Revving up the Revlimid® Debate
Lenalidomide as Maintenance Therapy for Multiple Myeloma after Autologous Stem Cell Transplant

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Learning Objectives
- Review characteristics of multiple myeloma
- Discuss the rationale of maintenance therapy
- Describe previous results of maintenance therapy
- Assess literature evaluating lenalidomide as maintenance therapy
I. Epidemiology\textsuperscript{1,2,3}
   a. Annual incidence in the United States is 3-4 cases/100,000 population
      i. 20,520 new cases
      ii. 10,610 deaths
   b. Accounts for 1.3\% of all types of cancer
      i. Second most common hematologic malignancy
   c. More common in African Americans
   d. Male:female ratio 1.25:1
   e. Median age of diagnosis
      i. Men: 69
      ii. Women: 71
   f. Trends in 5 year survival rates
      i. 1975-77: 26\%
      ii. 1983-86: 29\%
      iii. 1999-06: 39\%

II. Etiology\textsuperscript{1,2}
   a. Exposures
      i. Environmental
         1. Exposure to agriculture, food, and petrochemical industries
      ii. Occupational
         1. Farmers exposed to pesticides and herbicides
         iii. Radiation
            1. Only been shown to have a weak correlation
         iv. Organic solvents
         v. Benzene
   b. Infection
      i. Human herpes virus-8 (HHV8)

III. Pathophysiology\textsuperscript{4,5}
   a. Multiple myeloma is part of a spectrum of diseases ranging from monoclonal
gammopathy of unknown significance (MGUS) to smoldering myeloma to multiple
myeloma (Figure 1)

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Figure 1—Progression of Multiple Myeloma
b. Malignancy of plasma cells
   i. Arises from chromosomal alterations in B-cells
      1. Normal B-cell maturation is associated with rearrangement of DNA sequences responsible for encoding the structure of mature immunoglobulins (Figure 2)

   ![Figure 2—Formation of plasma cells](image)

   ii. Microenvironmental changes of the bone marrow occur (Figure 2)
      1. Malignant plasma cells interact with stromal cells mediated by cell-adhesion molecules
      2. Interactions increase production of growth factors including interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF)
         a. Stimulates myeloma cells, angiogenesis, and osteoclasts
      3. Increased osteoclast activity occurs due to imbalance of receptor activator nuclear factor κB ligand (RANKL) and decreased production of osteoprotegerin (OPG)
      4. Osteoblast activity is suppressed via plasma cells inhibiting secretion of transcription factor

   ![Figure 3—Microenvironmental Changes](image)
c. Characteristics of myeloma
   i. Proliferation of plasma cells (> 10%) in the bone marrow
      1. Normal plasma cells in the bone marrow range from 1-2%
   ii. Overproduction of a monoclonal protein
      1. IgG (60%)
      2. IgA (20%)
      3. IgD (2%)
      4. IgE (<0.1%)
      5. Light chain (18%)
      6. Nonsecretory disease (<5%)

IV. Clinical Manifestation “CRAB”\textsuperscript{1,2,8,9}
   a. Calcium elevation
      i. Occurs in 20% of patients at diagnosis
      ii. Increased bone resorption caused by overexpression of osteoclast activity in the
          microenvironment
         1. Bone resorption leads to efflux of calcium into extracellular fluid
      iii. Kidney dysfunction occurs through decrease in glomerular filtration
         1. Prevents excess circulated calcium from being effectively cleared from
            the system
      iv. Symptoms include: lethargy, polyuria, polydipsia, constipation, nausea,
          vomiting, cardiac abnormalities, and CNS alterations
   b. Renal insufficiency\textsuperscript{8}
      i. Affects 20-30% of patients at time of diagnosis
      ii. Predominant mechanism is associated with excess light chain within the distal
          tubule forming casts leading to obstructive neuropathy
      iii. Hypercalcemia may cause volume depletion leading to prerenal kidney failure
          and may cause calcium deposits leading to interstitial nephritis
   c. Anemia\textsuperscript{8}
      i. Occurs in up to 70% of patients at time of diagnosis
      ii. Erythroid progenitors undergo upregulation leading to apoptosis and destruction
      iii. Also due to reduced levels of erythropoietin secondary to renal insufficiency
      iv. Patients commonly present with fatigue
   d. Bone disease\textsuperscript{9}
      i. Approximately 80% of patients will have abnormal radiographs
      ii. Enhanced bone resorption and decreased bone formation
         1. Myeloma cells stimulate osteoclast activity and suppress osteoblast
            function
         2. Increasing osteoclast activity promotes myeloma progression via bone
            marrow microenvironment
      iii. Effects can result in bone pain, fractures, spinal cord compression, and decreased
          quality of life

