

Second-line Chemotherapy for Advanced Hormone-refractory Prostate Cancer

Edward G. Garmey, MD, Oliver Sartor, MD, Susan Halabi, PhD, and Nicholas J. Vogelzang, MD

Dr. Garmey is Vice President for Clinical Development, Arqule Inc., in Woburn, Mass. Dr. Sartor is Professor in the Section of Hematology/Oncology at Tulane Medical School in New Orleans, La. Dr. Halabi is Associate Professor of Biostatistics and Bioinformatics and Associate Professor of Surgery at Duke University Medical Center in Durham, NC. Dr. Vogelzang is Director, Nevada Cancer Institute, in Las Vegas, Nev.

Address correspondence to:
Dr. Edward Garmey
Vice President for Clinical
Development
Arqule Inc.
19 Presidential Way
Woburn, MA 01801-5140
E-mail: egarmey@yahoo.com.

Abstract: Prostate cancer is the most common cancer occurring among men in the United States. In spite of the disease's favorable prognosis, approximately 30,000 U.S. men develop incurable metastatic disease each year, making prostate cancer the second-leading cause of cancer-related deaths among men in the United States. Although hormone-based therapies generally result in rapid responses, virtually all patients ultimately develop androgen-independent progressive disease. It is among these men with hormone-refractory prostate cancer (HRPC) that the role of chemotherapy continues to be investigated. To date, three drugs (estramustine, mitoxantrone, and docetaxel) have been approved by the US Food and Drug Administration (FDA) for first-line chemotherapy in HRPC, with other agents and combinations now under evaluation in ongoing clinical trials. Patients whose tumors progress through first-line chemotherapy have limited treatment options available to them and less than half of all men with HRPC will receive any second-line chemotherapy. To date, only one phase III randomized clinical trial has been completed in this setting and no therapies are FDA-approved. We review here the entirety of phase II and III data evaluating chemotherapy agents in second-line HRPC.

Background

Carcinoma of the prostate is the most common cancer to occur among men in the United States, with greater than 218,000 new cases estimated to have occurred in 2007 alone.¹ Prostate cancer primarily affects older men, with a median age at the time diagnosis in the United States of 68 years.¹ It is a highly curable disease when diagnosed early: according to recent Surveillance, Epidemiology, End Results (SEER) data, greater than 80% of U.S. men diagnosed with prostate cancer will remain alive at 5 years following diagnosis.¹ Indeed, the vast majority of men diagnosed with prostate cancer worldwide will die of nonprostate cancer-related

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causes. Nevertheless, a subpopulation of men diagnosed with prostate cancer (estimated at approximately 30,000 each year in the United States) will go on to develop metastases and ultimately die as a result of advanced disease.¹ Because of this, and its high relative incidence, prostate cancer represents the second-leading cause of cancer-related deaths among men in the United States.

Treatments for Metastatic Prostate Cancer

Hormone-mediated therapies, including orchiectomy and luteinizing hormone-releasing hormone, are commonly employed and effective in the initial treatment of metastatic prostate cancer. These forms of therapy, often termed androgen deprivation therapies (ADTs) result in castrate levels of testosterone (<50 ng/dl). Androgen deprivation, pioneered by Charles Huggins in 1941, generally results in rapid and demonstrable responses, including notable improvements in bone pain, regression of soft-tissue metastases, and declines in serum prostate-specific antigen (PSA) levels. In spite of these dramatic responses, however, ADTs do not represent a cure for metastatic prostate cancer: virtually all affected patients will ultimately develop androgen-independent disease and progress. Such progressions herald the onset of what is variably referred to as hormone-refractory prostate cancer (HRPC; used in this article), androgen-independent prostate cancer, or castrate-refractory prostate cancer.

Carefully analyzed studies of metastatic patients treated with ADT indicate that median progression-free survival is approximately 18 months after initiation of therapy; overall survival is approximately 30 months.² Hussain and colleagues recently presented data demonstrating that, among patients receiving ADTs who do not experience a decline in PSA level after 7 months of therapy to 4 ng/mL or lower, median survival is only 13 months.³

Treatment and Prognosis of HRPC

At present, there exists no curative treatment for HRPC. Therapies available to men with HRPC are limited and tend to vary widely, not only between countries but across competing centers and practices. The list of such therapies includes: secondary hormonal manipulations such as anti-androgens, ketoconazole, estrogens or glucocorticoids; bisphosphonates, external-beam radiotherapy, intravenous radioisotopes, chemotherapy, and/or supportive care. Choice of therapy and prognosis in HRPC will often be dictated by a variety of factors including whether or not the patient has radiographic evidence of metastatic disease. Of note in this regard is that the American Society of Clinical Oncology (ASCO) recently endorsed the Cancer Care Ontario (CCO) Guideline on Non-Hormonal

Therapy for Men With Metastatic Hormone-Refractory Prostate Cancer.⁴ This CCO guideline complements previous CCO guidelines on radiopharmaceuticals and bisphosphonates in men with metastatic hormone-refractory prostate cancer.

