and lenalidomide plus low-dose dexamethasone. Early data indicate excellent PFS and overall survival results with both. The 82% 2-year survival seen with ongoing lenalidomide-low-dose dexamethasone therapy (for patients ≥ 65 years) is particularly promising. This ECOG trial also brings into focus the need to assess best response and survival over time. The results of direct comparative trials are awaited with great anticipation.

For now, the current standard is MPT, which is a well-tolerated oral regimen with a manageable side effect/toxicity profile. A personalized approach to treatment selection is recommended, and can allow use of MP alone for very elderly or frail patients and stronger consideration of VMP in the setting of high-risk cytogenic features and/or renal impairment and/or if deep vein thrombosis risk is a particular concern. Neurotoxicity can be proactively managed for both MPT and VMP with appropriate dose modifications as necessary. It is wonderful to finally have effective new options available for tailored use.

**Conflict-of-interest disclosure:** The author is on the advisory boards of both Celgene and Millennium Pharmaceuticals.

### REFERENCES

### CLINICAL OBSERVATIONS

**Comment on Barlogie et al, page 3115**

**Biology, treatment, and time**

**Angela Dispenzieri** **MAYO CLINIC**

Barlogie and colleagues report that patients with abnormal baseline metaphase cytogenetics and enrolled on TT2 had better overall survival (OS) rates when randomized to thalidomide.
99-02 was a maintenance trial for patients undergoing tandem autologous stem cell transplantation (ASCT) who had either or neither increased β2 microglobulin or FISH deletion 13.² Although there was a modest survival benefit among patients receiving maintenance thalidomide, the authors did not disect the influence of genetic factors on OS but did note that thalidomide-treated patients with deletion 13 had no event-free survival benefit.² The Tunisian trial was a consolidation trial, in which patients were randomized to either 6 months of thalidomide or a second ASCT.³ In the Australian trial, after a single ASCT, all patients received prednisolone maintenance, but half were randomized to receive 1 year of thalidomide consolidation as well.⁴ In both, preliminary OS data favored the thalidomide arm as shown in the table, but no data were provided about interactions between thalidomide and myeloma genetics. Among the 4 randomized trials comparing melphalan and prednisone (MP) and MP plus thalidomide (MPT), the results are inconsistent.⁵ ⁶ ⁷ The 2 trials that included thalidomide both as induction and maintenance did not show a survival benefit.⁵ ⁷ The other 2 trials, both conducted by the IFM, tested 18 months of MP versus MPT in patients aged 65 to 75⁶ and in those 75 or older.⁶ Both of these studies demonstrated an OS benefit for the MPT arm,⁶ ⁷ and it appeared that thalidomide canceled the deleterious effect of FISH deletion 13.⁶

Despite this very important contribution by Barlogie et al, questions remain about thalidomide use with regards to timing, dose, duration of therapy, and optimal patient populations. It is unclear whether thalidomide is best used as in TT2, from induction through transplantation, consolidation, and maintenance. It is noteworthy that post hoc Barlogie et al found no impact of the duration or cumulative dose of thalidomide on clinical outcomes. In fact, 43% of patients stopped thalidomide at a median of 30 months, which is a lower attrition rate than for other trials. As shown in the table, the median duration of thalidomide treatment, regardless of trial design, was about 12 months. Therefore, it appears that relatively brief exposure to thalidomide may provide survival benefits in a subset of patients.

The question of which patient populations thalidomide best serves relates both to the substrate of the patient (eg, age and comorbidity) and to the myeloma biology, and it is quite likely that the inconsistent results in the MPT trials reflect this heterogeneity. A major challenge for synthesizing the impact that the treatment regimens have on myeloma genetic characteristics lies in the differential methodology employed. Barlogie and colleagues’⁷ work relies heavily on metaphase cytogenetics and on gene expression profiling, whereas those of the IFM and others are largely FISH-based. The different information derived makes cross-validation among studies difficult, but each may add to the current work by continuing to unravel complex interactions between myeloma biology, treatment, and long-term outcomes.

**Conflict-of-interest disclosure:** The author declares no competing financial interests.

### REFERENCES


### Summary of results from 7 randomized trials

<table>
<thead>
<tr>
<th>Trial design</th>
<th>Time of thal</th>
<th>Thal dose, mg</th>
<th>Intended thal, mo</th>
<th>Actual thal, mo</th>
<th>Median follow-up, mo</th>
<th>Outcomes</th>
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<td>TT2*</td>
<td>T2</td>
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<td>Continuous</td>
<td>&gt; 30</td>
<td>72</td>
<td>8-y OS: 57% vs 44%</td>
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<tr>
<td>IFM 99-02</td>
<td>ASC × 2</td>
<td>400</td>
<td>Continuous</td>
<td>&gt; 30</td>
<td>72</td>
<td>5-y OS: 56% vs 43%</td>
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<td>Tunisian</td>
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<td>33</td>
<td>3-y OS: 85% vs 65%</td>
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<tr>
<td>ALLG MM6</td>
<td>ASC × 1—prednisolone maintenance ≤ thal × 1 y</td>
<td>C</td>
<td>200</td>
<td>12</td>
<td>NA</td>
<td>2-y OS: 91% vs 80%</td>
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<tr>
<td>IFM 99-06</td>
<td>MP vs MPT vs Mel 100 × 2 (age 65-75)</td>
<td>I</td>
<td>400</td>
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<td>11</td>
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<td>MP vs MPT (age &gt; 75)</td>
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<td>NA</td>
<td>MS: 28 vs 33 mo</td>
</tr>
</tbody>
</table>

*Barlogie et al study.
†Included patients with 1 or fewer risk factors (beta-2 microglobulin < 3.0 mg/L or deletion 13 by FISH).
Biology, treatment, and time

Angela Dispenzieri

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