V. Diagnosis\textsuperscript{10}
   a. Established by the International Myeloma Working Group (IMWG)
   b. Components include
      i. Percentage of plasma cells in bone marrow
      ii. Quantity monoclonal protein
      iii. CRAB symptoms
c. ~2% of patients will present with nonsecretory disease and have no evidence of a monoclonal protein

Table 1—IMWG Diagnostic Criteria

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Plasma Cells</th>
<th>Monoclonal Protein</th>
<th>CRAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS*</td>
<td>&lt; 10%</td>
<td>Absent; &lt; 3 g/dL</td>
<td>Absent</td>
</tr>
<tr>
<td>Smoldering Myeloma (asymptomatic)</td>
<td>&gt; 10%</td>
<td>Present; &gt; 3 g/dL</td>
<td>Absent</td>
</tr>
<tr>
<td>Symptomatic Multiple Myeloma</td>
<td>&gt; 10%</td>
<td>Present; &gt; 3 g/dL</td>
<td>Present</td>
</tr>
</tbody>
</table>

*Monoclonal Gammapathy of Undetermined Significance

VI. Prognostic Factors
   a. Cytogenetics (Table 2)
      i. Most important prognostic factor
      ii. High risk cytogenetics are associated with poor prognosis as compared to standard risk which has been associated with improved survival
   b. Other prognostic factors
      i. β-2 microglobulin
         1. Excreted via kidneys
         2. High levels are seen in patients with renal failure
         3. Elevated levels are associated with worsened outcomes
      ii. LDH
         1. Increased levels are associated with drug resistance and shortened survival
      iii. Hemoglobin levels
      iv. Hypercalcemia
      v. Low serum albumin
      vi. Presence of circulating plasma cells

Table 2—Cytogenetic Abnormalities

<table>
<thead>
<tr>
<th>Standard (75%)</th>
<th>High Risk (25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdiploidy</td>
<td>t(4;14)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>t(14;16)</td>
</tr>
<tr>
<td>t(6;14)</td>
<td>t(14;20)</td>
</tr>
<tr>
<td></td>
<td>Del(17p)</td>
</tr>
<tr>
<td></td>
<td>Deletion 13</td>
</tr>
</tbody>
</table>

VII. Staging
   a. Durie-Salmon staging system was introduced in 1975
      i. Classification predicted myeloma cell tumor burden (Table 3)
         1. Factors
            a. Hemoglobin
            b. Serum creatinine
            c. Serum calcium
            d. Skeletal survey
            i. Subject to observer bias
            e. Level and type of monoclonal protein
Table 3—Durie-Salmon Staging System

<table>
<thead>
<tr>
<th>Stages</th>
<th>Hgb</th>
<th>Serum calcium</th>
<th>Skeletal Survey</th>
<th>M Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&gt;10 g/dL</td>
<td>&lt;12 mg/dL</td>
<td>Normal or solitary plasmacytoma only</td>
<td>IgG &lt; 5 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IgA &lt; 3 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bence Jones protein &lt;4 g/24h</td>
</tr>
<tr>
<td>II</td>
<td>Neither Stage I or III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>&lt;8.5 g/dL</td>
<td>&gt;12 mg/dL</td>
<td>≥3 lytic lesions</td>
<td>IgG &gt; 7 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IgA &gt; 5 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bence Jones protein &gt;12 g/24h</td>
</tr>
</tbody>
</table>

Subclassification
- A: Normal renal function (Scr <2.0 mg/dl)
- B: Abnormal renal function (Scr ≥ 2 mg/dl)

b. In the 1980s, serum β-2 microglobulin was shown to be the most reliable and simple predictor of outcome
c. International Staging System (ISS)
  i. Provides a measure of prognostic classification (Table 4)
  ii. Staging is characterized based on serum β2 microglobulin and serum albumin

