Evidence-Based Series 6-5 Version 2

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Lenalidomide in Multiple Myeloma

Members of the Hematology Disease Site Group

Report Date: May 30, 2012

An assessment conducted in November 2016 deferred the review of Evidence-based Series (EBS) 6-5 Version 2, which means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Document Summary and Review Tool

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822  Fax: 905 526-6775  E-mail: ccopgi@mcmaster.ca


Guideline Report History

<table>
<thead>
<tr>
<th>GUIDELINE VERSION</th>
<th>SYSTEMATIC REVIEW</th>
<th>PUBLICATIONS</th>
<th>NOTES AND KEY CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original version</td>
<td>2000-2012</td>
<td>Full Report</td>
<td>Web publication</td>
</tr>
<tr>
<td>May 2012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Version 2</td>
<td>2012-2015</td>
<td>New data found in Section 4: Document Summary and Review Tool</td>
<td>Updated Web publication</td>
</tr>
<tr>
<td>September 2015</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table of Contents

Section 1: Guideline Recommendations 1
Section 2: Evidentiary Base 15
Section 3: EBS Development Methods and External Review Process 114
Section 4: Document Summary and Review Tool 128
Lenalidomide in Multiple Myeloma:
Guideline Recommendations

C. Chen, F. Baldassarre, S. Kanjeekal, J. Herst, L. Hicks, M. Cheung,
and the Hematology Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: May 30, 2012

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2012 and 2015, and for details on how this Clinical Practice Guideline was ENDORSED.

PURPOSE
The purpose of this guideline is to provide recommendations for the use of lenalidomide alone or in combination with other agents in patients with previously untreated or relapsed/refractory multiple myeloma.

QUESTIONS
1. Does lenalidomide (alone or in combination with other therapies) improve outcomes in patients with previously untreated multiple myeloma (including smoldering and symptomatic patients, and transplant and non-transplant candidates) compared with non-lenalidomide-containing treatments?
2. Does lenalidomide (alone or in combination with other therapies) improve outcomes in patients with relapsed or refractory (relapsed/refractory) multiple myeloma compared with non-lenalidomide-containing treatments?
3. Which multiple myeloma patients, both in the previously untreated and relapsed or refractory groups, are more or less likely to benefit from treatment with lenalidomide?
4. Does lenalidomide, used as a maintenance or consolidation treatment (following transplant and non-transplant treatments) improve outcomes in myeloma patients compared with either non-lenalidomide-containing or no maintenance or consolidation treatments?
5. What are the best strategies for managing lenalidomide-induced toxicity?
TARGET POPULATION
Adult patients with previously untreated, relapsed, or refractory multiple myeloma.

INTENDED USERS
- Healthcare practitioners treating patients with multiple myeloma.
- Policy makers involved in the planning of treatment and the financing of drugs for multiple myeloma.

RECOMMENDATIONS AND KEY EVIDENCE
Question 1. Previously untreated multiple myeloma.
01. Previously untreated smoldering multiple myeloma
In asymptomatic patients with no evidence of myeloma-related hypercalcemia, renal dysfunction, anemia, or bone disease (smoldering multiple myeloma), the routine use of lenalidomide alone or in combination cannot be recommended.

02. Previously untreated symptomatic multiple myeloma

b. Lenalidomide and dexamethasone: the combination of lenalidomide and dexamethasone is an acceptable first-line treatment option in patients of any age. The recommended dose of lenalidomide is 25 mg/day on days 1-28 every 35-day cycle for the first three cycles, followed by 25 mg/day on days 1-21 every 28-day cycle thereafter. A reasonable alternative is to proceed directly to the 28-day cycle dosing from the start if preferred. The use of low-dose dexamethasone, 40 mg/day on days 1, 8, 15 and 22 of a 28-day cycle, is preferred for safety; however, some patients with acute myeloma complications such as acute renal dysfunction, hypercalcemia, or hyperviscosity syndrome may benefit from high-dose dexamethasone (i.e., 40 mg/day on days 1-4, 9-12, and 17-20 of a 28-day cycle).

c. Other lenalidomide combinations: The combination of lenalidomide with other drugs is not recommended in this setting.

