# Supplementary Online Content

Kazandjian D, Hill E, Dew A, et al. Carfilzomib, lenalidomide, and dexamethasone followed by lenalidomide maintenance for prevention of symptomatic multiple myeloma in patients with high-risk smoldering myeloma: a phase 2 nonrandomized controlled trial. Published online September 16, 2021. *JAMA Oncol*. doi:10.1001/jamaoncol.2021.3971



This supplementary material has been provided by the authors to give readers additional information about their work.

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**eTable 1.** Eligibility Criteria for Carfilzomib, Lenalidomide, and Dexamethasone With Lenalidomide Maintenance (KRd-R) for High-Risk Smoldering Myeloma

| **Inclusion Criteria** |
|---|
| 1. Patients must have histologically or cytologically confirmed smoldering myeloma confirmed by the Principal Investigator in discussion with the Laboratory of Pathology, National Cancer Institute or the Department of Laboratory Medicine, Clinical Center, as needed, and based on the International Myeloma Working Group (IMWG) Criteria.<br>• Serum M-protein ≥3 g/dl and/or bone marrow plasma cells ≥10 % and <60%<br>• Absence of anemia: Hemoglobin >10 g/dL<br>• Absence of renal failure: serum creatinine < 2.0 mg/dL<br>• Absence of hypercalcemia: Calcium <10.5 mg/dL<br>• Absence of lytic bone lesion on X-ray, computed tomography (CT), or positron emission tomography/computed tomography (PET/CT) and not more than 1 lesion on spinal Magnetic resonance imaging (MRI)<br>• Involved/un-involved serum free light chain ratio <100 |
| 2. Measurable disease within the past 4 weeks defined by any one of the following:<br>• Serum monoclonal protein ≥ 1.0 g/dl<br>• Urine monoclonal protein >200 mg/24 hour<br>• Serum immunoglobulin free light chain >10 mg/dL AND abnormal kappa/lambda ratio (reference 0.26-1.65) |
| 3. Age >18 years |
| 4. Eastern Cooperative Oncology Group performance status <2 |
| 5. Patients must have normal organ and marrow function as defined below:<br>• Absolute neutrophil count >1.0 K/uL<br>• Platelets >75 K/uL<br>• Hemoglobin >8 g/dL<br>• Total bilirubin <1.5 times the institutional upper limit of normal (ULN)<br>• Aspartate/alanine transaminase <3.0 times the institutional ULN<br>• Serum creatinine ≤1.5 times the institutional upper limit of normal (If serum creatinine above 1.5 times the upper limit of normal, creatinine clearance or estimated glomerular filtration rate must be ≥50 ml/min) |
| 6. In addition to having smoldering myeloma, patients must also be classified as high-risk per 2008 Mayo Clinic or Spanish PETHEMA criteria. NOTE: Criteria set forward by Rajkumar, Landgren, Mateos may also be used to define high risk disease, namely clonal bone marrow plasma cells ≥10% and any one or more of the following:<br>• Serum M-protein ≥3 gm/dL<br>• IgA isotype<br>• Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes<br>• Serum involved/uninvolved free light chain ratio ≥8, <100 |

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- Progressive increase in M protein level (evolving type of smoldering myeloma; increase in serum M protein by ≥25% on 2 successive evaluations within a 6-month period)
- Clonal bone marrow plasma cells 50%-60%
- Abnormal BMPC immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of ≥1 uninvolved immunoglobulin isotypes
- t(4;14) or del(17p) or 1q gain
- Increased circulating bone marrow plasma cells
- MRI with diffuse abnormalities or 1 focal lesion
- PET/CT with focal lesion, increased uptake without underlying osteolytic bone destruction

7. All study participants must be registered into the mandatory REMS® program, and be willing and able to comply with the requirements of REMS®.
8. Women of child-bearing potential and men must agree to use adequate contraception. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 10-14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 and must either commit to continued abstinence from heterosexual intercourse or begin two acceptable methods of birth control, one highly effective method and one additional effective method at the same time, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.
9. Ability of subject to understand and the willingness to sign a written informed consent document.