Table 4—International Staging System (ISS) classification

<table>
<thead>
<tr>
<th>Staging</th>
<th>Criteria</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum β2 microglobulin &lt; 3.5 mg/L</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Serum albumin ≥ 3.5 g/dL</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Neither stage I or II</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>Serum β2 microglobulin ≥ 5.5 mg/L</td>
<td>29</td>
</tr>
</tbody>
</table>

VIII. Treatment

a. Role of autologous stem cell transplant (ASCT)
   i. Studies have shown overall survival advantage 55-57 months compared to conventional chemotherapy 37-40 months
b. No evidence supporting the use of therapy for MGUS or smoldering myeloma
c. Transplant eligible versus ineligible
   i. Patients are deemed ineligible due to a combination of age, poor physical condition, comorbid conditions
d. ASCT eligible patients
   i. Non-alkylating based drug regimens induction for 2-4 cycles (Table 5)

Table 5—Chemotherapy Regimens in Induction Therapy

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Overall response rates</th>
<th>Complete response + near complete response CR+nCR</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine/doxorubicin/dexamethasone (VAD)</td>
<td>50%</td>
<td>5%</td>
<td>Not commonly used due to inferior response to other regimens; high incidences of VTE, sepsis, and neurotoxicity</td>
</tr>
<tr>
<td>Lenalidomide/low dose dexamethasone</td>
<td>75%</td>
<td>15%</td>
<td>Risk of DVT, decreased mobilization of stem cells</td>
</tr>
<tr>
<td>Thalidomide/dexamethasone</td>
<td>60%</td>
<td>8%</td>
<td>VTE, cerebral ischemia, MI, and peripheral neuropathy</td>
</tr>
</tbody>
</table>
Table 5—Chemotherapy Regimens in Induction Therapy

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Overall response rates</th>
<th>Complete response + near complete response CR+nCR</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib/dexamethasone</td>
<td>82%</td>
<td>15%</td>
<td>Neurotoxicity</td>
</tr>
<tr>
<td>Bortezomib/dexamethasone/thalidomide (VTD)</td>
<td>94%</td>
<td>32%</td>
<td>No data regarding prolonged overall survival and quality of life</td>
</tr>
</tbody>
</table>

IX. Maintenance Therapies

a. Defined as any therapy administered following the completion of induction treatment in responding or non-progressing patients

b. Rationale

i. Despite stem cell transplants (SCTs), chemotherapy, and novel agents, multiple myeloma remains an incurable disease

ii. Relapse usually occurs within 3-5 years after transplantation

c. Interferon α

i. MOA

1. Inhibits self renewing capacity of multiple myeloma stem cells

ii. Studies have shown conflicting evidence regarding benefit of overall survival

iii. Significant toxicities are seen with the use of this medication

1. Depression

2. Hepatotoxicity

3. Muscle aches

iv. Toxicities and cost outweigh the limited benefits of this therapy

d. Glucocorticoids

i. MOA

1. Suppresses production of interleukins and induces cellular apoptosis

ii. Glucocorticoids increase progression free survival

iii. Overall survival remains controversial due to conflicting results

iv. Not widely used due to long term toxicities

e. Bortezomib

i. MOA

1. Inhibits the proteosome pathway by reversibly binding to the 20S proteosome complex resulting in cell cycle arrest and apoptosis

ii. Bortezomib shows similar results in terms of PFS and OS to thalidomide

iii. Toxicities remain a concern

1. Viral reactivation

2. Peripheral neuropathy

3. GI toxicities

4. Cytopenias

iv. Long term follow up data is still under investigation

f. Thalidomide

i. MOA

1. Antiangiogenic and immunomodulation properties (Figure 4)
Figure 4—Mechanism of Action of Thalidomide
Table 6

Maintenance therapy with thalidomide improves survival in patients with multiple myeloma.