Key Evidence
01. Previously untreated smoldering multiple myeloma
a. During the document assessment and review process, final analysis of the QUIREDEX trial comparing lenalidomide in combination with dexamethasone to the conventional “watch-and-wait” approach until symptomatic disease progression showed a significant survival benefit for the use of early lenalidomide (33). While the Hematology DSG acknowledges the new evidence, at this time, a recommendation cannot be made in this population prior to review of the trial and assessment of its quality by the DSG membership.

02. Previously untreated symptomatic multiple myeloma
a. No randomized controlled trials (RCTs) that compared lenalidomide as a single agent to a non-lenalidomide regimen for first-line therapy both in transplant and non-transplant candidates were located.
b. The study by Zonder et al (2) showed an improved, median one-year, progression-free survival (PFS) (78% versus [vs.] 52%; p=0.002), and improved overall response (OR) (77% vs. 48%; p<0.0001) in patients treated with lenalidomide plus dexamethasone versus patients treated with placebo and dexamethasone. Rajkumar et al (3) demonstrated a longer median PFS for lenalidomide in combination with low-dose dexamethasone versus lenalidomide plus high-dose dexamethasone (25.3 vs. 19.1 months; p=0.026), with an improved safety profile (grade ≥3 adverse events: p=0.02 for neutropenia, p=0.0003 for deep-vein thrombosis [DVT], and p=0.04 for infections) in favour of the low-dose dexamethasone arm.

c. No fully published RCTs of lenalidomide in combination with other drugs in transplant and non-transplant patients with previously untreated multiple myeloma were identified.

Qualifying Statements

The Zonder and Rajkumar studies (2,3) supporting Recommendation 2.b have limitations: both studies were stopped early due to benefit, and the Rajkumar et al study used the OR rate as the primary outcome. The Zonder et al study (2) was sponsored by the pharmaceutical company producing the drug, and the Rajkumar et al study (3) was sponsored by a government body. In the Rajkumar study, the improved safety profile and lower rate of early deaths associated with low-dose dexamethasone has led to widespread adoption of this approach, and from a safety perspective, the Hematology Disease Site Group (DSG) endorses this low-dose dexamethasone approach. It should be noted, however, that high-dose dexamethasone, though more toxic, was associated with higher response rates than was low-dose dexamethasone. Therefore, select patient populations such as those with acute renal dysfunction, hypercalcemia, or hyperviscosity syndrome may still benefit from the robust efficacy of high-dose dexamethasone.

Question 2. Relapsed or refractory multiple myeloma.

a. Single-agent lenalidomide: Lenalidomide alone for first-line therapy in myeloma cannot be recommended for standard use for patients with relapsed/refractory multiple myeloma

b. Lenalidomide and dexamethasone: Lenalidomide plus dexamethasone is recommended for myeloma patients who have received at least one prior line of therapy. The recommended dose is lenalidomide 25 mg/day on days 1-21 plus dexamethasone, either low-dose 40 mg/day on days 1,8,15, and 22 or high-dose at 40 mg/day on days 1-4, 9-12, and 17-20, with either being given on a 28-day cycle.

c. Other lenalidomide combinations: The combination of lenalidomide with other drugs is not recommended in this setting.

Key Evidence

a. No randomized trials that compared lenalidomide as a single agent to a non-lenalidomide regimen in previously treated patients were located.

b. Two seminal studies (4,5) showed an improved time to progression (TTP) with lenalidomide plus dexamethasone as compared with dexamethasone plus placebo.
Our meta-analysis of these two studies showed that lenalidomide improved TTP (hazard ratio [HR], 0.35; 95% CI, 0.29 to 0.42; p<0.0001), overall survival (OS) (HR, 0.54; 95% CI, 0.36 to 0.80; p<0.002) and ORs (HR, 0.50; 95% CI, 0.44 to 0.58; p<0.0001) as compared to a non-lenalidomide regimen.

i. Although high-dose dexamethasone dosing with lenalidomide was used in the two pivotal RCTs of relapsed/refractory myeloma, low-dose weekly dexamethasone with lenalidomide appears less toxic when used in the first-line setting (3). From a safety perspective, the Hematology DSG considers low-dose dexamethasone a reasonable option for use in the relapsed/refractory setting. Once again, select subgroups with acute myeloma complications may still benefit from the greater response rates achievable with high-dose dexamethasone.

c. No RCTs of lenalidomide in combination with other drugs in patients with previously treated multiple myeloma were identified.

