Regimen Protocols

ELO-LD: Elotuzumab/lenalidomide/dexamethasone

Constituents of Regimen: elotuzumab (ELO), lenalidomide (L) and dexamethasone (D)

Common Names or Abbreviations for Regimen: ELO-LD; ELO, len, dex

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

- Elotuzumab: BMS-901608, ELO, HuLuc, UNII: 1351PE5UGS
- Lenalidomide: CC-5013, CC5013, CDC 501, IMID-1, Revlimid®, UNII: F0P408N6V4
- Dexamethasone: Decadron®, Dex, UNII: 7S5I7G3JQL

Mechanism(s) of Action:

- **Elotuzumab:** ELO is a humanized, IgG1 monoclonal antibody that targets signaling lymphocyte activation molecule family member 7 (SLAMF7) also known as CS1, CD319, or CRACC to activate natural killer (NK) cells, enabling selective killing of myeloma cells with minimal effects on normal tissue.[1] Preclinical models show elotuzumab exerts its anti-multiple myeloma (MM) efficacy via the enhancement of NK-cell-mediated antibody-dependent cellular cytotoxicity (ADCC) of SLAMF7-expressing myeloma cells.[2] ELO has been shown to activate NK cells and promote myeloma cell death in peripheral blood lymphocyte (PBL)/myeloma cell co-cultures. The combination of ELO plus lenalidomide demonstrated superior anti-myeloma activity on established MM xenografts in vivo and in PBL/myeloma cell co-cultures in vitro than either agent alone.[2] It has been recently reported that lenalidomide augments nanoscale rearrangements in cortical actin at the human natural killer cell immune synapse and lowers the threshold for NK cell activation; allowing activation by low levels of ligands on tumor cells.[3] Consequently, synergy may occur between ELO activation of SLAMF7 on NK cells and the lenalidomide mediated reduction of the threshold of activation of NK cells. Taken together, the combination of elotuzumab and lenalidomide may enhance NK cell function directly and confer anti-MM efficacy by means beyond ADCC alone.

NCCN Recommended Indication: N/A. No current indication exists. Elotuzumab is not currently approved by the FDA for use in MM outside of clinical trial [August 2015]. The studies cited included patients with relapsed/refractory multiple myeloma (RRMM); most notable is the data from the pivotal phase III ELOQUENT-2 trial.[4,5] A randomized, open-label, phase III trial (ELOQUENT-1; CA204-006) will determine if the addition of ELO to Len/Dex improves progression-free survival (PFS) in patients with newly diagnosed, untreated MM; this study is currently on going and results will be reported here once they become available [NCT01335399].

NCCN Preferred Regimen or Other: N/A. ELO-LD is not currently a preferred regimen.

NCCN Category of Evidence: N/A. There is no current category of evidence for ELO-LD as elotuzumab is not currently approved by the FDA for use in MM outside of a clinical trial [August 2015]. The pivotal phase III ELOQUENT-2 trial data will be part of a new drug application (NDA) submission to the FDA. In May 2014, the FDA granted elotuzumab *Breakthrough Therapy Designation* for use in combination with lenalidomide and dexamethasone in patients who have received one or more prior treatments.

Dose Schedule: For the phase III, open label, multicenter, active comparator controlled ELOQUENT-2 trial: Intravenous (IV) ELO 10 mg/kg was given on days 1, 8, 15, and 22 during the first two (2) cycles, and then on days 1 and 15 starting with the third cycle. Patients also received lenalidomide 25 mg/d on days 1 through 21 of each cycle. Dexamethasone was administered orally at a dose of 40 mg during the week without elotuzumab and by IV at a dose of 8 mg plus 28 mg orally on the days of elotuzumab administration.[4]

For Phase II Portion of the Trial: IV ELO 10 mg/kg or 20 mg/kg was given on days 1, 8, 15, and 22 for cycles 1–2 and on Days 1 and 15 for subsequent cycles; oral lenalidomide (25 mg; Days 1–21) and oral dexamethasone (28 mg plus 8 mg IV on ELO dosing days, or 40 mg once weekly). ELO was infused at up to 2 mL/min for cycles 1–4 and in the trial, could be escalated up to 5 mL/min for subsequent cycles. **Note: The dose 10 mg/kg was chosen for subsequent phase III trials.**[5]

Safety: There are no black box warnings for elotuzumab as the drug is not yet FDA approved. Black box warnings for lenalidomide and dexamethasone exist however. Common side effects and warnings include:

Black box warnings for lenalidomide include embryo-fetal toxicity, hematologic toxicity, and venous and arterial thromboembolism.