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate the efficacy of thalidomide in combination with pamidronate</td>
<td>Phase III randomized controlled trial between April 2000 and October 2003</td>
</tr>
<tr>
<td>as maintenance treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients &lt; 65 years of age</td>
<td>Prior myeloma treatment</td>
</tr>
<tr>
<td></td>
<td>Secondary malignancies</td>
</tr>
<tr>
<td></td>
<td>Abnormal cardiac function</td>
</tr>
<tr>
<td></td>
<td>Chronic respiratory disease</td>
</tr>
<tr>
<td></td>
<td>Abnormal liver function tests</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects underwent initial chemotherapy (VAD), stem cell transplant,</td>
<td>Primary outcome: complete or very good partial response rates (CR/VGPR)</td>
</tr>
<tr>
<td>then were randomized to no maintenance treatment, maintenance treatment</td>
<td>Secondary outcomes: event free survival (EFS), overall survival (OS)</td>
</tr>
<tr>
<td>with thalidomide (400 mg daily) and pamidronate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 597</td>
<td></td>
</tr>
<tr>
<td>67% of patients achieved CR/VGPR compared to 55% and 57% in subjects</td>
<td></td>
</tr>
<tr>
<td>receiving no maintenance or maintenance with pamidronate, respectively (p = 0.03)</td>
<td></td>
</tr>
<tr>
<td>3 year event free survival was 36% in patients with no maintenance,</td>
<td></td>
</tr>
<tr>
<td>37% in those with maintenance of pamidronate, and 87% of patients with thalidomide (p &lt;0.04)</td>
<td></td>
</tr>
<tr>
<td>4 year overall survival was 77% with no maintenance, 74% in patients</td>
<td></td>
</tr>
<tr>
<td>with pamidronate, and 87% for those with thalidomide (p= 0.02) (Figure 5)</td>
<td></td>
</tr>
<tr>
<td>Discontinuation of thalidomide therapy was seen in 78 patients (39%)</td>
<td></td>
</tr>
<tr>
<td>o Peripheral neuropathy was the major toxicity (68%)</td>
<td></td>
</tr>
<tr>
<td>o Fatigue (34%)</td>
<td></td>
</tr>
<tr>
<td>o Constipation (20%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conclusion</th>
<th></th>
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<tbody>
<tr>
<td>Maintenance therapy with thalidomide after high dose chemotherapy and ASCT improved event free survival and overall survival</td>
<td></td>
</tr>
<tr>
<td>Thalidomide was associated with significant adverse events causing significant discontinuation</td>
<td></td>
</tr>
<tr>
<td>Thalidomide as maintenance therapy is a reasonable option for maintenance therapy</td>
<td></td>
</tr>
</tbody>
</table>
Table 7

Thalidomide and hematopoietic-cell transplantation for multiple myeloma.

<table>
<thead>
<tr>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess whether thalidomide improves survival outcomes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III randomized controlled trial between October 1998 and February 2004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed myeloma</td>
</tr>
<tr>
<td>75 years of age or younger</td>
</tr>
<tr>
<td>No more than 1 cycle of prior therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients were stratified according to serum β2 microglobulin</td>
</tr>
<tr>
<td>Randomly assigned to placebo group or thalidomide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: 5 year EFS</td>
</tr>
<tr>
<td>Secondary outcomes: CR and OS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 323</td>
</tr>
<tr>
<td>At 5 years</td>
</tr>
<tr>
<td>OS: 65% in both groups (p = 0.90) (Figure 7)</td>
</tr>
<tr>
<td>EFS: 56% in the thalidomide group compared to 44% in the placebo group (p = 0.01) (Figure 8)</td>
</tr>
<tr>
<td>Median follow up of 42 months</td>
</tr>
<tr>
<td>CR of 62% and 43% in the thalidomide group as compared to the placebo group, respectively (p &lt; 0.001)</td>
</tr>
<tr>
<td>At 2 years thalidomide was discontinued in 30% of patients and at 4 years &gt; 40% of patients had discontinued therapy</td>
</tr>
<tr>
<td>Significant incidences of DVT 34% in the thalidomide group compared to placebo group 18% (p &lt; 0.001)</td>
</tr>
<tr>
<td>Grade 2 or higher peripheral neuropathy was more common in the thalidomide group (27% vs 17%; p &lt; 0.001)</td>
</tr>
</tbody>
</table>

Figure 7—Overall Survival

Figure 8—Event Free Survival

<table>
<thead>
<tr>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide increased EFS and frequency of CR</td>
</tr>
<tr>
<td>Significant toxicities are associated with this medication including DVT and peripheral neuropathy</td>
</tr>
</tbody>
</table>

S. Villarreal, 10
Table 8

A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma.