Qualifying Statements

Both the above-mentioned studies (4,5) were stopped at the first pre-planned interim analysis for benefit and were funded by the drug's manufacturer. However, the studies enrolled more than 300 patients before stopping and had a large number of events.

The recommendation to use low-dose dexamethasone with lenalidomide in the relapsed/refractory setting is generalized from the Rajkumar study (3) in newly diagnosed disease and is based primarily on improved safety. There are no comparative studies directly evaluating low-dose dexamethasone dosing in the relapsed/refractory setting.

Question 3. Subgroups of patients most likely to benefit from treatment with lenalidomide.

a. For patients with newly diagnosed multiple myeloma, there is insufficient evidence to recommend lenalidomide in specific subgroups of patients. When lenalidomide is combined with dexamethasone, the use of low-dose versus high-dose dexamethasone may be preferable from a safety perspective, regardless of age.

b. For patients with relapsed/refractory multiple myeloma, lenalidomide plus dexamethasone is a reasonable treatment option for the following patient subgroups:
   i. Patients with at least one prior line of therapy: those patients who are less heavily treated (only one prior line of therapy vs. two or more) appear to benefit the most.
   ii. Patients who have received prior thalidomide or autologous stem cell transplantation (ASCT).
   iii. Younger or older patients: Advanced age should not be an absolute contraindication for the use of lenalidomide, as long as any adverse events are carefully monitored.
   iv. Patients with mild-to-moderate renal failure (creatinine clearance ≥30 mL/min and ≤60 mL/min): For patients with severe renal failure (creatinine clearance <30 mL/min), the Hematology DSG cautions against the use of lenalidomide until additional evidence for its use in this subgroup becomes available.
   v. Patients with IgA subtype, pre-existing peripheral neuropathy, and different levels of Eastern Cooperative Oncology Group (ECOG) performance status.
c. For patients with relapsed/refractory multiple myeloma, the following treatment guidelines for lenalidomide and dexamethasone may be considered:
   i. Full-dose lenalidomide may be initiated (25 mg/day dose), but it is reasonable to consider dose reductions for use beyond 12 months.
   ii. A longer period of lenalidomide use, if possible until progression, is a reasonable target.
   iii. Dexamethasone dose reductions may be used as needed for improved tolerability.

Key Evidence
The subgroup analyses of data are derived primarily from the Rajkumar study (3) in the first-line setting and from pooled data from the Weber and Dimopoulos randomized studies (3-9) in the relapsed/refractory setting. These data have been integrated with the clinical expertise of the Hematology DSG to provide support for these recommendations:

a. There is limited evidence available at this time to recommend lenalidomide in specific subgroups of previously untreated patients. When lenalidomide is combined with dexamethasone, the use of low-dose dexamethasone may be preferable in both older and younger patients. Two subgroup analyses evaluating age of patients participating in the Rajkumar study (3) reported improved overall survival in all age groups when treated with low-dose versus high-dose dexamethasone (10,11).

b. i. This recommendation derives from study stratification results and a pooled subgroup analysis done by Stadtmauer et al (6) from the Weber and Dimopoulos studies (4,5).

ii. The subgroup analysis by Wang et al (12) showed that partial cross-resistance between thalidomide and lenalidomide may exist, but prior thalidomide exposure should not absolutely contraindicate the use of lenalidomide in the relapsed/refractory setting. The recommendation for patients who have had a prior ASCT is based on study stratification results and a pooled subgroup analysis by Dimopoulos et al (13).

iii. The recommendation for the use of lenalidomide in older as well as younger patients is based on a subgroup analysis of the Weber and Dimopoulos studies (4,5) reported by Chanan-Khan et al (7).