Regarding prognosis, in a retrospective study of HRPC patients without radiographic evidence of metastatic disease, survival following a post-ADT PSA rise was reported to be 68 months.⁵ Prospective trials in this setting have not to date been reported in a peer-reviewed fashion; however, results from a cooperative group sponsored trial evaluating anti-androgen withdrawal revealed 40-month survival for nonmetastatic HRPC patients.⁶ Evaluating HRPC patients with radiographically detectable metastatic disease treated with sequential anti-androgen withdrawal and ketoconazole, Small and colleagues reported that median survival was 17 months.⁷ Interestingly in this latter study, dramatic differences were noted between patients with and without a 50% decline in PSA level (using a landmark analysis at 4 weeks): men without such a decline survived for a median of 15 months, whereas those men with a decline survived for a median of 41 months.

First-line Chemotherapy for HRPC

Three drugs have been approved by the U.S. Food and Drug Administration (FDA) for first-line chemotherapy in HRPC. These include:

Estramustine Estramustine, which disrupts microtubule-associated proteins in vitro, was approved in 1981 for the “palliative treatment of patients with metastatic and/or progressive carcinoma of the prostate.”⁸ Though this agent demonstrates no isolated impact on the rates of progression or survival associated with HRPC, some studies indicate a synergistic activity with docetaxel.

Mitoxantrone Mitoxantrone (Novantrone, OSI Oncology), a type II topoisomerase inhibitor that disrupts DNA synthesis and DNA repair, was approved (in combination with corticosteroids) in 1996 for “use in combination with corticosteroids as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.”⁸ Mitoxantrone’s approval was based on results from two multicenter, randomized studies demonstrating the efficacy of this drug (given in combination with low-dose prednisone) to relieve pain and improve quality of life compared to prednisone alone. Important to note, however, is that neither of these trials, or any subsequent trial of mitoxantrone, demonstrated a statistically significant impact on overall survival among men with HRPC.

Table 1. Active Phase III Trials in First-line Chemotherapy for Hormone-refractory Prostate Cancer

| Trial | ClinicalTrials.gov Identifier | Timeline and Accrual |
|--|-------------------------------|--|
| A Randomized Double-Blinded Placebo Controlled Phase III Trial Comparing Docetaxel and Prednisone With and Without Bevacizumab In Men With Hormone Refractory Prostate Cancer (CALGB 90401) | NCT00110214 | This trial was initiated in April, 2005, and completed its accrual of 1,050 patients on December 21, 2007. |
| A Phase 3, Randomized, Open-Label Study Evaluating DN-101 in Combination With Docetaxel in Androgen-Independent Prostate Cancer (AIPC) (ASCENT-2) | NCT00273338 | This trial was initiated in January, 2006 and has recently been discontinued by its sponsor due to inferior survival experienced by DN-101 recipients reported by the study's DSMB on 11/5/07. |
| A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Prednisone in Patients With Metastatic Hormone-Refractory Prostate Cancer Who Are Chemotherapy-Naive | NCT00089856 | This trial of the GVAX vaccine products was initiated in July, 2004, and is projected to accrue 600 total patients. |
| A Phase III Randomized, Open-Label Study of Docetaxel in Combination With CG1940 and CG8711 Versus Docetaxel and Prednisone in Taxane-Naive Patients With Metastatic Hormone-Refractory Prostate Cancer With Pain | NCT00133224 | This trial was initiated in July, 2005, and is anticipated to accrue 600 total patients. |
| A Phase III Study of Docetaxel and Atrasentan Versus Docetaxel and Placebo for Patients With Advanced Hormone Refractory Prostate Cancer (SWOG 0421) | NCT00134056 | This trial was initiated in August, 2006, and is anticipated to accrue 930 total patients. |
| A Randomized, Double Blind, Placebo Controlled Phase 3 Trial of Immunotherapy With Autologous Antigen Presenting Cells Loading With PA2024 (Provenge) in Men With Metastatic Androgen Independent Prostatic Adenocarcinoma | NCT00065442 | This trial was initiated in July, 2003, and is projected to accrue 500 total patients. |

Docetaxel Docetaxel (Taxotere, Sanofi-Avenis), a semi-synthetic analog of paclitaxel (Taxol, Ortho Biotech) that binds to microtubules reversibly with high affinity, was approved in 2004 by the FDA (and subsequently the European Agency for the Evaluation of Medicinal Products [EMA]) for “use in combination with prednisone as a treatment for patients with androgen independent metastatic prostate cancer.”⁸ Docetaxel’s approval was based on the results of a large pivotal phase III clinical trial (TAX 327) that compared docetaxel (given in combination with prednisone and administered either every three weeks or weekly) to mitoxantrone and prednisone. For the primary endpoint of survival, docetaxel given every three weeks was statistically superior to mitoxantrone (medians of 18.9 months and 16.5 months respectively).⁹ Furthermore, docetaxel demonstrated statistically-significant elevations in the rates of pain reduction and PSA response (reduction in PSA level from baseline $\geq 50\%$) compared to mitoxantrone.