**Exclusion Criteria**

1. Patients who are receiving any other investigational agents
2. Concurrent systemic treatment or prior therapy within 4 weeks for smoldering myeloma.
3. Patients with a diagnosis of multiple myeloma as defined by the 2014 IMWG diagnostic criteria
4. Contraindication to any concomitant medication, including antivirals, anticoagulation prophylaxis, tumor lysis prophylaxis, or hydration given prior to therapy
5. History of allergic reactions attributed to compounds of similar chemical or biologic composition to carfilzomib or lenalidomide agents used in study, such as bortezomib or thalidomide, in addition to patients with known allergy to sulfobutyl ether β-cyclodextrin (Captisol®)
6. Uncontrolled hypertension or diabetes
7. Pregnant or lactating females. Pregnant women are excluded from this study.
8. Significant cardiovascular disease with New York Heart Association Class II, III or IV symptoms, or hypertrophic cardiomegaly, or restrictive cardiomegaly, or myocardial infarction within 3 months prior to enrollment, or unstable angina, or unstable arrhythmia
9. Active hepatitis B or C infection
10. Refractory GI disease with refractory nausea/vomiting, inflammatory bowel disease, or bowel resection that would prevent absorption
11. Significant neuropathy >Grade 2 at the time of first dose or within 14 days of enrollment
12. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or

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psychiatric illness/social situations within 2 weeks that would limit compliance with study requirements.

13. History of other malignancy (apart from basal cell carcinoma of the skin, or in situ cervix carcinoma) except if the patient has been free of symptoms and without active therapy during at least 2 years or if, at the clinical discretion of the investigator, the risks of this study do not outweigh the potential benefits on a case-to-case basis.
14. Major surgery within 1 month prior to enrollment

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**eTable 2.** Any Grade Treatment-Related Adverse Events Occurring in ≥10% and Grade 3/4 Occurring in ≥1 Patient

| Adverse Event (N=54) | Any Grade n (%) | Grade 3 n (%) | Grade 4 n (%) |
|---|---|---|---|
| Any adverse event | 54 (100) | 26 (48.1) | 4 (7.4) |
| Any non-hematologic adverse event | 54 (100) | 21 (38.9) | – |
| Fatigue | 30 (55.6) | – | – |
| Rash | 30 (55.6) | 4 (7.4) | – |
| Diarrhea | 25 (46.3) | 2 (3.7) | – |
| Constipation | 21 (38.9) | – | – |
| Insomnia | 20 (37.0) | – | – |
| Thrombocytopenia | 20 (37.0) | 2 (3.7) | 1 (1.9) |
| Lymphopenia | 19 (35.2) | 7 (13.0) | 1 (1.9) |
| Leukopenia | 18 (33.3) | 3 (5.6) | 1 (1.9) |
| Neutropenia | 18 (33.3) | 10 (18.5) | 2 (3.7) |
| Gastroesophageal reflux | 17 (31.5) | – | – |
| Nausea | 17 (31.5) | – | – |
| Alanine transaminitis | 16 (29.6) | 2 (3.7) | – |
| Myalgia | 16 (29.6) | – | – |
| Elevated alkaline phosphatase | 15 (27.8) | 1 (1.9) | – |
| Anemia | 15 (27.8) | 4 (7.4) | – |
| Dysgeusia | 15 (27.8) | – | – |
| Dyspnea | 15 (27.8) | 1 (1.9) | – |
| Injection site reaction | 13 (24.1) | – | – |
| Upper respiratory infection | 13 (24.1) | – | – |
| Peripheral edema | 12 (22.2) | – | – |
| Aspartate transaminitis | 11 (20.4) | – | – |
| Hypophosphatemia | 11 (20.4) | 2 (3.7) | – |
| Phlebitis | 11 (20.4) | – | – |
| Pruritus | 11 (20.4) | – | – |
| Thromboembolic event | 11 (20.4) | 6 (11.1) | – |
| Lung infection | 10 (18.5) | 3 (5.6) | – |
| Bloating | 9 (16.7) | – | – |
| Hypertension | 9 (16.7) | 1 (1.9) | – |
| Hypoalbuminemia | 9 (16.7) | – | – |
| Peripheral sensory neuropathy | 8 (14.8) | – | – |
| Cough | 7 (13.0) | – | – |
| Elevated bilirubin | 7 (13.0) | 1 (1.9) | – |
| Elevated creatinine | 7 (13.0) | 1 (1.9) | – |
| Headache | 7 (13.0) | – | – |
| Hyperglycemia | 7 (13.0) | 3 (5.6) | – |
| Hypernatremia | 6 (11.1) | – | – |
| Hypomagnesemia | 6 (11.1) | – | – |
| Elevated creatine phosphokinase | 5 (9.3) | 1 (1.9) | – |
| Hypokalemia | 4 (7.4) | 1 (1.9) | – |
| Arthralgia | 4 (7.4) | 1 (1.9) | – |
| Neoplasm | 3 (5.6) | 1 (1.9) | – |
| Heart failure | 2 (3.7) | 1 (1.9) | – |
| Hyponatremia | 2 (3.7) | 1 (1.9) | – |
| Other skin disorder | 2 (3.7) | 1 (1.9) | – |
| Atrial fibrillation | 1 (1.9) | 1 (1.9) | – |
| Hyperkalemia | 1 (1.9) | 1 (1.9) | – |
| Soft tissue infection | 1 (1.9) | 1 (1.9) | – |

