Prostate cancer continues to be a global health issue with more than 700,000 men diagnosed worldwide every year, including more than 200,000 in the U.S. Unfortunately, despite early detection and improved treatment, more than 25,000 men will die of prostate cancer in the U.S. this year. Metastases to the bone occur in more than 90% of advanced prostate cancer patients and approximately 40% experience soft-tissue lesions.
Prostate cancer is hormone-sensitive at the time of initial diagnosis. Most advanced-disease patients respond to conventional androgen deprivation with castration, either medical or surgical. The duration of disease control with castration is 18 to 24 months with an overall survival of 30 to 36 months. The terms hormone-refractory prostate cancer (HRPC) and androgen-independent prostate cancer (AIPC) are commonly used to describe patients whose disease progresses after castration.

There are several new agents in development to treat prostate cancer resistant to initial castration. In the castrate state, ligands to the androgen receptor are derived predominantly from the adrenal glands. Approximately 10% of circulating testosterone remains after androgen-deprivation therapy due to the peripheral conversion of adrenal steroids. The need to suppress androgen production in the adrenal glands and at tissue levels persists in HRPC/AIPC.

Chemotherapeutic docetaxel has received U.S. Food and Drug Administration (FDA) approval for improving survival in HRPC patients, although that benefit has been modest. No second-line hormonal therapies have been FDA-approved as their efficacies have been limited.

**Abiraterone (CB7598)** is a steroidal irreversible inhibitor of CYP17 (17 alpha hydroxylase/17, 20 lyase), thus blocking two important enzymatic activities in the synthesis of testosterone. **Abiraterone acetate (CB7630)** is a pro-drug of abiraterone and is rapidly converted after oral administration. Activity was seen in phase 1 and 2 trials as manifested by both durable prostate-specific antigen (PSA) declines and objective responses. Side effects have included hypertension, hypokalemia, and lower extremity edema, all consistent with abiraterone’s mechanism of action. Doses explored ranged from 250 mg to 2,000 mg, and 1,000 mg has been selected for a phase 2 trial after demonstrating consistent pharmacologic effects without additional side effects.

Abiraterone’s results in 52 chemotherapy-naive HRPC patients reveal more than 60% of patients with PSA declines of more than 50%, and 25% with declines of more than 90%. Objective responses were documented in 12 of 21 patients.

In the postchemotherapy (docetaxel) group, two phase 2 studies have been conducted with one-half of the patients achieving a greater than 50% PSA decline lasting a median of 24 weeks.

A randomized phase 3, double-blind, placebo-controlled study of abiraterone/prednisone vs. placebo/prednisone (2:1) in more than 800 patients has recently finished accrual. A similar phase 3 trial in patients not thought to need chemotherapy yet is in the midst of accrual.

Another compound, MDV3100, is a novel small-molecule androgen receptor that binds more tightly to the androgen receptor (AR) than bicalutamide. Unlike bicalutamide, MDV3100 inhibits AR function by blocking nuclear translocation of the AR and DNA binding. To date, 140 HRPC patients have been treated with MDV3100. The initial results are encouraging with PSA declines of more than 50% documented in 62% of chemotherapy-naive patients and 51% of chemotherapy-treated patients, with median time to progression in excess of 200 days for both groups. A dose of 240 mg per day is the maximum tolerated dose, and the most common toxicity is fatigue. A phase 3 randomized 2:1, double-blind, placebo-controlled trial of MDV3100 at 160 mg per day vs. placebo in more than 1,000 patients is under way.

Also in this class of innovative hormone therapies is **TAK-700**, an orally
active, potent nonsteroidal inhibitor of 17, 20 lyase. Initial phase 1/2 safety and efficacy trials are under way in prostate cancer.

The addition of biologic therapy to chemotherapy remains of interest. Studies of bevacizumab and docetaxel in high-risk, neoadjuvant prostate patients reveal encouraging activity. Magnetic resonance imaging of the prostate showed median tumor size decreases of 45%; 39% of patients were considered to have PRs.

**AT-101** is an oral pan-Bcl-2 inhibitor with single-agent activity in HRPC. When given in combination with docetaxel and prednisone, 24 of 36 patients met PR criteria with a more than 50% decline in PSA. In addition, nine of 19 patients with measurable disease had PRs per Response Evaluation Criteria in Solid Tumors (RECIST). Phase 3 studies of the combination are now under way.

The anti-interleukin (IL)-6 monoclonal antibody CNT0328 has been studied with docetaxel, and more than 50% of patients had responses by PSA; plus three of 12 patients with measurable disease had PRs. Fatigue was the predominant toxicity attributed to the combination.

Several chemotherapeutics are being evaluated in docetaxel-resistant HRPC. Specifically the epothilones, **Ixabepilone** and **sagopilone** are two agents in this class with demonstrated phase 2 activity manifested by both PSA declines and soft-tissue shrinkage. Further trials are under way to explore the advantages of these agents, which are less affected by the multidrug resistance cellular pumps.

A novel approach to the treatment of advanced prostate cancer is being developed by Dendreon Corporation, a Seattle biotechnology company. Dendreon has filed for FDA approval of the first so-called therapeutic cancer vaccine, **Provenge**. Provenge does not aim to prevent disease like childhood vaccines. Instead, Provenge is designed to train the body’s immune system to attack the cancer once the patient has already developed the disease. Provenge is produced by taking cells from a patient’s tumor, incorporating them into an individualized vaccine, then returning them to a physician to be injected back into the patient. Active treatment consists of three injections of Provenge given over the course of one month. Investigators reported last April that in a phase 3 study of 512 patients with advanced prostate cancer, Provenge extended survival by 4.1 months. The most common side effects were flulike symptoms for a day or two after treatment, less harsh than those from chemotherapy. A decision on the FDA approval is expected in the first half of 2010.

Supportive care for the prostate patient must be remembered. The bisphosphonates have been shown to decrease fractures and improve bone health. **Denosumab**, a fully human monoclonal antibody against RANK ligand, improves bone mineral density and decreases fractures. Placebo-controlled studies and evaluations in comparison to bisphosphonates are under way.

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