These data were substantiated by a parallel trial, Southwest Oncology Group (SWOG) 9916, that compared the combination of docetaxel and estramustine

(administered every 3 weeks) to a similar schedule of mitoxantrone and prednisone. Here, median overall survival again favored patients receiving docetaxel, with medians of 17.5 months versus 15.6 months respectively and an unadjusted hazard ratio for death of 0.80 (95% confidence interval [CI], 0.67 to 0.97).¹⁰ Statistically significant increases in rates of PSA response and objective tumor response were reported as well among men receiving docetaxel and estramustine.

Despite these survival differences, it is clear now that docetaxel is not a cure for HRPC. The mortality rate among men with HRPC was essentially 100% for both of the above-referenced trials. In the SWOG trial (the only one of the two trials in which progression data were published), median progression-free survival was 6.3 months among patients receiving docetaxel compared to 3.2 months among patients receiving mitoxantrone.¹⁰

Active Trials in First-line Chemotherapy for HRPC

A number of agents are now being evaluated in phase III trials for the first-line treatment of HRPC. These agents and their respective trials are included in Table 1.

Second-line Chemotherapy for HRPC

Patients whose tumors progress through first-line chemotherapy have limited treatment options available to them. Market research demonstrates that less than half of men in the United States with HRPC will receive any second-line chemotherapy. Unfortunately, progress toward the identification, evaluation, and approval of candidate agents has been sluggish. Indeed, to date, only one phase III randomized clinical trial has been completed in this setting and no drugs are yet FDA-approved for the indication.

Following below is a description of results from phase II and III investigations performed to date to evaluate nonhormonally mediated second-line chemotherapy interventions in HRPC progressing through frontline chemotherapy.

Phase II Clinical Trials

Alkylating Agents At the ASCO 2007 meeting, Nelius and colleagues reported on phase II data describing the use of second-line cyclophosphamide therapy (administered together with dexamethasone in a metronomic manner) for men with metastatic HRPC progressing through prior docetaxel therapy. Seventeen patients with a median age of 68 years were enrolled. Median PSA at baseline was 134 ng/mL (range, 46–6,554). Of these patients, 4 demonstrated a PSA response (ie, $\geq 50\%$ decrease), an additional 5 patients demonstrated PSA declines less than 50%, and 8 demonstrated PSA progression. Of patients experiencing PSA declines, median time to maximum decline was 12 weeks (range, 4–36). Median time-to-progression and survival were 24 and 60 weeks respectively among patients experiencing PSA declines and 4 weeks each among patients with PSA progression. No grade 3 or 4 toxicities were reported.¹¹

Anthracycline-based Combinations At the ASCO 2006 meeting, Zhong and associates reported on their experience with the combination of epirubicin, estramustine, and celecoxib (Celebrex, Pfizer) in docetaxel-pretreated patients. Thirteen patients with a median age of 71.5 years and receiving a median of four treatment cycles were evaluable for efficacy and safety. Six patients had stable disease and 2 patients experienced a complete response (based on Response Evaluation Criteria in Solid Tumors [RECIST]). Nine patients (69%) experienced a PSA response. Overall, the median survival time was 441 days (range, 10–995) and there occurred five serious adverse events (1 each of DVT, diarrhea, bowel obstruction, cord compression, and myocardial infarction). No nephrotoxicity or cardiomyopathies were noted.¹²

Mitoxantrone Multiple phase II studies evaluating mitoxantrone therapy as a control arm in the setting of second-line HRPC are cited below.

Taxanes Three phase II trials to date evaluated docetaxel monotherapy in second-line therapy for HRPC. In the first of these trials, published by Joshua and colleagues in 2005, 20 men with tumors progressing through frontline mitoxantrone therapy were treated with weekly docetaxel (40 mg/m²/week given 3 of every 4 weeks) until tumor progression or the onset of prohibitive toxicity. Nine of 20 patients (45%) experienced a PSA response maintained for at least 1 month. Median time to progression was 5 months (range, 0–13) and median survival time was 13 months (range, 1–24). Median survival time from the initiation of frontline mitoxantrone was 19 months. Men with a previous PSA response to mitoxantrone were no more likely to respond to docetaxel. Therapy was generally well-tolerated: 2 of 20 patients experienced grade 3 diarrhea and 6 of 20 patients experienced grade 3–4 hematologic toxicities.¹³

