Ld–continuous: Lenalidomide/Dexamethasone

Constituents of Regimen: lenalidomide, dexamethasone

Common Names or Abbreviations for Regimen: Ld-continuous; Rd-continuous

Other Names of Regimen Constituents:
- Lenalidomide: Revlimid®, CC-5013, CDC 501, IMID-1
- Dexamethasone: Decadron®, DM, DXM

Mechanism of Action:

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including multiple myeloma. Lenalidomide causes a delay in tumor growth in some in vivo nonclinical hematopoietic tumor models including multiple myeloma. Immunomodulatory properties of lenalidomide include activation of T cells and natural killer (NK) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (eg, TNF-α and IL-6) by monocytes. In multiple myeloma cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.[1]

U.S. FDA-Approved Indication(s):

Lenalidomide in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma. [Note: lenalidomide is also approved for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1 -risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities; for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.][1]

NCCN Recommended Indication, Category of Evidence and Preferred Regimen or Other[2]:

- Primary therapy for transplant candidate (category 1; preferred regimen)
- Primary therapy for non-transplant candidate (category 1; preferred regimen)
- Therapy for previously treated multiple myeloma (category 1; preferred regimen)

Dose Schedule[1]:
- Lenalidomide 25 mg PO once daily on Days 1-21 q28 days
- Dexamethasone 40 mg PO once daily on Days 1, 8, 15, and 22 q28 days
    - For patients >75 years old, administer 20 mg PO once daily on Days 1, 8, 15, and 22 q28 days

Primary and Secondary Efficacy Outcomes:

Randomized, Open-Label Clinical Trial in Patients with Newly Diagnosed Multiple Myeloma (FIRST Trial)[3]

- 1,623 patients were randomized to three different treatment arms:
  - Rd Continuous (n = 535): Rd was given continuously until progressive disease
  - Rd18 (n = 541): Rd was given for up to eighteen 28-day cycles
  - MPT (n = 547): melphalan, prednisone and thalidomide (MPT) was given for a maximum of twelve 42-day cycles
- The primary efficacy endpoint was progression-free survival (PFS) and secondary endpoints included overall survival (OS) and response rate:

	Rd Continuous (N = 535)	Rd18 (N = 541)	MPT (N = 547)
PFS — IRAC (months)[g]			
Number of PFS events	278 (52.0)	348 (64.3)	334 (61.1)
Mediana PFS time, months (95% CI)[b]	25.5 (20.7, 29.4)	20.7 (19.4, 22.0)	21.2 (19.3, 23.2)
HR [95% CI][c] ; p-value[d]			
Rd Continuous vs MPT	0.72 (0.61, 0.85); <0.0001		
Rd Continuous vs Rd18	0.70 (0.60, 0.82)		
Rd18 vs MPT	1.03 (0.89, 1.20)		
Overall Survival (months)[h]			
Number of Death events	208 (38.9)	228 (42.1)	261 (47.7)
Median[a] OS time, months (95% CI)[b]	58.9 (56.0, NE)[f]	56.7 (50.1, NE)	48.5 (44.2, 52.0)
HR [95% CI][c]			
Rd Continuous vs MPT	0.75 (0.62, 0.90)		
Rd Continuous vs Rd18	0.91 (0.75, 1.09)		
Rd18 vs MPT	0.83 (0.69, 0.99)		
Response Rate[e] – IRAC, n (%)[g]			
CR	81 (15.1)	77 (14.2)	51 (9.3)
VGPR	152 (28.4)	154 (28.5)	103 (18.8)
PR	169 (31.6)	166 (30.7)	187 (34.2)
Overall response: CR, VGPR, or PR	402 (75.1)	397 (73.4)	341 (62.3)

CR = complete response; d = low-dose dexamethasone; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; M = melphalan; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; R = lenalidomide; Rd Continuous = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤ 18 cycles; T = thalidomide; VGPR = very good partial response; vs = versus.

[a] The median is based on the Kaplan-Meier estimate.
[b] The 95% Confidence Interval (CI) about the median.
[c] Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.
[d] The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.
[e] Best assessment of response during the treatment phase of the study
[f] Including patients with no response assessment data or whose only assessment was "response not evaluable."
[g] Data cutoff date = 24 May 2013.
[h] Data cutoff date = 3 March 2014.

Safety:

Randomized, Open-Label Clinical Trial in Patients with Newly Diagnosed Multiple Myeloma (FIRST Trial)[3]

