in the protein’s DNA contact regions that weaken the binding of the protein to its targeted DNA but retain a similar protein structure. It is this second class that both gives rise to the adverse prognosis of DLBCL and often demonstrates allele-specific “gain-of-function mutations”\(^5,6\) that confers new properties on a mutant p53 protein. These mutant proteins apparently bind to other transcription factors (like p73) and alter their functions, making the cell more resistant to apoptosis and chemotherapy. These “gain-of-function” phenotypes have been demonstrated in cell cultures and in transgenic mice.\(^7\)

The observations made in these papers suggest the possibility that allele-specific “gain-of-function” mutations can act in humans to contribute to poor overall survival. Unlike many tumor suppressor gene mutations, most of the p53 mutations found in tumors are missense mutations (92 in the DLBCL study), rather than deletions or insertions (10 in that study) that destroy the structure of the protein. That observation suggests that tumors may select for a p53 missense mutation that provides a helpful “gain-of-function” for tumor growth and survival before and during treatments. This idea will clearly need additional studies examining the possible altered transcriptional patterns brought about in a p53 mutant allele-specific fashion in DLBCL and FL. There ought to be a transcriptional “signature of genes” of that mutant p53 protein, disrupting the function of other transcription factors. The concept that tumor suppressor genes contribute to the origins and development of cancers by their loss of a function will now have to be modified to include the oncogene-like activity of a mutant p53 protein that has a “gain-of-function.”

**REFERENCES**

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 cytogenetic 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.

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**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.
Crossover confusion: MPT still best

Brian G. M. Durie