Continuous Lenalidomide (LEN) Therapy vs. Observation Following Non-Immunomodulatory Compound Based Induction Therapy in Newly Diagnosed Multiple Myeloma (NDMM): MM-027 Trial

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BACKGROUND
• Non-immunomodulatory induction therapy (Tx) is associated with high response rates and is recommended by the current NCCN guidelines for MM frontline Tx.
• Continuous LEN Tx is associated with improved outcomes in phase (Ph) 3 trials of NDMM.6
  – Progression-free survival (PFS) consistently improved by 45–59% using LEN maintenance Tx vs. other Tx or placebo.
  – Overall survival (OS) improved 18–20%.4,7
• Hence, continuous Tx can substantially affect clinical outcomes, and further studies in this setting are essential.12–6

STUDY DESIGN
• The MM-027 trial is a Ph 3b, multicenter, randomized, open-label study (Figure).
• The study is being conducted in the USA.
• Patients (pts) will be stratified according to International Staging System (ISS), prognostic factors at diagnosis, and response to non-immunomodulatory compound based induction Tx.
• A summary of the inclusion and exclusion criteria is presented in Table 1.
• Primary study objective:
  – Examine PFS with LEN maintenance Tx vs. observation after non-immunomodulatory compound based induction Tx in NDMM pts who are either ≥ 65 years (yrs), or < 65 yrs and ineligible or decline stem cell transplantation (SCT).

Figure. Trial in Progress: Study Design MM-027

Primary endpoint: PFS
Secondary endpoints: ORR (CR, VGPR, and PR), TTP, OS, Safety
Exploratory endpoints: MRD, biomarkers, Moa LEN

Table 1. Study Criteria
<table>
<thead>
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<th>Inclusion</th>
<th>Exclusion</th>
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<tr>
<td>Previously untreated MM</td>
<td>Previous antymeloma treatment Tx other than the required 6–12 cycles induction therapy without LEN, POM, or THAL.</td>
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| Symptomatic disease: | Laboratory abnormalities:
  – Monoclonal plasma cells in bone marrow > 10% and/or presence of a biopsy-proven plasmacytoma
  – Monoclonal protein in serum and/or urine
  – At least 1 myeloma-related organ dysfunction (CRAB criteria) |
  – ANC < 1,000/μL
  – Platelet count < 50,000/μL
  – Serum SGOT/AST or SGPT/ALT > 3.0 x ULN
  – Serum bilirubin levels > 1.5 x ULN |
| Pts must be treated with ≥ 6 cycles ≤ 12 cycles of induction TX without LEN, POM, or THAL and must have achieved ≥ SD |
| Pts ≥ 65 yrs, or < 65 yrs and ineligible or decline SCT |
| Pts must have cytogenetic assessment and ISS stage from initial diagnosis |

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CRAB, calcium, renal failure, anemia, bone lesions; DVT, deep-vein thrombosis; ESR, grade; ISS, International Staging System; LEN, lenalidomide; MM, multiple myeloma; PE, pulmonary embolism; POM, pomalidomide; pts, patients; SCT, stem cell transplantation; SD, stable disease; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; THAL, thalidomide; Tx, treatment; ULN, upper limit of normal; yrs, years.

TREATMENT
• Arm A will be given in 4-week cycles until documented progressive disease and will be reviewed by an independent physician (Table 2).
  – According to the worst grade of toxicity, dose adjustments will be made (Table 2).
• There will be no dose re-escalation permitted in the study.
• Renal function will warrant dose adjustments as shown in Table 2.
• The use of hematopoietic growth factors is encouraged if absolute neutrophil count is ≤ 1,000/μL, but the use remains at the discretion of the treating physician.
• Antithrombotic Tx is mandatory for Arm A pts, but remains at the discretion of the treating physician.

Table 2: Dose Reduction
<table>
<thead>
<tr>
<th>Dose level</th>
<th>LEN</th>
<th>Observation</th>
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<tr>
<td>Starting dose1</td>
<td>10 mg/day (D1–21/28)</td>
<td>(D1–21/28)</td>
</tr>
<tr>
<td>Dose level -11</td>
<td>5 mg/day (D1–21/28)</td>
<td>(D1–21/28)</td>
</tr>
<tr>
<td>Dose level -22</td>
<td>5 mg each other day (D1–21/28)</td>
<td>(D1–21/28)</td>
</tr>
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</table>

10CD ≥ 30 mL/m2; 2≥ 30 mL/m2; – Toxicity adjustment
1D, day; LEN, lenalidomide

SAMPLE SIZE AND POWER CONSIDERATIONS
• Targeted accrual will be a total of 172 pts (86 per arm).
• Group size calculation based on:
  – Assumption of median PFS of 20 months (mos) in the LEN arm and 10 mos in the observation arm.
  – 90% power and a 2-sided 0.05 level test.
  – Accounting for a non-evaluable rate of 15%.

TRIAL STATUS
• Status: active (enrollment).
• No interim analysis planned for PFS.
• The end of study is defined as the occurrence of 103 events or 1 yr follow-up on each pt from randomization for minimal residual disease (MRD) purposes, whichever occurs later.
• Updates on OS and second primary malignancy will be conducted 4 times per year after PFS analysis for at least a period of 5 yrs after the end of randomization or until all subjects have died.

SUMMARY
• The trial will add further evidence for the role of single-agent LEN maintenance following non-immunomodulatory compound based induction in NDMM.
• Clinically relevant information will be provided on the impact of comorbidities on outcomes in all pts.
• Will gather insight on the occurrence of toxicity during continuous Tx.
• Molecular analysis will yield valuable insights in tumor biology and depth of response and how MRD measurements correlate with outcome.
• Will evaluate the potential correlation of cereblon level to clinical outcomes.
• Planned myeloid cell morphology analysis may also help unravel the biology of second primary malignancy.

REFERENCES

ACKNOWLEDGMENTS
The authors acknowledge financial support for this study from Celgene Corporation. The authors received medical writing assistance from Ecuador Medical Solutions under contract with PRG and printing support from MedTech Media sponsored by Celgene Corporation.

DISCLOSURES
S.J.U. Celgene Corporation, Drugs, Millennium – consultant/advisor; Celgene, Drugs, Amylin/PharmaCaelus, Janssen – research funding; V.H., C.B., A.T., S.S. Celgene Corporation – employment and equity ownership; N.S.R.- A: Angen – consultant/advisor

Presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO); Chicago, IL, USA; May 30 – June 3, 2014.