Purpose
- Evaluate the effect of thalidomide as maintenance in transplant eligible multiple myeloma patients

Study Design
- Phase III, randomized, controlled trial between November 2001 and May 2005

Inclusion
- Newly diagnosed multiple myeloma
- Durie-Salmon stage II or III
- 18-65 years of age

Methods
- Subjects were randomly assigned to 3 cycles of VAD or TAD then underwent SCT and received maintenance therapy with either interferon-α or thalidomide 50 mg daily

Outcome
- Primary outcome: 3 year EFS
- Secondary outcomes: overall response rate (ORR), VGPR/CR rates, PFS, and OS

Results
- N = 556
- EFS improved from 22 months to 34 months (p <0.001) (Figure 9)
- OS were comparable in both arms, 60 months in the control arm compared to 73 months for the thalidomide group (p = 0.77) (Figure 10)
- ORR reported as 88% compared to 79% (p = 0.005) in the thalidomide group and interferon group respectively
- CR of 31% in the thalidomide group compared to 23% in the interferon group (p = 0.04)

Figure 9—Event Free Survival
Figure 10—Overall Survival

Conclusion
- Similar to previous trials, thalidomide did increase event free survival
- Overall survival was unchanged between the two groups, although subsequent follow-up showed a trend favoring thalidomide at 5 years
- It is unknown whether previous exposure to thalidomide in induction/post intensification will elicit a resistance relapse compared to thalidomide naïve subjects
i. Toxicities are a major concern
   2. ~60% patients discontinued due to neurologic toxicity

ii. Optimal dose and duration remains controversial

g. Lenalidomide\textsuperscript{34,35}
   i. Semisynthetic compound derived with structural modifications of thalidomide (Figure 11)

Figure 11—Chemical Structures of Thalidomide and Lenalidomide 34

ii. Mechanism of action—Pleiotropic effects
   1. Immunomodulation
      a. Alters different components of the immune system
         i. Inhibits production of pro-inflammatory cytokines TNF-\(\alpha\), IL-1, IL-6, IL-12, and IL-10
         ii. Stimulate CD8+ cells and CD4+ cells
         iii. Modulation of natural killer cells
   2. Anti-angiogenesis properties
      a. Decreases the expression of vascular endothelial growth factor (VEGF)
      b. 2-3x more potent than thalidomide
   3. Direct tumor toxicity
      a. Causes cell cycle arrest in G0-G1 phase
      b. Increase apoptosis through decreasing activation of pro-survival kinases
   4. Alteration of multiple myeloma microenvironment
      a. Decreases formation of osteoclast forming cells

iii. Potency profile of lenalidomide\textsuperscript{36}
   1. Compared to thalidomide, lenalidomide is 50-2,000 times more potent in stimulating T-cell proliferation
   2. Lenalidomide is 50-100 times more potent in inhibiting cytokine production (IL-2 and IFN-\(\gamma\))
Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104.

**Purpose**
- To determine the efficacy of lenalidomide as maintenance treatment after ASCT

**Study Design**
- Phase III randomized controlled trial from April 2005 to July 2009

**Inclusion**
- Stage I–III disease
- ≤ 1 yr from diagnosis
- ≥ 2 months of induction with stable disease or better
- Age < 70 years

**Methods**
- Randomized post-ASCT to lenalidomide (15 mg/day) or placebo

**Outcome**
- Primary outcome: time to progression (TTP)
- Secondary outcomes: PFS, OS, feasibility of long-term lenalidomide

**Results**
- N = 460
- Median TTP significantly improved with lenalidomide therapy compared to placebo
  - 42.3 months vs 21.8 months (Figure 13)
  - Regardless of β2-microglobulin or induction therapy, TTP was still maintained
- No difference in overall survival (Figure 14)
- Lenalidomide was associated with 61% reduction in the risk of disease progression compared to placebo
- Deaths in the study and placebo arm were 19 and 28 respectively
- Lenalidomide compared to placebo had significantly higher adverse events
  - Hematologic: 45% vs 11% (p < 0.001)
  - Non-hematologic: 34% vs 24% (p = 0.0350)
- 15 cases of new malignancies seen in the lenalidomide group compared to 6 in the placebo group