iv. Lenalidomide is known to be primarily excreted by the kidneys, which poses a risk for cumulative drug-related toxicity. The recommendation for careful use in mild-to-moderate renal dysfunction (creatinine clearance ≥30 mL/min and ≤60 mL/min) is based on a subgroup analysis of pooled data from the Weber and Dimopoulos studies (4,5) reported by Dimopoulos et al (9). Given the small sample of patients with severe renal failure (creatinine clearance <30 mL/min) enrolled in these studies, the Hematology DSG cannot make recommendations for or against use in this population.

v. Lenalidomide and dexamethasone were found to be consistently superior to dexamethasone alone in subgroup analyses by several authors (14-16), and this recommendation is supported by the clinical expertise of the Hematology DSG.
c. i. This guideline is supported by the Dimopoulos et al subgroup analysis of patients remaining on lenalidomide beyond 12 months (17). They report that those requiring dose reductions were able to stay on the study longer, tolerated therapy as well as those not requiring dose reductions, and achieved longer PFS.

ii. This guideline is based on two subgroup analyses by San Miguel et al (18) and Harousseau et al (19) suggesting that continued therapy after achieving a partial remission (PR) was beneficial, possibly by leading to higher quality of response that in turn prolongs survival.

iii. This guideline is based on a subgroup analysis by San Miguel et al (20) identifying that dose reductions of dexamethasone were associated with improved survival outcomes.

**Qualifying Statements**

All the subgroup analyses upon which these recommendations or guidelines are based are retrospective, post hoc analyses. In isolation, they represent a weak evidence base and, therefore, have been integrated with the expert opinion and clinical experience of the Hematology DSG. The validation of these recommendations through further clinical investigation is required.

**Question 4: Lenalidomide maintenance or consolidation.**

a. Non-transplant patients: In non-transplant patients with multiple myeloma, there is insufficient evidence to support the use of lenalidomide maintenance or consolidation treatment following initial therapy.

b. Transplant patients: In the absence of a final full publication of supporting trials in the post-transplant setting (currently in the form of conference abstracts (21-24)), the Hematology DSG suggests that lenalidomide maintenance at 10-15 mg/day continuously until progression is a reasonable option. Upon publication of the final analyses of supporting studies, providing the strength and direction of results remain unchanged from currently available abstract publications, lenalidomide maintenance at 10-15 mg/day continuously until progression is recommended.

**Key Evidence**

a. In non-transplant patients, an ongoing randomized trial evaluating lenalidomide as maintenance following melphalan, prednisone, and lenalidomide (MPR) therapy (25) shows preliminary results but does not provide adequate mature evidence to support a recommendation for use.

b. The search identified three companion abstract publications relevant to this question of maintenance after transplant (21-23) that reported a significant improvement in complete response (p<0.01) and PFS (p<0.0001) with maintenance versus no maintenance. In addition, an ongoing randomized study presented in preliminary form strongly supports the benefit of post-transplant maintenance with an OS advantage over no maintenance. The median TTP was 43.6 versus 21.5 months; PFS was also favourable for the lenalidomide group (HR, 0.43; one-sided unadjusted p<0.0001) (24). These combined data provide emerging support for the use of
lenalidomide maintenance post-transplant, which the Hematology DSG, therefore, considers a reasonable post-transplant option.

Qualifying Statements
The study by Palumbo et al (25) has recently been published in full (26), though only preliminary abstract data were captured in this review. The study by Attal et al (21-23) was published only in abstract form at the time of our literature search, though it was a final analysis of a completed trial. It has since been published in full (27), but the complete publication was not analyzed for this review. This study was stopped early for benefit and was sponsored by the manufacturer of lenalidomide (see clinical trials.gov http://clinicaltrials.gov/ct2/show/NCT00430365?term=NCT00430365&rank=1). The study by McCarthy et al (24) was also captured in our search as an interim analysis, but has since undergone full publication (28). Even in interim analysis, an OS benefit favoring the lenalidomide maintenance arm was demonstrated. The Hematology DSG cautions that, although these data are compelling, further maturation of data is required before full recommendations for maintenance in post-transplant patients can be made.

