KPD: Carfilzomib/Pomalidomide/Dexamethasone Previously Treated Multiple Myeloma

Constituents of Regimen: Carfilzomib, pomalidomide, dexamethasone

Common Names or Abbreviations for Regimen: KPD, CPD

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

- Carfilzomib: PR-171, Kyprolis®, CFZ, UNII code: 72X6E3J5AR
- Pomalidomide: POM, CC-4047, 19171-19-8, ACTIMID, IMID1, IMNOVID, Pomalyst®, UNII Code: D2UX06XLB5
- 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] Pomalidomide, an immunomodulatory drug (IMiD) which is a derivative of thalidomide, has been shown, in preclinical and primarily in vitro studies, to mediate direct antiproliferative effects on tumor cells, as well as immune-modulatory effects on T-cells, natural killer (NK) cells, and monocytes.[6-16] The mechanism by which the glucocorticoid dexamethasone induces apoptosis in multiple myeloma (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,[17-20] transrepression of NF-κB, phosphorylation of RAFTK (Pyk2), or induction of Bim is important in exerting its therapeutic activity.[21-28]

The rationale for combining carfilzomib with an IMiD such as pomalidomide, and the glucocorticoid dexamethasone is essentially the same as that provided for combining bortezomib with lenalidomide and dexamethasone, and carfilzomib with lenalidomide plus dexamethasone with the additional rationale that patients who are relapsed and/or refractory to other IMiDs need alternative therapeutic strategies and that the three-drug combination approaches, such as that of carfilzomib/lenalidomide/dexamethasone for relapsed MM has been shown to be superior to the two-drug combination of lenalidomide and dexamethasone in a phase III comparison trial.[29] Supporting the combination is that proteasome inhibitors and IMiDs have different but overlapping mechanisms of anti-MM activity in preclinical studies.[3] Proteasome inhibitor-induced tumor cell death has been associated with activation of c-Jun-N-terminal kinase, mitochondrial membrane depolarization, release of cytochrome c, and activation of both intrinsic and extrinsic caspase pathways.[3] IMiDs primarily trigger the caspase-8–mediated apoptotic pathway and also down-regulates nuclear factor κ-B

activity via a mechanism distinct from that of the proteasome inhibitors.[8] IMiDs like pomalidomide 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.[14] Another thalidomide derivative IMiD, 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.[30] It has been recently shown that pomalidomide induces poly-functional T-cell activation, with increased proportion of coinhibitory receptor BTLA(+) T-cells and Tim-3(+) NK cells.[31] Baseline levels of Ikaros and Aiolos protein in tumor cells did not correlate with response or survival. Pomalidomide led to rapid decline in Ikaros in T and NK cells in vivo, and therapy-induced activation of CD8(+) T-cells correlated with clinical response. Both another proteasome inhibitor, bortezomib,[32] and the immunomodulatory drugs have been shown to enhance the activity of dexamethasone, and synergy has been demonstrated between bortezomib and lenalidomide.[8] 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[33]; and carfilzomib plus lenalidomide plus dexamethasone has recently been shown to be superior to lenalidomide plus dexamethasone alone for relapsed MM.[29]

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).*

Currently no NCCN recommendations for this combination regimen

NCCN Evidence Blocks™ (see EB-1 for explanation of Evidence Blocks Categories)[34]:

Currently no NCCN Evidence Blocks for this combination regimen

Dose Schedule:

KPD (CPD) for relapsed and/or refractory MM[35,36]

- **Carfilzomib:** Carfilzomib 20 mg/m^2 for cycle 1, then 27 mg/m^2 for subsequent cycles over 30 minutes on days 1, 2, 8, 9, 15, and 16 every 28 days
- **Pomalidomide:** 4 mg orally on days 1-21 of a 28-day cycle
- **Dexamethasone:** 40 mg orally on days 1, 8, 15, 22 of a 28-day cycle

Primary and Secondary Efficacy Outcomes:

- A multicenter phase I/II trial of carfilzomib and pomalidomide with dexamethasone (Car-Pom-d) in patients with relapsed/refractory multiple myeloma.[35,36]
    - Primary objective was to evaluate the safety and determine the maximum tolerated dose (MTD) of the regimen
    - A total of 32 patients were enrolled
    - Patients that relapsed after prior therapy or were refractory to the most recently received therapy were eligible
    - All patients were refractory to prior lenalidomide
    - Established MTD carfilzomib 20/27 mg/m^2, pomalidomide 4 mg, dexamethasone 40 mg
    - Adverse events (AEs) occurring in >20% of patients included fatigue (42%), anemia (33%), pneumonia (33%), dyspnea (25%), and thrombocytopenia (25%)
    - 50% (n=6) of patients experienced grade ≥3 AEs
    - Hematological adverse events occurred in ≥60% of all patients, including 11 patients with grade ≥3 anemia
    - Dyspnea was limited to grade 1/2 in 10 patients
    - Peripheral neuropathy was uncommon and limited to grade 1/2
    - Eight patients had dose reductions during therapy, and seven patients discontinued treatment due to adverse events
    - Two deaths were noted on study due to pneumonia and pulmonary embolism (n=1 each)
    - Expansion cohort of 20 patients (n=20) for a total population of 32 patients; 27 evaluable patients: Very good partial response (VGPR) (n=2); partial response (PR) (n=7); median response (MR) (n=6), stable disease (SD) (n=8), and progressive disease (PD) (n=4)