In an article published in 2006, Rosenberg and colleagues evaluated retrospectively the records of men with HRPC who were treated on a randomized frontline phase II trial of ixabepilone (Ixempra, Bristol-Myers Squibb) with or without estramustine and who subsequently received second-line taxane therapy. Among men they evaluated, PSA responses were experienced by 51% of all second-line patients (95% CI, 33–66%) and by 61% of patients who experienced a previous response with frontline ixabepilone (95% CI, 42–78%). Though patients with ixabepilone-refractory disease (those who experienced no PSA response) were less likely to respond to second-line taxane therapy, in fact 36% of these patients were still able to achieve a second-line PSA response.¹⁴

Finally, in 2006, Michels and colleagues published their findings from a study of 68 men with HRPC who received frontline and second-line therapy with docetaxel and mitoxantrone (in either sequence). Of these men, 35 received docetaxel followed by mitoxantrone and 33 received mitoxantrone followed by docetaxel. Patients who received frontline docetaxel demonstrated a trend toward longer median survival when compared to men treated with frontline mitoxantrone: 22 months (95% CI, 17.2–26.8) versus 15 months (95% CI, 10.4–19.6). In both groups, the median number of second-line chemotherapy cycles was three and median progression-free survival fell between 2 and 3 months. Second-line docetaxel led to a higher rate of PSA response compared to second-line mitoxantrone (38% vs 12%; $P=.012$). Of cautionary interest, both second-line docetaxel and second-line mitoxantrone therapy were associated with significant levels of treatment-related adverse events and

concomitantly high rates of required dose reductions, dose delays, or dose discontinuations (64% and 46% of patients, respectively).¹⁵

Taxane-Platinum Combinations Two recent abstracts described phase II evaluations of docetaxel-platinum combinations in the second-line treatment of HRPC. The first of these, presented at ASCO 2006 by Feinstein and colleagues, was a phase II evaluation of docetaxel and oxaliplatin (Eloxatin, Sanofi-Aventis) in men previously treated with up to two prior chemotherapy regimens. Only 6 chemotherapy-pretreated patients receiving docetaxel (60 mg/m²) and oxaliplatin (110 mg/m²) every 21 days could be evaluated. These men had an average pretreatment PSA of 1,194.4, with 3 of the 6 patients subsequently experiencing a PSA response and 1 additional patient experiencing a more than 25% reduction in PSA level. Four of 6 men demonstrated a partial response of their soft-tissue disease. Overall, 6% of men experienced grade 3 or 4 adverse events and all-level treatment-related events included: neutropenia (41% of patients), thrombocytopenia (11.8%) and anemia (5.9%). Nonhematologic toxicities observed included neuropathy (53% of patients) diarrhea (47%), nausea (41%), fatigue (76%), and anorexia (29.4%).¹⁶

More recently, Oh and colleagues reported at the 2007 Prostate Cancer Symposium results from their phase II evaluation of docetaxel and carboplatin in HRPC progressing through a minimum of two cycles of prior docetaxel monotherapy. Here, 34 patients with a median age of 68 years (range, 47–81 years) were treated for a median of four cycles (range, 1–12) with the two-drug combination. PSA response was noted in 6 of 34 patients (18%), with a median duration of PSA response (among responders) of 7.4 months. Of 21 patients with measurable disease at baseline, 3 patients experienced a confirmed partial response with an additional 10 patients experiencing stable disease for a minimum of 2 months. Median time to progression was 4.3 months (95% CI, 2.3–5.6) and median overall survival was 12.4 months (95% CI, 7.0–17.0). No treatment-related deaths were observed and toxicities, mostly grade 1 and 2, included anemia, leukopenia and hyperglycemia.¹⁷

Other Platinum-based Combinations At ASCO 2007, Loriot and colleagues reported phase II data describing the use of a carboplatin and etoposide combination in docetaxel pretreated men with HRPC. Forty-one patients previously treated with docetaxel administered both with (n=24) and without (n=17) estramustine were enrolled. Overall, a PSA response was observed in nine patients (22%). Pain relief (as measured by a visual analog scale) was observed in 18 patients (45%). Median progression-free survival and overall survival were 9 weeks and 19

months, respectively. Grade 3–4 toxicities included anemia (observed in 25% of patients) and febrile neutropenia (observed in 2% of patients).¹⁸

Vinca Alkaloids At ASCO 2006, Silva and colleagues reported phase II results describing the use of intravenous vinorelbine for men with HRPC. Previous chemotherapy was allowed if it had been discontinued at least 6 months prior to enrollment. Prior therapy was received by 38 of 44 enrolled patients: 19 patients received one prior regimen and 19 patients received two prior regimens. Mean age among all patients was 71 years (95% CI, 45–80) and median PSA level at enrollment was 286 ng/mL (range, 38–950). These patients received a mean of nine cycles of therapy (range, 3–44), with a median follow-up time of 13 months. A PSA response was observed in 7 of 44 patients, with an additional 17 of 44 patients (39%) maintaining stable PSAs and 13 of 44 patients (29%) experiencing PSA progressions. The average duration of PSA response and the average time to PSA progression were each 7 months. No grade 3 or higher toxicities were reported.¹⁹