The most common side effects of lenalidomide in multiple myeloma (≥20%, per Celgene package insert, Revlimid® 2015)[6] include fatigue, neutropenia, constipation, diarrhea, muscle cramps, anemia, pyrexia, peripheral edema, nausea, back pain, upper respiratory tract infection, cough, dyspnea, dizziness, thrombocytopenia, tremor, insomnia, decreased appetite and rash.

Additional warnings and precautions for lenalidomide in MM are rare, but should be considered, and include:

- Allergic reactions: Hypersensitivity, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis. If these occur, lenalidomide should be discontinued.
- Tumor lysis syndrome (TLS): Cases of TLS have been reported. Monitor for if disease burden high.
- Hepatotoxicity: Hepatic failure (including fatalities) has occurred. Liver function should be monitored. If 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.
- Patients should not become pregnant when taking lenalidomide. Two reliable methods of contraception should be used while on therapy.

A total of 635 patients were treated in the phase III ELOQUENT-2 trial.[4] The median duration of treatment was 17 months in the ELO-LD group and 12 months in the LD control group; 65% and 79% of patients, respectively, discontinued treatment, most frequently due to disease progression. Adverse events that were reported in 25% or more of patients in either study group are shown here. Serious adverse events were reported in 65% and 57% of patients in the ELO-LD group and LD control group respectively. In the ELO-LD group, 34% of patients had grade 3 or 4 neutropenia as compared with 44% in the LD control group grade 3 or 4 lymphocytopenia was reported in 77% and 49% of patients, respectively.

Adverse Events*				
Event	**Elotuzumab + Lenalidomide + Dexamethasone Group (N=318)**		**Lenalidomide + Dexamethasone Group (N=317)**	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Common hematologic toxic effect† [% (No.)]				
Lymphocytopenia	99% (316)	77% (244)	98% (311)	49% (154)
Anemia	96% (306)	19% (60)	95% (301)	21% (67)
Thrombocytopenia	84% (266)	19% (61)	78% (246)	20% (64)
Neutropenia	82% (260)	34% (107)	89% (281)	44% (138)
Common nonhematologic adverse events [% (No.)]				
General disorder				
Fatigue	47% (149)	8% (27)	39% (123)	8% (26)
Pyrexia	37% (119)	3% (8)	25% (78)	3% (9)
Peripheral edema	26% (82)	1% (4)	22% (70)	<1% (1)
Nasopharyngitis	25% (78)	0	19% (61)	0
Gastrointestinal disorder				
Diarrhea	47% (149)	5% (16)	36% (144)	4% (13)
Constipation	36% (113)	1% (4)	27% (86)	<1% (1)
Musculoskeletal or connective tissue disorder				
Muscle spasms	30% (95)	<1% (1)	26% (84)	1% (3)
Back pain	28% (90)	5% (16)	28% (89)	4% (14)
Other disorder				
Cough	31% (100)	<1% (1)	18% (57)	0
Insomnia	23% (73)	2% (6)	26% (82)	3% (8)

* Listed are adverse events that were reported in at least 25% of patients in either study group on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. In addition to the listed events, 35 of 635 patients (6%) had a second primary cancer: 22 (7%) in the elotuzumab group and 13 (4%) in the control group. The incidence rates of second hematologic cancers were identical in the elotuzumab and control groups (2% in each group); rates of second solid tumors were 3% and 2%, rates of nonmelanoma skin cancers were 3.1% and 1.5%, and rates of the myelodysplastic syndrome were 0.9% and 1.6%, respectively. After adjustment for exposure to study therapy, the incidence rates of second primary cancers per 100 patient-years were similar at 3.5 and 2.8, respectively. Four patients (3 in the elotuzumab group and 1 in the control group) had tumors that were diagnosed at screening or during the first cycle of therapy.

† Data are based on abnormalities in results on laboratory testing.

28 patients were enrolled in a phase I portion of the study, and 73 patients were enrolled in phase II[5]

- In the study, the most common treatment-emergent adverse events (AEs) in the elotuzumab + lenalidomide + dexamethasone trial were diarrhea (66%), muscle spasms (62%), fatigue (56%), constipation (51%), nausea (48%), and upper respiratory tract infection (47%). Serious AEs were seen in 58% of patients.
- The most common serious AEs included pneumonia (12%) and infusion reactions (10%) at a flow rate ≤2 mL/min. Most patients who were able to have their flow rate increased to >2 mL/min, and no new AEs were seen in this group.

Required Supportive Care/Prophylaxis:

- All patients in phase II portion of the study received a premedication regimen consisting of a corticosteroid and an antihistamine before ELO dosing to mitigate infusion reactions (IRs). To minimize the risk of hypersensitivity reactions, premedications such as diphenhydramine and hydrocortisone should be administered prior to ELO infusion and remain readily available at the bedside if treatment emergent IRs occur.
- Premedication of ELO with a 5HT3 (serotonin) antagonist (such as granisetron or ondansetron) with or without corticosteroids (dexamethasone) should be considered for antiemetic prophylaxis.
- MM is an inherently hypercoagulable disease. Patients who receive immunomodulatory containing regimens are at an increased risk for venous thromboembolic events. Thus, thromboprophylaxis with aspirin or low molecular weight heparin is advised in patients receiving immunomodulatory drug regimens, due to the high incidence of venous thrombosis observed.
- 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*)
- 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.