Question 5: Management of toxicity.

a. Venous thromboembolism (VTE)
For newly diagnosed patients, and for relapsed and refractory patients who are not at high risk for bleeding or VTE, either low-dose aspirin (ASA) given orally at 100 mg/day or enoxaparin (low molecular weight heparin or LMWH) at 40 mg/day given subcutaneously can be used in patients treated with lenalidomide-based therapy to prevent thrombo-embolic side effects. For patients at high risk of VTE or bleeding, there is insufficient evidence to support a specific thromboprophylactic approach.

b. Cytopenias
Insufficient evidence is available to recommend a uniform approach for the management of cytopenias. Lenalidomide dose reductions can be considered for patients who have responded clinically and biochemically to the full dose of lenalidomide. For those who require the full dose of lenalidomide for efficacy, the use of granulocyte-colony stimulating factor (GCSF) support can be considered for neutropenia.

c. Second primary malignancies (SPM)
Insufficient evidence is available to date to confirm or refute the association of SPM with lenalidomide use or to identify specific subgroups of patients at risk of SPM when treated with lenalidomide.

Key Evidence
a. This recommendation is based on a published substudy of previously untreated patients participating in a lenalidomide-based study who were randomized to either ASA 100 mg daily or enoxaparin 40 mg/day subcutaneously for VTE prophylaxis (29). Equally low rates of VTE with no major hemorrhagic complications in either arm were reported, and therefore, the Hematology DSG recommends either option as reasonable. Given the favourable safety profile of both ASA and enoxaparin in prophylactic dosing, the generalization of these recommendations to the relapsed/refractory setting is not unreasonable until randomized data in this setting becomes available. Patients at high risk for VTE (DVT in prior 12 months) or bleeding
were not enrolled in this study; therefore, these recommendations cannot be extended to this subset.

b. The recommendation for lenalidomide dose reductions was based on a subgroup analysis of data pooled from the Weber and Dimopoulos trials (4,5) by Dimopoulos et al (17). This analysis suggested that, by allowing patients to tolerate therapy longer, dose reductions may be beneficial in prolonging PFS. In addition, the Weber and Dimopoulos RCTs routinely used G-CSF support with full-dose lenalidomide as the initial dose-modification step for severe neutropenia, an approach that may also be appropriate (4,5). Based on the clinical expertise of the Hematology DSG, these data led to the recommendations for dose reductions in those patients with responsive disease and consideration for G-CSF if full-dose lenalidomide for efficacy is required.

Qualifying Statements

a. The Larocca et al superiority trial (29) showed no difference between two drugs for the prevention of VTE; untreated patients were 65 years of age or younger, the power of the study ranged from 47% to 80%, and for ethical reasons a placebo arm was not available. However, this was the first and only RCT studying VTE prophylaxis in patients with multiple myeloma treated with lenalidomide. Despite these study limitations, the Hematology DSG members believed that based on their clinical experience, these results could be generalized to other patient groups. If the 100-mg dose for ASA is not available, the Hematology DSG suggests that replacement with the 81-mg dose is reasonable.

b. Erythropoietin-stimulating agents (ESA) may also be considered for the management of anemia related to lenalidomide therapy. In the absence of evidence for ESA use specific to lenalidomide therapy, published evidence-based guidelines for ESA use in cancer may be applied (30,31). In a subgroup analysis of the Weber and Dimopoulos studies that was published as a letter to the editor and excluded from our systematic review, the rates of venous thromboembolism were significantly higher with the concomitant use of ESA and lenalidomide versus lenalidomide without ESA (32). Therefore, the concomitant use of ESA with lenalidomide may potentiate the risk of thrombosis. As these observations mandate further validation, the Hematology DSG advises consideration of risks and benefits before initiating ESA with lenalidomide, followed by careful monitoring for VTE signs and symptoms. Transfusion of either red cells or platelets, in conjunction with lenalidomide dose reductions/interruptions, may be appropriate for severe or symptomatic anemia or thrombocytopenia.

FUTURE RESEARCH

Several ongoing trials were identified that are studying direct comparisons among novel agents, rational lenalidomide-based combination therapies, novel agents used for consolidation and maintenance, new strategies for the management of toxicity, and long-term toxicities. Section 2, Appendix 7 provides details of these studies.

