neutropenia, thrombocytopenia.
  - Venous and arterial thromboembolism:
    - Deep vein thrombosis, pulmonary embolism, and arterial thrombosis as well as risk of myocardial infarction and stroke have been reported in patients with MM who were treated with lenalidomide and dexamethasone therapy.

Additional Warnings and Precautions: Lenalidomide

- Allergic reactions: Hypersensitivity, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis. If these occur, lenalidomide should be discontinued.
- Tumor lysis syndrome (TLS): Although rare in MM, fatal instances of TLS have been reported during treatment with lenalidomide. The patients at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.
- Hepatotoxicity: Hepatic failure (including fatalities) has occurred. Liver function should be monitored at baseline and regularly while on treatment. If drug-related hepatotoxicity is suspected, lenalidomide should be stopped.
- Second primary malignancies (SPM): A higher incidences of SPM were observed in controlled trials of patients with multiple myeloma receiving lenalidomide.

- Impaired stem cell mobilization: A decrease in the number of CD34+ cells collected after treatment (>4 cycles) with lenalidomide has been reported. In patients who are ASCT candidates, referral to a transplant center should occur early in treatment to optimize timing of the stem cell collection.
- Patients should avoid pregnancy for at least 4 weeks before starting lenalidomide; patients should not become pregnant when taking lenalidomide.

Warnings and Precautions: Carfilzomib[28]

- Embryo-fetal toxicity.
- Cardiac arrest, congestive heart failure, myocardial ischemia death due to cardiac arrest has occurred within a day of carfilzomib administration.[28]
    - New onset or worsening of pre-existing congestive heart failure with decreased left ventricular function or myocardial ischemia have occurred following administration of carfilzomib.
    - Cardiac failure events (eg, cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients.
    - Monitor for cardiac complications and manage promptly.
- Pulmonary hypertension:
    - Pulmonary arterial hypertension (PAH) was reported in 2% of patients treated with carfilzomib and was Grade 3 or greater in less than 1% of patients.
- Dyspnea: Reported in 35% of patients enrolled in clinical trials.
    - Grade 3 dyspnea occurred in 5%; no Grade 4 events, and 1 death (Grade 5) was reported. Monitor and manage dyspnea immediately; interrupt carfilzomib until symptoms have resolved or returned to baseline.
- Infusion reactions: Infusion reactions were characterized by a spectrum of systemic symptoms including fever, chills, arthralgia, myalgia, facial flushing, facial 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 of carfilzomib. Administer dexamethasone prior to carfilzomib to reduce the incidence and severity of reactions.
- Tumor lysis syndrome (TLS): Tumor lysis syndrome occurred following carfilzomib administration in <1% of patients.

- Thrombocytopenia: Carfilzomib causes thrombocytopenia with platelet nadirs occurring around Day 8 of each 28-day cycle and recovery to baseline by the start of the next 28-day cycle. In patients with multiple myeloma, 36% of patients experienced thrombocytopenia, including Grade 4 in 10%.
- Hepatic toxicity and hepatic failure: Cases of hepatic failure, including fatal cases, have been reported (<1%). Carfilzomib can cause elevations of serum transaminases and bilirubin.
- Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome: Cases of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) including fatal outcome have been reported in patients who received carfilzomib. Monitor for signs and symptoms of TTP/HUS.
- Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving carfilzomib. Discontinue carfilzomib if PRES is suspected and evaluate.

Recommended Supportive Care/Prophylaxis: Patients on this regimen are at an increased risk for infection, or arterial or venous thromboembolic events (VTE), and embryo-fetal toxicity.

- Embryo-fetal toxicity: **REVLIMID REMS™** program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.
    - Females: Must obtain two negative pregnancy tests prior to initiating therapy, avoid pregnancy (abstinence or two forms of birth control) for at least 4 weeks before starting lenalidomide, during treatment with lenalidomide, and for at least 4 weeks after completing therapy with lenalidomide.
    - Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide and for up to 28 days after discontinuing lenalidomide, even if they have undergone a successful vasectomy. Male patients taking lenalidomide must not donate sperm.
    - Blood donation: Patients must not donate blood during treatment with lenalidomide and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to lenalidomide.
- Infections[29-31]:
    - Pneumococcal infections are common in patients with multiple myeloma. Pneumococcal vaccination should be completed at the time of diagnosis and repeated in 5 years to minimize preventable illness (link to CDC guidelines http://www.cdc.gov/vaccines/vpd-vac/pneumo/vacc-in-short.htm).
    - Shingles prophylaxis is recommended for all patients receiving carfilzomib.

