## From the Editor

# Prostate Cancer Standards—Are Trial Results Affecting Practice?

Debu Tripathy, MD
Editor-in-Chief

The title of this commentary may sound critical or impart a tone of disappointment. However, it is, in part, a result of more rapid output from clinical trials and the introduction of new drugs or older drugs in a different setting. In the review of new therapeutic paradigms for advanced prostate cancer by Li et al in this issue of *The American Journal of Hematology/Oncology®*, this phenomenon is nicely illustrated. In the past few years, we have seen advances in all the therapeutic categories for prostate cancer—antiandrogen, cytotoxic, and bone-directed therapy, along with early-phase trials with PARP inhibitors and immunotherapy. The paradox of rapid progress is that successful trials of different designs leave uncertainty regarding which of several strategies is optimal. Additionally, as standards for first-line therapy change, interpretation of later-line trials becomes murky because the populations no longer reflect subjects from past studies in terms of prior treatments.

As pointed out in this article, the use of sequential androgen-targeting agents has become popular owing to fewer toxicities and the numerous new agents available in this category. However, there is little evidence demonstrating whether this strategy is effective and, if it is, which of the many permutations of sequence is best. While there is likely some degree of cross-resistance, this is not complete, yet the few available data suggest that the activity is modest. The timing of bone-targeted radium-223 that not only improves bone pain but has an overall antitumor effect, with improvement in survival and the role of specific concomitant androgen-directed therapies (and eventually in clinical trials with chemotherapy) also needs further investigation to be optimally used in the clinic.

The most recent set of advances have come in the initial treatment of metastatic prostate cancer. Three pivotal trials testing different partners with androgen deprivation therapy—namely docetaxel, enzalutamide, and abiraterone—have shown survival advantages that appear to be similar, although different follow-up times and endpoints make comparisons difficult. Of course, cross-trial comparisons must be viewed cautiously even when the populations and methods/parameters are comparable. There is considerable debate over whether there are specific factors that would favor the use of chemotherapy in the front line—so far, this has not been adopted extensively. All said, these important milestones are calling for even more trials so that effects on practice, such as therapy choices after progression, can be better determined. We are seeing this same challenge in other tumor types with the reporting of landmark studies. It may be time to design trials that also designate the next line of therapy—these likely would not be industry-supported trials, so cooperative groups and other consortia are beginning to discuss these strategies.