At ASCO 2007, Sewak and colleagues reported data from their phase II study evaluating the use of vinorelbine, given in combination with paclitaxel, for men with HRPC. This study included but was not limited to men whose tumors progressed through prior cytotoxic chemotherapy, thus confounding the interpretation of the data. Thirty patients with a median age of 70.5 and mean PSA at enrollment of 413 ng/mL were enrolled. Of these patients, 20% experienced a PSA response and 63% maintained stable disease for at least 4 weeks. Median progression-free survival and overall survival were 5.1 months and 9.7 months, respectively. Observed grade 3 and 4 toxicities included neutropenia (seen in 8% of patients), anemia (3%), infection (2%), and lethargy (1%). One patient died of neutropenic sepsis.²⁰

Experimental Agents and Combinations—Abiraterone Acetate Abiraterone acetate (CB7630, Cougar) inhibits 17 α -hydroxylase and C17,20-lyase and is demonstrated to decrease serum androgen to undetectable levels. HRPC progressing through ADTs continue to express androgen receptors and are dependent on signaling through these receptors for their growth. It is hypothesized that further reducing androgen hormone production can decrease endocrine and autocrine effects on prostate cancer cells. In an abstract presented at the 2007 Chemotherapy Foundation Symposium, Danila and colleagues reported on their evaluation of abiraterone acetate in patients with HRPC progressing through first-line chemotherapy with docetaxel-based regimens. They described enrollment to date of 44 patients with a median age of 72 years
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(range, 63–78 years) and median PSA at enrollment of 92.01 ng/mL (range, 31.62–323.55). Data were presented on 10 patients who were followed for a minimum of 12 weeks: among these patients, 4 (40%) experienced a sustained PSA response and 4 (40%) discontinued treatment due to biochemical (1 patient), radiographic (2), or symptomatic (1) progression of their disease. One of 5 patients with evaluable radiographic data experienced a partial response based on RECIST criteria. The adverse event profile was described as minimal.²¹

Ixabepilone Ixabepilone is a semisynthetic analog of epothilone B that binds to tubulin and therein promotes tubulin polymerization and microtubule stabilization, leading in turn to the arrest of cells in the G2-M phase of the cell cycle and tumor cell apoptosis. Ixabepilone has previously been observed to exert antineoplastic activity in taxane-resistant cell lines. Recently, Rosenberg and colleagues published data from a randomized, noncomparative, open-label clinical trial that evaluated the second-line use of either ixabepilone or mitoxantrone (given in combination with prednisone) for men with HRPC progressing through first-line chemotherapy. Forty-one patients were accrued into each arm with a median of three treatment cycles administered in both groups. Median survival was 10.4 months among men treated with ixabepilone and 9.8 months among men treated with mitoxantrone. A PSA response was observed in 17% of men treated with ixabepilone (95% CI, 7–32) and 20% of men treated with mitoxantrone (95% CI, 9–35). Of note, an exploratory analysis performed by the authors revealed that, across treatment groups, there occurred a significantly increased response to second-line therapy among those patients who previously responded to taxane therapy. Specifically, among patients with a prior PSA response to frontline taxane therapy, 36% (95% CI, 13–65) achieved a response with second-line ixabepilone and 35% (95% CI, 5–59) achieved a response with mitoxantrone. Finally, partial responses based on RECIST criteria were observed in 1 of 24 evaluable ixabepilone patients and 2 of 21 evaluable mitoxantrone patients.

The most common grade 3–4 toxicity associated with second-line therapy in this trial was neutropenia, observed in 54% of ixabepilone patients and 63% of mitoxantrone patients, respectively. Febrile neutropenia and neutropenic infection occurred in 4 patients treated with mitoxantrone and 3 patients treated with ixabepilone (including 1 patient who died from neutropenic sepsis). Treatment-related nonhematologic toxicities were observed in 5% of patients treated with ixabepilone (including anorexia, stomatitis, fatigue, muscle weakness, and prolonged pro-

thrombin time) and 5% of patients treated with mitoxantrone (including prolonged prothrombin time and liver function abnormalities). Dose reductions or dose delays were required in 20 of 41 ixabepilone patients and 10 of 41 mitoxantrone patients.²²

