been shown to be superior to androgen depletion monotherapies and are no longer recommended. In practice, most patients who are treated with a GnRH agonist receive an antiandrogen for the first 2–4 weeks of treatment to protect against the flare.

Intermittent Androgen Deprivation Therapy (IADT) The use of hormones in an "on-and-off" approach was initially proposed as a way to prevent the selection of cells that are resistant to androgen depletion and to reduce side effects. The hypothesis is that by allowing endogenous testosterone levels to rise, the cells that survive androgen depletion will induce a normal differentiation pathway. It is postulated that by allowing the surviving cells to proliferate in the presence of androgen, sensitivity to subsequent androgen depletion will be retained and the chance of developing a castration-resistant state will be reduced. Applied in the clinic, androgen depletion is continued for 2–6 months beyond the point of maximal response. Once treatment is stopped, endogenous testosterone levels increase, and the symptoms associated with hormone treatment abate. PSA levels also begin to rise, and at some level, treatment is restarted. With this approach, multiple cycles of regression and proliferation have been documented in individual patients. It is unknown whether the intermittent approach increases, decreases, or does not change the overall duration of sensitivity to androgen depletion. The approach is safe, but long-term data are needed to assess the course in men with low PSA levels. A randomized trial showed similar survival time between patients treated with intermittent versus continuous treatment, with a slightly higher risk of prostate cancer–specific mortality in the intermittent group, and higher cardiovascular mortality in patients on continuous therapy. The intermittent therapy was better tolerated.

Outcomes of Androgen Depletion The anti–prostate cancer effects of the various androgen depletion/blockade strategies are similar, and the outcomes predictable: an initial response, then a period of stability in which tumor cells are dormant and nonproliferative, followed after a variable period of time by a rise in PSA and tumor regrowth as a castration-resistant lesion that for most men is invariably lethal. Androgen depletion is not curative because cells that survive castration are present when the disease is first diagnosed. Considered by disease manifestation, PSA levels return to normal in 60–70% of cases, and measurable lesions regress in about 50%; improvements in bone scan occur in 25% of cases, but the majority of cases remain stable. The duration of response and survival is inversely proportional to disease extent at the time androgen depletion is first started, whereas the degree of PSA decline at 6 months has been shown to be prognostic. In a large-scale trial, PSA nadir proved prognostic.

An active question is whether hormones should be given in the adjuvant setting after surgery or radiation treatment of the primary tumor or whether to wait until PSA recurrence, metastatic disease, or symptoms are documented. Trials in support of early therapy have often been underpowered relative to the reported benefit or have been criticized on methodologic grounds. One trial showing a survival benefit for patients treated with radiation therapy and 3 years of androgen depletion, relative to radiation alone, was criticized for the poor outcomes of the control group. Another showing a survival benefit for patients with positive lymph nodes who were randomized to immediate medical or surgical castration compared to observation ($p = .02$) was criticized because the confidence intervals around the 5- and 8-year survival distributions for the two groups overlapped. A large randomized study comparing early to late hormone treatment (orchiectomy or GnRH analogue) in patients with locally advanced or asymptomatic metastatic disease showed that patients treated early were less likely to progress from M0 to M1 disease, to develop pain, and to die of prostate cancer. This trial was criticized because therapy was delayed "too long" in the late-treatment group. Noteworthy is that the American Society of Clinical Oncology Guidelines recommend deferring treatment until the disease has recurred and the prognosis has been reassessed. These guidelines do not support immediate therapy.

METASTATIC DISEASE: CASTRATE

Castration-resistant prostate cancer (CRPC) is defined as disease that progresses despite androgen suppression by medical or surgical therapies where the measured levels of testosterone are 50 ng/mL or lower. The rise in PSA indicates continued signaling through the AR signaling axis, the result of a series of oncogenic changes that include overexpression of androgen biosynthetic enzymes that can lead to increased intratumoral androgens, and overexpression of the receptor itself that enables signaling to occur even in the setting of low levels of androgen. The majority of CRPC cases are not "hormone-refractory," and considering them as such can deny patients safe and effective treatment. CRPC can manifest in many ways. For some, it is a rise in PSA with no change in radiographs and no new symptoms. In others, it is a rising PSA and progression in bone with or without symptoms of disease. Still others will show soft tissue disease with or without osseous metastases, and others have visceral spread.

For the individual patient, it is first essential to ensure that a castrate status be documented. Patients receiving an antiandrogen alone, whose serum testosterone levels are elevated, should be treated first with a GnRH analogue or orchiectomy and observed for response. Patients on an antiandrogen in combination with a GnRH analogue should have the antiandrogen discontinued, because approximately 20% will respond to the selective discontinuation of the antiandrogen.

Chemotherapy and New Agents Through 2009, docetaxel was the only systemic therapy proven to prolong life. As a single agent, the drug produced PSA declines in 50% of patients, measurable disease regression in 25%, and improvement in both preexisting pain and prevention of future cancer-related pain. Since then, six agents with diverse mechanisms of action that target the tumor itself or other aspects of the metastatic process have been proven to prolong life and were FDA approved. The first was sipuleucel-T, the first biologic approach shown to prolong life in which antigen-presenting cells are activated ex vivo, pulsed with antigen, and reinfused. The second, cabazitaxel, a non–cross-resistant taxane, was shown to be superior to mitoxantrone in the post-docetaxel setting. This was followed by the CYP17 inhibitor abiraterone acetate, which lowers androgen levels in the tumor, adrenal glands, and testis, and the next-generation antiandrogen enzalutamide, which not only has a higher binding affinity to the AR relative to first-generation compounds, but uniquely inhibits nuclear location and DNA binding of the receptor complex. Both abiraterone acetate and enzalutamide were first approved for postchemotherapy treated patients on the basis of placebo-controlled phase III trials—a further indication that these tumors are not uniformly hormone-refractory. The indication for abiraterone acetate was later expanded to the prechemotherapy setting, based on a second trial using a co-primary endpoint of radiographic progression–free survival and overall survival. Similar results were seen with enzalutamide, for which an expanded indication is also anticipated. Alpharadin (radium-223 chloride), an alpha-emitting bone-seeking radioisotope, has been shown to prolong life in patients with symptoms related to osseous disease. The alpharadin result validated the bone microenvironment as a therapeutic target independent of direct effects on the tumor itself, as no declines in PSA were observed in the trial. Notable is that in addition to a survival benefit, the drug also reduced the development of significant skeletal events.

Other bone-targeted agents, such as the bisphosphonates and the RANK ligand inhibitor denosumab, protect against bone loss associated with androgen depletion and also reduce skeletal-related events by targeting bone osteoclasts. In one trial, denosumab was shown to be superior to zoledronic acid with respect to skeletal-related events, but had a slightly higher frequency of osteonecrosis of the jaw.

In clinical practice, most men seek to avoid chemotherapy and are first treated with a biologic agent and/or newer hormonal agent approved for this indication. It is crucial to the management of the individual patient to define therapeutic objectives before initiating treatment, as there are defined standards of care for different