RELATED GUIDELINES


Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Copyright
This report is copyrighted by Cancer Care Ontario; the report and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer
Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information
For further information about this report, please contact:

Dr. C. Chen, Dept of Medical Oncology and Hematology
Princess Margaret Hospital, 610 University Avenue Toronto, Ontario, M5G 2M9
Phone: 416-9464563   E-mail: christine.chen@uhn.ca
or
Dr. Matt Cheung, Odette Cancer Centre at Sunnybrook Health Sciences
2075 Bayview Avenue, Toronto, Ontario
Phone: 416-480-5000   E-mail: matthew.cheung@sunnybrook.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822   Fax: 905 526-6775   E-mail: ccopgi@mcmaster.ca
REFERENCES


## GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>abs</td>
<td>abstract</td>
</tr>
<tr>
<td>AE</td>
<td>adverse events</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>ASA</td>
<td>acetylsalicylic acid; aspirin</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>ASCT</td>
<td>autologous stem cell transplant</td>
</tr>
<tr>
<td>ASH</td>
<td>American Society of Hematology</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>Bleed</td>
<td>incidence of minor bleeding</td>
</tr>
<tr>
<td>Bort</td>
<td>bortezomib</td>
</tr>
<tr>
<td>CCO</td>
<td>Cancer Care Ontario</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CG</td>
<td>control group</td>
</tr>
<tr>
<td>COMP</td>
<td>Composite measure: proportion of patients developing a first episode of objectively confirmed symptomatic deep-vein thrombosis, pulmonary embolism, arterial thrombosis, any acute cardiovascular event, sudden death in the first 6 months after randomization</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CrCl</td>
<td>creatinine clearance</td>
</tr>
<tr>
<td>Cyclo</td>
<td>cyclophosphamide</td>
</tr>
<tr>
<td>d, ds</td>
<td>day, days</td>
</tr>
<tr>
<td>DEX</td>
<td>dexamethasone</td>
</tr>
<tr>
<td>DSG</td>
<td>Disease Site Group</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep-vein thrombosis</td>
</tr>
<tr>
<td>EBS</td>
<td>Evidence-Based Series</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>Elot</td>
<td>elotuzumab</td>
</tr>
<tr>
<td>GCSF</td>
<td>granulocyte colony-stimulating factor</td>
</tr>
<tr>
<td>HI</td>
<td>high dose</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IG</td>
<td>intervention group</td>
</tr>
<tr>
<td>IMID</td>
<td>Immunomodulatory drugs</td>
</tr>
<tr>
<td>IMMW</td>
<td>International Multiple Myeloma Workshop</td>
</tr>
<tr>
<td>ISS</td>
<td>International Staging System</td>
</tr>
<tr>
<td>LEN</td>
<td>lenalidomide</td>
</tr>
<tr>
<td>LMWH</td>
<td>low molecular weight heparin</td>
</tr>
<tr>
<td>LOW</td>
<td>low dose</td>
</tr>
<tr>
<td>μL</td>
<td>microlitre</td>
</tr>
<tr>
<td>MEL</td>
<td>melphalan</td>
</tr>
<tr>
<td>MP</td>
<td>melphalan prednisone</td>
</tr>
<tr>
<td>MPR</td>
<td>melphalan prednisone and lenalidomide</td>
</tr>
<tr>
<td>MPR-R</td>
<td>melphalan prednisone and lenalidomide with lenalidomide maintenance</td>
</tr>
<tr>
<td>NA</td>
<td>not applicable</td>
</tr>
<tr>
<td>Neut</td>
<td>neutropenia</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NR</td>
<td>not reported</td>
</tr>
<tr>
<td>NS</td>
<td>not significant</td>
</tr>
<tr>
<td>od</td>
<td>once a day</td>
</tr>
<tr>
<td>OR</td>
<td>overall response</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>PLC</td>
<td>placebo</td>
</tr>
<tr>
<td>PN</td>
<td>peripheral neuropathy</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
<tr>
<td>Pred</td>
<td>prednisone</td>
</tr>
<tr>
<td>pts</td>
<td>patients</td>
</tr>
<tr>
<td>RAP</td>
<td>Report Approval Panel</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SPM</td>
<td>second primary malignancies</td>
</tr>
<tr>
<td>vs</td>
<td>versus</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thrombo embolism</td>
</tr>
<tr>
<td>TTP</td>
<td>time to progression</td>
</tr>
</tbody>
</table>