Irofulven/Capecitabine At ASCO 2006, Hart and colleagues presented data from their phase II study evaluating irofulven, given in combination with either prednisone (IP) or capecitabine (Xeloda, Roche; IC). These combinations were compared to results with mitoxantrone and prednisone (MP) in the treatment of docetaxel-pretreated men with HRPC. Irofulven is a semisynthetic derivative of the natural product illudinin S and acts as a DNA binding agent. For its part, capecitabine is a prodrug that is enzymatically converted to 5-fluorouracil where it subsequently inhibits DNA synthesis. Seventy-eight patients with median ages of 69, 70, and 61 years were randomized to IP, IC, or MP and treated subsequently with a minimum of five months of therapy. Among these patients, partial responses were observed in 2 of 31 IP patients (6%), 6 of 31 IC patients (19%), and 0 of 16 MP patients. Stable disease lasting greater than 12 weeks was observed in 12 of 31 IP patients (39%), 13 of 31 IC patients (42%), and 10 of 16 MP patients (62%). PSA response was noted in 2 of 31 IP patients (6%), 5 of 31 IC patients (16%), and 0 of 16 patients MP patients. Finally, time-to-progression was 2.1 months (IP), 2.1 months (IC), and 1.1 months (MP) respectively. Of 65 patients evaluated for safety, the most commonly-observed grade 3–4 toxicities were neutropenia (10% of IP patients, 6% of IC patients, and 31% of MP patients, respectively) and thrombocytopenia (15% of IP patients, 12% of IC patients, and no MP patients, respectively).²³

9-Nitrocarnithecine In 2004, Amin and colleagues published results of a Cancer and Leukemia Group B (CALGB) 9901 phase II study which evaluated 9-nitrocarnithecine (9-NC) as second-line chemotherapy for men with metastatic HRPC progressing through at least one prior cytotoxic chemotherapy regimen. 9-NC inhibits the nuclear enzyme topoisomerase I, leading, in turn, to tumor cell apoptosis. Among 33 total patients evaluable for analysis following two cycles of therapy, no PSA responses were observed with a median time to PSA progression of 2 months (95% CI, 0.9–2.8). Seven of 33 patients were noted to have stable disease and median overall survival was 10 months (95% CI, 5–12). Overall, 7 patients were noted to be alive following a median follow-up of 23 months. Based on these results, the authors concluded that further study of 9-NC in the treatment of HRPC is not warranted.²⁴

Pemetrexed At ASCO 2006, Hahn and colleagues presented phase II data describing the use second-line pemetrexed (Alimta, Eli Lilly) in men with HRPc progressing through one prior regimen of taxane-based chemotherapy. Pemetrexed, an antimetabolite compound, inhibits three enzymes employed by cancer cells in purine and pyrimidine synthesis: thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. These authors reported that 21 patients with a median age of 67 years (95% CI, 53–79) and median PSA level at enrollment of 97.8 (95% CI, 0.7–754.3) received a total of 83 treatment cycles with a median of three cycles per patient (95% CI, 0–12). Among these patients, PSA response was observed in 4 of 21 patients (19.0%), stable disease was observed in 8 of 21 patients (38.1%) and progressive disease was observed in 9 of 21 patients (42.9%). PSA responses were maintained for 5, 12, 5, and 3 weeks respectively and stable disease was maintained for 15, 12, 15, 21, 18, and 12 weeks respectively. No survival data were reported. Regarding toxicity, 6 of 21 patients (28.6%) experienced a total of 17 treatment-related grade 3 events, including thrombocytopenia (1 case), anemia (2), mucositis (1), rash (1), and fatigue (1). Three of 21 patients (14.3%) experienced a total of eight grade 4 events, including neutropenia (2 cases), thrombocytopenia (3), anemia (1), and neutropenic fever (1).²⁵

Phase III Clinical Trials

Satraplatin To date, only one phase III randomized clinical trial has been completed in the treatment of second-line HRPc progressing through previous cytotoxic chemotherapy. Now closed to accrual, Satraplatin and Prednisone Against Refractory Cancer (SPARC) was a multinational, double-blind, placebo-controlled trial involving 137 sites worldwide that compared satraplatin (given with daily prednisone and granisetron antiemesis prophylaxis) to prednisone alone in men with HRPc progressing through a minimum of two courses of one prior cytotoxic chemotherapy regimen. Satraplatin is a orally bioavailable third-generation platinum analog with demonstrated in-vitro activity against taxane-resistant cell lines in a variety of tumor types. Although this drug appears to have similar mechanisms of cytotoxicity as cisplatin, it is notable for the relative absence of nephrotoxicity typically associated with the former drug as well as for the absence of neurotoxicities and ototoxicities associated with other platinum agents. Satraplatin's dose-limiting toxicity is dose-dependent and reversible myelosuppression.