- Currently accruing: Multicenter, open-label, single-arm, phase 1b/2 study of the safety and efficacy of combination treatment with pomalidomide, dexamethasone, and carfilzomib (PdC) in subjects with relapsed and relapsed/refractory multiple myeloma. NCT01665794; NCT01464034; NCT02185820
    - Primary outcomes: MTD, PR after four courses
    - Secondary endpoints: Overall response rate (ORR), time to progression (TTP), duration of response (DOR), progression-free survival (PFS), overall survival (OS)

Drug-specific Safety:

Black Box Warnings: Pomalidomide[37]

- Embryofetal toxicity:
    - Pomalidomide 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 pomalidomide treatment
    - Females of reproductive potential must use two forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after pomalidomide treatment.
    - To avoid embryo-fetal exposure to lenalidomide, pomalidomide is only available through a restricted distribution program, the POMALYST REMS™ program is available at **www.CelgeneRiskManagement.com** or by telephone at 1-888-423-5436
- 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: Pomalidomide[37]

- Hematologic toxicity: Neutropenia and thrombocytopenia have been reported in up to 50% of patients. Monitor patients for hematologic toxicities, especially neutropenia, with complete blood counts weekly for the first 8 weeks and monthly thereafter.
- Dizziness and confusional state: 18% of patients experienced dizziness and 12% of patients experienced a confusional state; 1% of patients experienced Grade 3/4 dizziness, and 3% of patients experienced Grade 3/4 confusional state. Instruct patients to avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.
- Neuropathy: 18% of patients experienced neuropathy (approximately 9% peripheral neuropathy). There were no cases of Grade 3 or higher neuropathy adverse reactions reported.
- Allergic reactions: Hypersensitivity, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis. If these occur, pomalidomide should be discontinued.
- Tumor lysis syndrome (TLS): Cases of TLS have been reported, although rare in MM.
- Hepatotoxicity: Pomalidomide is metabolized in the liver. Avoid pomalidomide in patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x upper limit normal (ULN). The influence of hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x ULN were excluded in clinical studies.
- Renal toxicity: Pomalidomide is primarily excreted by the kidneys. Avoid pomalidomide in patients with a creatinine >3.0 mg/dL.
- Second primary malignancies (SPM): A higher incidences of SPM were observed in controlled trials of patients with multiple myeloma receiving pomalidomide.

Warnings and Precautions: Carfilzomib[38]

- Cardiac arrest, congestive heart failure, myocardial ischemia death due to cardiac arrest has occurred within a day of carfilzomib administration.
    - 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.
- Embryo-fetal toxicity: Carfilzomib can cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated.

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: **POMALYST 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 pomalidomide, during treatment with pomalidomide, and for at least 4 weeks after completing therapy with pomalidomide.
  - Males: Pomalidomide 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 pomalidomide and for up to 28 days after discontinuing pomalidomide, even if they have undergone a successful vasectomy. Male patients taking pomalidomide must not donate sperm.
  - Blood donation: Patients must not donate blood during treatment with pomalidomide 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 pomalidomide.
- Infections[39-41]:
  - 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[42,43]: 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[44]:
  - 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:
    - Pomalidomide is primarily metabolized by CYP1A2 and CYP3A, and is a substrate for P-glycoprotein (P-gp). Avoid the use of strong CYP1A2 inhibitors. If medically necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-gp, reduce POMALYST dose by 50%. Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

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.
- **Pomalidomide*:***
    - Renal impairment: pomalidomide and its metabolites are primarily excreted by the kidneys. Patients with serum creatinine >3.0 mg/dL were excluded in clinical trials.
    - Hepatic impairment: Pomalidomide is metabolized in the liver. Patients with serum bilirubin >2.0 mg/dL and AST/ALT >3 times ULN were excluded in clinical trials. Avoid pomalidomide in patients with hepatic impairment.
    - 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.
- **Dexamethasone[45]:**
    - 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[42,43,45-47]***:***

- 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.[42,46]
    - 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.[45]
    - 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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Primary Author: Sandra E. Kurtin, RN, MS, AOCN©, ANP-C, Clinical Assistant Professor of Medicine, Adjunct Clinical Assistant Professor of Nursing. The University of Arizona Cancer Center, Tucson, Arizona
External Reviewer: Chris Fausel, PharmD, MHA, BCOP
Internal Reviewer: Eugene R. Tombler, PhD, Medical Director for MediCom Oncology and *Managing Myeloma*
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