*Adverse events graded using the National Cancer Institute Common Terminology Criteria for Adverse Events. Clinically insignificant laboratory events were not reported per protocol. (–) denotes no events

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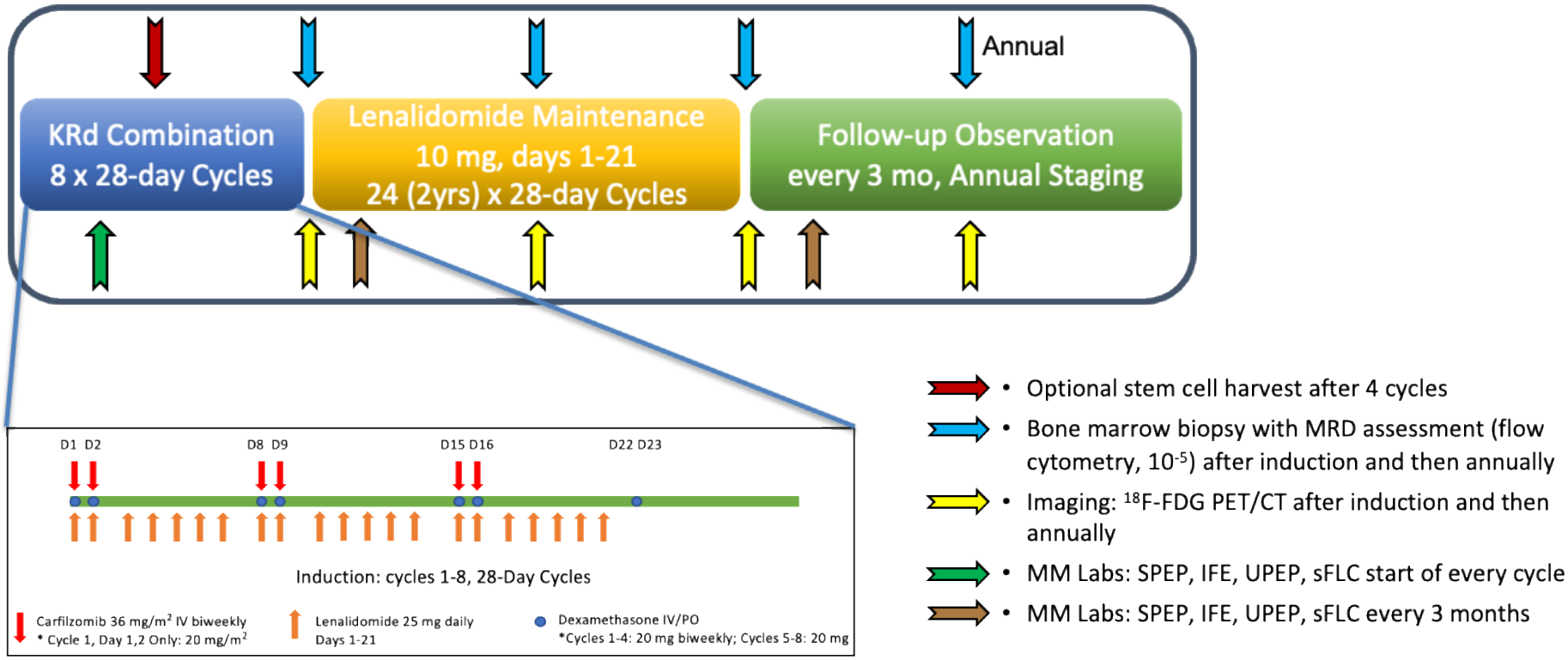
**eFigure.** Study Design, Drug Dosing, and Procedure Schedule for Carfilzomib, Lenalidomide, and Dexamethasone With Lenalidomide Maintenance in High-Risk Smoldering Myeloma

Abbreviations: $^{18}$F-FDG PET/CT, 18-fluorodeoxyglucose-positron emission tomography/computed tomography; IFE, immunofixation; KRd, carfilzomib, lenalidomide, and dexamethasone; MM, multiple myeloma; MRD, minimal residual disease; sFLC, serum free light chain; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis

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