The design and initiation of the SPARC trial was based on a previous European Organisation for the Research and Treatment of Cancer-sponsored phase III trial that evaluated satraplatin's use in men with chemotherapy-

naive HRPc. Though this previous trial was terminated prematurely by its sponsor, ad hoc analysis revealed that a PSA response was experienced by 33% of enrolled patients receiving satraplatin plus prednisone (compared to 9% of patients treated with prednisone alone; $P=.046$). In addition, progression-free survival was significantly extended among patients receiving satraplatin plus prednisone: 5.2 months (95% CI, 2.8–13.7) versus 2.5 months (95% CI, 2.1–4.7; $P=.023$).²⁶

Patients in SPARC were randomized in a 2:1 ratio in favor of satraplatin and the study's coprimary endpoints were progression-free survival (PFS) and overall survival. PFS here was measured through a novel composite instrument that included radiographic progression, symptomatic progression (pain, performance status, weight loss, and other clinical events), new skeletal events, or death. Note that PSA progression was not included as a PFS-defining event. For its part, pain was assessed based on average weekly present pain intensity (PPI) and analgesic-use scores. All patients were followed for overall survival and exploratory analyses were performed to assess tumor response (according to RECIST criteria), pain response, and PSA response.

Treatment with satraplatin resulted in a 33% reduction in the overall risk of disease progression (hazard ratio [HR]=0.67; 95% CI, 0.57–0.77; $P<.001$). The effect of satraplatin on PFS appeared to increase over time. At the median PFS, the improvement was 13% (11 vs 9.7 weeks), which extended to an 89% difference at the 75th PFS percentile (36 vs 19 weeks). The rate of pain response was significantly higher in patients who received satraplatin vs. placebo (24.2% vs 13.8%; $P<.005$) as were the rate of PSA response (25.4% vs 12.4%; $P<.001$) and the median time to pain progression (66.1 vs 22.3 weeks; $P<.001$). Finally, the PFS benefits of satraplatin appeared to extend across a variety of patient subgroups and remained statistically significant regardless of prior docetaxel use (vs other frontline chemotherapy agents), age, bisphosphonate use, presence of pain at baseline, or Eastern Cooperative Oncology Group (ECOG) score.

Final survival analysis in the SPARC trial has not yet been presented or published in a scientific setting. However, satraplatin's sponsors, GPC-Biotech AG, Martinsried, Germany, and Pharmion Inc., Boulder, Colo., recently announced via press release that the trial did not achieve the endpoint of overall survival ($P=.80$ in stratified log rank analysis). They reported that median survival was 61.3 weeks for the satraplatin arm compared to 61.4 weeks for the control group with a HR for death of 0.97 (95% CI, 0.83–1.13).

Satraplatin treatment was associated with modest myelosuppression and it was the primary reason for satraplatin dosage reductions (19.7%). Specifically, among

patients treated with satraplatin, grade 3–4 neutropenia occurred in 21.1% of patients, although febrile neutropenia was rare (0.3%). Grade 3–4 thrombocytopenia occurred in 21.1% of patients, although of note is that only 1 case of Grade 4 thrombocytopenia was observed. Finally more red blood cell and platelet transfusions were required among patients receiving satraplatin (16.2% and 4.8%) than placebo (8.0% and 0.3%). Most patients experienced at least one nonhematologic treatment-emergent adverse event (TEAE), with the incidence noted to be higher among patients receiving satraplatin (91.4%) versus placebo (52.9%; $P < .001$). Gastrointestinal events (including constipation, diarrhea, nausea and vomiting) represented the most frequent nonhematologic TEAEs and twice as many patients receiving satraplatin experienced such events (57.9%) versus those receiving placebo (28.1%; $P < .001$). Of note, however, is that few patients treated with satraplatin experienced either Grade 3–4 diarrhea (2.1%) or grade 3–4 vomiting (1.6%).

The PSA results of phase II and III trials in second-line HRPC described above are summarized in Table 2.

Future Directions and Challenges in the Evaluation of Chemotherapy for Advanced Metastatic HRPC

A key priority in the continued and future evaluation of chemotherapy (both first- and second-line chemotherapy) will be the identification of clinical trial endpoints that both satisfy the regulatory requirements for market approval and address the needs of patients living with a debilitating, heterogeneous, and ultimately fatal disease. Specifically, investigators, sponsors, and regulators will need to continue an ongoing conversation on which endpoints can most readily be accepted as valid surrogates of patient survival and/or clinical benefit. A key reference point in this regard will continue to be the “Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” that was released by the FDA in May, 2007.²⁷ However, given the rapid evolution of new cancer therapeutics, it can only be assumed that regulatory guidance will similarly evolve, complicating, in turn, the design, implementation, and interpretation of new trials. Indeed, to quote the above-referenced document:

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations...Although general principles outlined in this guidance should help applicants select endpoints for marketing applica-

tions, we recommend that applicants meet with the FDA before submitting protocols intended to support NDA or BLA marketing applications...Applicants can submit protocols after these meetings and request a special protocol assessment (SPA) that provides confirmation of the acceptability of endpoints and protocol design to support drug marketing applications.²⁷

