Recent progress in our understanding of the pathogenesis of advanced prostate cancer has heralded a new era in treatment. Numerous agents now populate the treatment landscape, and an impressive number of novel agents are in development. However, many questions remain unanswered, paving the path for discovery in the future.

Recent advances in our understanding of the pathogenesis of castration-resistant prostate cancer (CRPC) have led to an array of new therapeutic strategies in prostate cancer. As noted by Drs. Burgess and Raghavan, expansion of the treatment armamentarium with drugs that work by different mechanisms of action has generated optimism regarding the care of patients with advanced disease.

This rapidly evolving treatment landscape has unearthed new opportunities, while at the same time introducing new questions in the field. These questions include how to optimally sequence or combine recently approved agents; whether, in the context of advanced disease, intermediate endpoints can replace overall survival for regulatory approval of future agents; and whether application of these agents in men with high-risk localized disease can increase cure rates. The notion of using recently approved novel androgen-signaling-pathway blocking agents—including abiraterone ([Zytiga] should it be approved by the US Food and Drug Administration [FDA] for this indication) and potentially enzalutamide ([Xtandi] should Level 1 evidence support this indication)—prior to chemotherapy raises the question of integration of these agents with current therapies, including the timing and use of the therapeutic vaccine sipuleucel-T (Provenge) and antiresorptive therapies. There is a theoretical concern that immediate subsequent treatment with immunosuppressive agents, such as steroids, could deleteriously affect the benefits of sipuleucel-T. Because abiraterone is administered with concomitant steroid therapy, treatment with abiraterone may need to be sequenced following sipuleucel-T when used. At the present time, it is unclear how long it is necessary to wait before initiating another treatment following sipuleucel-T. In the IMPACT study, steroids were not given within 28 days of sipuleucel-T initiation and were not resumed until there was objective evidence of disease progression.[1] The integration of novel androgen biosynthesis inhibitors and second-generation anti-androgens into the present treatment paradigm raises the question of the future utility of current second-line hormone therapies, including ketoconazole and first-generation anti-androgens. Additionally, as these effective therapies enter clinical practice, the dosing and scheduling of antiresorptive therapies is another dilemma. Trials leading to the approval of zoledronic acid (Zometa) and denosumab (Xgeva) for the prevention of skeletal-related events were conducted in an era when patients had limited treatment options for disease control.[2,3] Since many of the effective new therapies have a beneficial impact on the rate of skeletal-related events, patients may require different schedules or, optimally, biomarkers to guide clinical decision-making. Moreover, an additional clinical dilemma is the utility of antiresorptive agents with regard to the not-yet-approved agent, Alpharadin (Ra-223 dichloride), a bone-targeted alpha emittor that prolongs survival in men with CRPC. Another question open to investigation is whether, or when, to discontinue treatment with either abiraterone or enzalutamide after disease progression, for which there are several definitions including prostate-specific antigen (PSA) level, clinical/symptomatic progression, or radiographic progression. In the COU-301 trial, a rise in PSA level, or lack of PSA decline, on therapy was not a criterion for discontinuation of abiraterone, and thus patients may continue to gain clinical benefit from remaining on therapy.[4] Just as standard androgen-deprivation therapy (ADT) is continued in CRPC, there is the question regarding the value of continued CYP17 inhibition and complete androgen receptor (AR) blockade following disease progression. Alternatively, should these agents be discontinued and readministered at a later time when adaptive mechanisms such as upregulation of CYP17 may have changed?
We know that prior therapies influence response to subsequent anticancer regimens. As these agents are used in sequence, it is unclear if their benefit to survival will be additive or will be blunted by cross-resistance mechanisms. Abiraterone treatment has been associated with increased expression of AR splice variants that lack the ligand-binding domain and are therefore constitutively active.[5] Enzalutamide treatment has been associated with increased intratumoral levels of testosterone.[6] Cross-talk with other signaling networks may also play a role in ligand-independent activation of the AR.[7] Currently, there are no data on the efficacy of enzalutamide in patients who have received abiraterone, nor on use of abiraterone after enzalutamide. Studies of potential mechanisms of resistance to ADT support the rationale for combined CYP17 inhibition with a potent anti-androgen such as enzalutamide. This raises pragmatic issues of compound toxicity and the emergence of adaptive pathways resistant to combination therapy.

Given the multiple new effective agents recently approved for advanced prostate cancer and the additional agents currently in development, a high priority in the field for both clinical practice and research is the identification of robust surrogate efficacy biomarkers and endpoints. Many patients with metastatic prostate cancer present with nonmeasurable bone-only disease, necessitating a reliance on PSA levels to assess response to treatment. Unfortunately, PSA may not be a reliable surrogate for survival benefit, thus highlighting the need to develop robust biomarkers to assess treatment response.[8] Although the development of an unprecedented number of novel agents that prolong overall survival is a triumph in the field, disease progression eventually occurs, raising concern about use of overall survival as a primary endpoint for new drug regulatory approval in the future. The development of reliable intermediate endpoints, such as progression-free survival, may optimize and accelerate drug development.

The compelling impact on survival of abiraterone and enzalutamide in advanced CRPC has led to excitement regarding use of these agents earlier in the disease course, including in patients with localized disease. Is this an opportunity to redefine complete androgen blockage in men with hormone-sensitive disease? This is an important question that needs to be answered. In high-risk localized disease, we evaluated abiraterone in a phase II neoadjuvant trial.[9] Preliminary results were presented at the 2012 Annual Meeting of the American Society of Clinical Oncology (ASCO) and showed that there was significantly greater suppression of tissue androgens with leuprolide (Lupron) plus abiraterone than with leuprolide alone and greater than anticipated pathologic complete responses. The enzalutamide neoadjuvant trial is currently accruing patients.[10] Integrating the use of these novel agents with other multimodality options opens the door for curative therapy for high-risk patients who frequently die of their disease. In addition, the future generation of phase III neoadjuvant and adjuvant trials will require the development of intermediate endpoints short of survival to inform clinical decision-making in a timelier manner. A multidisciplinary multinational group of investigators, the Intermediate Clinical Endpoints in Prostate Cancer (ICECaP), has been assembled to explore endpoints that would be recognized by regulatory agencies in early trials. Recent progress in our understanding of the pathogenesis of advanced prostate cancer has heralded a new era in treatment. Numerous agents now populate the treatment landscape, and an impressive number of novel agents are in development. However, many questions remain unanswered, paving the path for discovery in the future.

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REFERENCES


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