- Grade 3 or 4 adverse events (AEs) were somewhat less frequent with continuous lenalidomide-dexamethasone than with MPT (70% vs. 78%).
    - Thromboembolism: Ld = 8%; Ld18 = 6%; MPT = 5%
    - Cardiac events: Ld = 12%; Ld18 = 7%; MPT = 9%
    - Neuropathy: Ld = 1%; Ld18 = <1%; MPT = 9%
    - Rash: Ld = 6%; Ld18 = 5%; MPT = 5%
    - Secondary primary malignancies (SPM): Ld = 3% (n = 17); Ld18 = 6% (n = 30); MPT = 5% (n = 27) - hematological malignancies (MDS, leukemia) were more common in the MPT arm (12 cases).
- As compared with MPT, continuous lenalidomide-dexamethasone was associated with fewer hematologic and neurologic toxic events, a moderate increase in infections, and fewer second primary hematologic cancers.
- Patients experiencing 1 or more AEs: Ld = 85%; Ld18 = 80%; MPT = 89%
- Most common terminology criteria for adverse events (CTCAEs) grade ≥3 AEs included neutropenia and infections.
    - Grade ≥3 Neutropenia: Ld = 28%; Ld18 = 26%; MPT = 45%
        - Grade ≥3 Infection: Ld = 29%; Ld18 = 22%; MPT = 17% - 80% of the infections occurred in the absence of neutropenia; Ld was associated with a 5% increase in infections after the 72-week period; thought to be in part related to long-term use of glucocorticoids.
        - Pneumonia: Ld = 8%; Ld18 = 8%; MPT = 6%

Lenalidomide General Safety[1]:

Black Box Warnings

- Embryo-Fetal Toxicity: caused limb abnormalities in a developmental monkey study. In females of reproductive potential, obtain 2 negative pregnancy tests before starting lenalidomide .
- Hematologic Toxicity (Neutropenia and Thrombocytopenia): patients should have blood counts monitored and may require dose interruptions and/or reductions, in addition to blood product support and/or growth factors
- Venous and Arterial Thromboembolism: increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma. Thromboprophylaxis is recommended and the choice of regimen should be based on the patient's underlying risks.

- Second Primary Malignancies: patients with multiple myeloma who are treated with lenalidomide have an increased risk of developing acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS)
- Hepatotoxicity: hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. Preexisting viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors.
- Allergic Reactions: angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported.
- Tumor Lysis Syndrome: patients with higher tumor burden are at increased risk.
- 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 stem cell transplant candidates, referral to a transplant center should occur early in treatment to optimize the timing of the stem cell collection.

Tailoring of Regimen:

Lenalidomide[1]

- Thrombocytopenia: In patients who experience reduced platelet count, the following dose-modifications should be implemented:
    - Platelets <30,000 per mcL: interrupt lenalidomide, follow CBC weekly.
        - Platelets return to ≥30,000 per mcL: resume at next lower dose, but not <2.5 mg daily.
    - For each subsequent drop in platelets <30,000 per mcL: interrupt linalidomide.
        - Platelets return to ≥30,000 per mcL: resume at next lower dose, but not <2.5 mg daily.
- Neutropenia: In patients who experience reduced absolute neutrophil count (ANC), the following dose modifications should be implemented:
    - ANC <1,000 per mcL or febrile neutropenia: interrupt lenalidomide, follow CBC weekly.
        - ANC return to ≥1,000 per mcL: resume at 25 mg daily or initial starting dose.
        - ANC return to ≥1,000 per mcL + other toxicities: resume at next lower dose, but not <2.5 mg daily.
    - For each subsequent drop in ANC <1,000 per mcL: interrupt lenalidomide.
        - ANC returns ≥1,000 per mcL: resume at next lower dose, but not <2.5 mg daily.

- Renal Impairment: Dose-adjust lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of lenalidomide are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Use the following starting dose adjustments for patients with renal impairment:

Category	Renal Function (Cockcroft-Gault)	Dose in MM
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.

- Hepatic Impairment: Stop lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Recommended Supportive Care/Prophylaxis:

Patients on this regimen are at an increased risk for infection, venous or arterial thromboembolic events (VTEs) and embryo-fetal toxicity.[1]

- Embryo-fetal toxicity: **REVLIMID REMS®** program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.[1]
    - Females: Must obtain 2 negative pregnancy tests prior to initiating therapy, avoid pregnancy (abstinence or 2 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: 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.[4]

- 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.[5]
- General Supportive Care:
    - Bisphosphonates (zoledronic acid or pamidronate) are intended to decrease the risk of skeletal-related events and should be considered in all patients with multiple myeloma (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.[6]
- Drug-drug Interactions: Digoxin levels may be reduced. Concurrent administration with ESAs or estrogen compounds may increase the risk of thrombosis.[1]

Strategies to Reduce Treatment-Associated Side Effects:

- A CBC with differential should be obtained every 2 weeks during initial therapy (up to 12 weeks), and as clinically indicated for continued treatment to monitor for cytopenias and intervene with dose reduction, treatment interruption or discontinuation of the causative agent, transfusion (platelets) and/or growth factor support (neutropenia).[7]
- Thromboprophylaxis: Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.[5]
    - 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.[8]
    - 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.[9]

Monitoring Recommendations and Notes:

- Hematologic Toxicity: Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medication that may increase risk of bleeding.[1]
- Monitor patients for the development of second primary malignancies. Take into account both the potential benefit and the risk of second primary malignancies when considering treatment with lenalidomide.[1]
- Hepatotoxicity: Monitor liver enzymes periodically. Stop lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.[1]
- Hypo/hyperthyroidism: Cases of hypothyroidism and hyperthyroidism have also been reported. Optimal control of thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.[1]
- Objective monitoring of responses to the regimen should be performed on a monthly basis (by IMWG Uniform Response Criteria) and recorded.[2]

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