**Conclusion**
- Significant improvements seen in TTP
- No difference in overall survival
- Higher proportion of patients discontinued treatment due to adverse effects
- Although relatively small, there is a risk of acquiring secondary malignancies

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**Figure 13—Time to Progression**

**Figure 14—Overall Survival**
Table 10


**Purpose**
- To investigate the use of lenalidomide for maintenance therapy after ASCT

**Study Design**
- Phase III randomized controlled trial from July 2006 to August 2008

**Inclusion**
- Age < 65 years
- Non-progressive disease after ASCT (performed within the last 6 months)

**Methods**
- All patients received consolidation therapy after ASCT with lenalidomide 25 mg/d, 21 days/month x 2 months) followed by maintenance lenalidomide (10-15mg/d until relapse) or placebo

**Outcome**
- Primary outcome: progression free survival
- Secondary outcomes: TTP, OS, feasibility of long-term lenalidomide

**Results**
- N = 614
- Median PFS was 42 months in the lenalidomide arm compared to 24 months in the placebo group (p < 10^-8) (Figure 15)
  - Benefit was seen across all subgroups
- No difference in overall survival (81% vs 81%; p = 0.57) (Figure 16)
- Lenalidomide was associated with higher rates of adverse events than placebo
  - Neutropenia (43% vs 14%)
  - DVT (2% vs 0%)
  - Peripheral neuropathy (0.7% vs 0.2%)
- Higher rates of discontinuation due to side effects were seen in patients treated with lenalidomide (21% vs 15%)
- 16 cases of new primary malignancies were observed in the lenalidomide arm compared to 3 in the placebo arm

**Conclusion**
- Similar to CALGB study, significant longer time to progression was seen in the lenalidomide arm
- Overall survival was comparable in both groups
- Majority of patients in the lenalidomide group discontinued treatment due to adverse effects
X. Secondary Malignancies
   a. CALGB 100104\textsuperscript{37}
      i. 15 malignancies in the lenalidomide arm compared to 6 in the placebo arm
         1. Of the 15 malignancies 3 were MDS/AML
   b. IFN 2005-02\textsuperscript{38}
      i. 16 malignancies in the lenalidomide group compared to 3 in the placebo group
   c. Perspective of the FDA\textsuperscript{39}
      i. As of April 8, 2011 the FDA is reviewing all information on the potential risk and will provide new recommendations once the review is completed
      ii. Current recommendations
         1. Continue therapy as directed by providers
         2. Benefits should be carefully weighed
         3. Preliminary data shows an increase incidence of second primary malignancies when compared to controls
   d. Overall number of secondary malignancies is relatively small
   e. Results consistently show that patients receiving lenalidomide have an increase rate of secondary malignancies
   f. At this point in time, there is not enough data to warrant discontinuation of lenalidomide due to secondary malignancies, but should continue to be monitored

XI. Conclusion
   a. Lenalidomide prolongs progression free survival
      i. Is PFS a valid regulatory marker when evaluating maintenance therapy?
         1. More useful when assessing initial drug approval to unnecessarily delay new agents
   b. Overall survival benefit has yet to be proven
   c. Adverse effects
      i. Long term use toxic effects?
   d. Quality of life
      i. Medication is relatively well tolerated, however, patients must follow up with physicians at regular intervals
      ii. Cost to patients
   e. Secondary malignancies warrant close monitoring
      i. Is the risk of malignancies less significant than the benefit for multiple myeloma patients
      ii. If overall survival is not seen with lenalidomide therapy, secondary malignancies will be a much bigger issue
   f. Future direction
      i. Optimal dose?
      ii. Specific duration for lenalidomide therapy?
   g. Although lenalidomide does show improvement in progression free survival, the lack of overall survival, significant toxicity profile, and risk of secondary malignancies does not currently warrant use as maintenance therapy in multiple myeloma
References