Tailoring of Regimen: No specific data on the use of elotuzumab in the elderly or special populations has been reported. Lenalidomide should be dose reduced in patients with renal impairment. Steroids such as dexamethasone should be administered in lower doses in the elderly to **prevent steroid-associated psychosis**.

Primary and Secondary Efficacy Outcomes:

Phase III ELOQUENT-2 TRIAL[4]

- With N=321 patients in the elotuzumab plus lenalidomide plus dexamethasone group (ELO-LD) and N=325 in the lenalidomide plus dexamethasone (LD) control group, this study met its coprimary end points of PFS and the overall response rate.
- The one (1) year PFS rate for elotuzumab plus lenalidomide plus dexamethasone [ELO-LD] was 68% (95% confidence interval [CI], 63 to 73) vs 57% (95% CI, 51 to 62) for LD.
- The 2-year PFS rate for ELO-LD was 41% (95% CI, 35 to 47) vs 27% (95% CI, 22 to 33) for LD.
- The median PFS was 19.4 months (95% CI, 16.6 to 22.2) vs. 14.9 months (95% CI, 12.1 to 17.2) for ELO-LD and LD, respectively with a hazard ratio of 0.70 (95% CI: 0.57 to 0.85; *P*<.001), or a relative reduction of 30% in the risk of disease progression with ELO-LD compared to LD.
- The overall response rate (ORR) was 79% (95% CI 74-83) for ELO-LD vs 66% (95% CI 60-71) for LD.
- The best ORRs reported were as follows:

Response	**ELO-LD (N=321) %, (No.)**	**LD [control group] (N=325) %, (No.)**
ORR	79% (252)	66% (213)
95% CI -----%	74-83	60-71
Best ORR		
sCR + CR	4% (14)	7% (24)
VGPR	28% (91)	21% (67)
Combined response (sCR + CR + VGPR)	33% (105)	28% (91)
PR	46% (147)	38% (122)
MR	7% (22)	10% (33)
SD	9% (30)	17% (54)
PD	2% (8)	2% (8)
NE	3% (9)	5% (17)
ORR=overall response rate; sCR=stringent complete response rate; CR=complete response rate; VGPR=very good partial response; PR=partial response; MR=minimum response; SD=stable disease; PD=progressive disease; NE=not evaluable.		

Phase Ib/II 1703 Study[5]

- In the study, a stringent complete response/complete response (sCR/CR) was seen in 14% of patients.
- 43% had a very good partial response (VGPR), and 27% had a partial response (PR). Median time to objective response was 1 month (range 0.7–19).
- Median PFS was 29 months (10 mg/kg, 32 months; 20 mg/kg, 25 months).
- An 82% objective response rate was observed.

Strategies to Reduce Treatment-Associated Side Effects:

- Patients should be premedicated with corticosteroids, antiemetics and dexamethasone prior to each dose of ELO to prevent IRs and nausea/vomiting (see under "Required Supportive Care" as above).
- 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. Periodic monitoring of blood glucose levels, mood disturbance, and sleep patterns is recommended for all patients receiving corticosteroids.

Monitoring Recommendations and Notes: Adverse events (as listed above under *"Safety"*) should be monitored for and addressed at each visit.

- Nurses who infuse elotuzumab should monitor vital signs and assess for signs of hypersensitivity or infusion reactions before, during and after elotuzumab administration.
- Regular complete blood count with differential (CBC/diff) and chemistry monitoring to assess for myelosuppression and hepato/renal abnormalities is recommended.
- Patients should be educated regarding the side effects of medications as listed above (primarily peripheral neuropathy (PN), gastrointestinal, insomnia, mood swings, signs/symptoms of venous thromboembolism [VTE]) and urged to report side effects to the treatment team. Adherence to therapy can be improved by intervening side effects in a timely manner.
- Objective monitoring of responses to the regimen should be performed on a monthly basis (by International Myeloma Working Group (IMWG) Uniform Response Criteria) and recorded.

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5. Richardson PG, Jagannath S, Moreau P, et al. Final Results for the 1703 Phase 1b/2 Study of Elotuzumab in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma. *Blood* [*ASH Annual Meeting Abstracts*]. 2014:124(21):Abstract 302.
6. Celgene Corporation. Lenalidomide (Revlimid) package insert. Summit, NJ: 2015.

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