- VTE: Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.
- General supportive care[32]:
    - Bisphosphonates (zoledronic acid or pamidronate) are intended to decrease the risk of skeletal-related events and should be considered in all patients with MM receiving first-line therapy, regardless of presence of osteolytic bone lesions on conventional radiography. Dental health should be evaluated at baseline and an ongoing basis to assess for osteonecrosis of the jaw. Serum creatinine levels should be obtained prior to each bisphosphonate dose. Periodic 24-hour urine monitoring should be performed to assess for renal damage secondary to bisphosphonate use long-term.
- Drug-drug interactions:
    - Lenalidomide: Digoxin levels may be reduced. Concurrent administration with erythropoiesis-stimulating agents (ESAs) or estrogen compounds may increase the risk of thrombosis.

Tailoring of Regimen:

- **Carfilzomib*:***
    - Use with caution in patients with underlying cardiopulmonary disease.
    - Neutropenia: Guidelines for dose delay, dose reduction, or discontinuation of treatment are included in the package insert.
    - Thrombocytopenia: Guidelines for dose delay, dose reduction, or discontinuation of treatment are included in the package insert.

- *Lenalidomide - http://www.revlimid.com/*[33]
    - *Renal dose adjustments: Dose modification for lenalidomide is required in the presence of renal impairment.*[33,34]

Lenalidomide Dose Modification for Renal Impairment		
Category	**Renal Function (Cockcroft-Gault creatinine clearance [CLcr])**	**Dose Adjustment for Multiple Myeloma Patients**
Moderate Renal Impairment	CLcr 30-50 mL/min	10 mg every 24 hours
Severe Renal Impairment	CLcr <30 mL/min (not requiring dialysis)	15 mg every 48 hours
End Stage Renal Disease	CLcr <30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose following dialysis.

Lenalidomide (Revlimid®) Package Insert. RevPlyPI.020/MG.020 02/15[33]

- "Tumor flare reactions" and "impaired stem cell mobilization.
- Hepatic dose adjustments: Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.
- Neutropenia: Guidelines for dose delay, dose reduction, or discontinuation of treatment are included in the package insert.
- Thrombocytopenia: Guidelines for dose delay, dose reduction, or discontinuation of treatment are included in the package insert.
- Harvesting of peripheral blood stem cells is recommended prior to prolonged exposure to lenalidomide.

- **Dexamethasone**[35]
    - Patients with diabetes: Adjustment of the dexamethasone dose and/or anti-diabetic medications may be required. Insulin administration may be required for some patients.
    - Steroid intolerance: Titration of the dexamethasone over time improve tolerance and reduce adverse events/late effects may also be considered.

Strategies to Reduce Treatment-associated Side Effects*[35-39]*:

- Monitoring recommendations and notes: Adverse events (as listed above under "safety" should be monitored for and addressed at each visit.
- Avoid administration of carfilzomib prior to the weekend in the first 10-20 cycles of treatment.
- A complete blood count (CBC) with differential should be monitored regularly during continued treatment, for cytopenias; when observed, intervene with dose reduction, treatment interruption or discontinuation of the causative agent, transfusion (platelets) and/or growth factor support (neutropenia).
- Thromboprophylaxis: Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.[36,39]
    - Low-risk: Aspirin 81-325 mg with consideration of bleeding risks, other platelet inhibiting drugs
    - Higher-risk (≥2 risk factors): Full anti-coagulation with consideration of bleeding risks, other platelet inhibiting drugs.
    - Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.
- Corticosteroids such as dexamethasone can lead to many side effects such as hyperglycemia, mood swings, insomnia and proximal muscle weakness. Prior to starting a corticosteroid-containing regimen, patients should be screened for a history of diabetes, mood disorders and psychiatric illnesses.[35]
    - Periodic monitoring of blood glucose levels (to assess for hyperglycemia), mood disturbance and sleep patterns related to corticosteroids is recommended.
- Regular physical activity should be encouraged to combat muscle weakness, fatigue and to reduce the incidence of VTEs.
- Adherence to therapy can be improved by providing patients and their caregivers with drug information, the treatment plan, prevention strategies, reportable signs and symptoms, and strategies for management. Prompt identification of adverse effects with early intervention may reduce the severity of AEs.

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KRD: Previously Treated Multiple Myeloma; Primary Therapy for Newly Diagnosed, Transplant Eligible Multiple Myeloma Patients