Specifically, considerable controversy continues to exist surrounding the utility of PSA measurements. Although these measurements remain unrecognized by any regulatory body as a reliable surrogate for ultimate survival in HRPC, they remain the benchmark for the demonstration of efficacy in phase II trials. Furthermore, investigators continue to search in the context of both phase II and phase III trials for the most predictive methods of PSA analysis, including but not limited to competing indices of absolute PSA decrease and rate of PSA decrease. Of note here, analyses of data derived from both the TAX327 and SWOG 9916 databases reveal that, among men participating in those two studies, a PSA decline of at least 30% (in contrast to the more standardly measured decline of $\geq 50\%$) was the optimal PSA-based surrogate for overall survival.^{28,29}

Others investigators are focusing on circulating tumor cells (CTCs) as a surrogate for survival. Moreno and colleagues, for example, recently presented data at ASCO 2007 from a prospective multicenter study evaluating the relationship between the presence of CTCs and overall survival in men treated for HRPC. Among 240 evaluable patients, median survival for 40 patients (19%) with a reduction of CTCs below 5 CTCs/7.5 mL 2–5 weeks following initiation of therapy was significantly longer than median survival for 78 patients (38%) that remained above 5 CTCs/7.5 mL (>20 vs 9.3 months; $P < .0001$). In multivariate analyses, furthermore, which included stage at diagnosis, age, ECOG score, Gleason score, lactate dehydrogenase, alkaline phosphatase, and PSA level, CTCs remained the most significant independent predictor of survival.³⁰

Still other investigators are focusing on the clinical experience of men with HRPC (including both pain responses and the prevention of pain progression) as a potential marker for overall survival. Returning to the TAX327 database, for example, among participants in that trial who experienced a pain response (defined as either a two-point decrease in PPI score without an increase in analgesic score or at least a 50% reduction in analgesic score without an increase in PPI score), overall survival was a median of 18.6 months, and this compared to a median of 12.5 months among those men who did not experience a pain response (HR=0.60; 95% CI, 0.48–0.75).²⁸

Table 2. Clinical Trials Evaluating PSA Response (Decline \geq 50% from Baseline) in Second-line Chemotherapy for Hormone-refractory Prostate Cancer

| Agent(s) | First Author (Publication/Presentation) | n | % Patients PSA Decrease \geq 50% |
|--|--|-----|------------------------------------|
| <i>Phase II Trials</i> | | | |
| Alkylating Agents | | | |
| Cyclophosphamide | Nelius (ASCO, 2007) | 17 | 23.5 |
| Irofulven | Hart (ASCO, 2006) | 31 | 6.5 |
| Irofulven/Capecitabine | Hart (ASCO, 2006) | 31 | 16.1 |
| Anthracyclines | | | |
| Epirubicin | Zhong (ASCO, 2006) | 13 | 69.2 |
| Mitoxantrone | Michels (<i>Cancer</i> , 2006) | 35 | 12.0 |
| Mitoxantrone | Hart (ASCO, 2006) | 16 | 0.0 |
| Mitoxantrone | Rosenberg (<i>Cancer</i> , 2007) | 41 | 19.5 |
| Antimetabolites | | | |
| Pemetrexed | Hahn (ASCO, 2006) | 21 | 19.1 |
| Capecitabine Irofulven | Hart (ASCO, 2006) | 31 | 16.1 |
| Camptothecins | | | |
| 9-Nitrocampthotecin | Amin (<i>Urol Oncol</i> , 2004) | 33 | 0.0 |
| Endocrine/Autocrine | | | |
| Abiraterone (CB7630) | Danila (Chemotherapy Foundation Symposium XXV, 2007) | 10 | 40.0 |
| Epothilones | | | |
| Ixabepilone | Rosenberg (<i>Cancer</i> , 2007) | 41 | 17.1 |
| Taxanes | | | |
| Docetaxel | Joshua (<i>Int Med J</i> , 2005) | 20 | 45.0 |
| Docetaxel | Rosenberg (<i>Cancer</i> , 2005) | 49 | 51.0 |
| Docetaxel | Michels (<i>Cancer</i> , 2006) | 33 | 38.0 |
| Taxane-Platinum Combinations | | | |
| Docetaxel/Oxaliplatin | Feinstein (ASCO, 2006) | 6 | 50.0 |
| Docetaxel/Carboplatin | Oh (ASCO PCS, 2007) | 34 | 17.7 |
| Nontaxane-based Platinum Combinations | | | |
| Carboplatin/Etoposide | Loriot (ASCO, 2007) | 41 | 22.0 |
| Vinca Alkyloids | | | |
| Vinorelbine | Silva (ASCO, 2006) | 38 | 18.4 |
| Vinorelbine/Paclitaxel | Sewak (ASCO, 2007) | 30* | 6.0 |
| <i>Phase III Trials</i> | | | |
| Platinums | | | |
| Satraplatin | Sternberg (ASCO, 2007) | 629 | 25.4 |

ASCO=American Society of Clinical Oncology; PCS=Prostate Cancer Symposium; PSA=prostate-specific antigen.

*Included but not limited to men with tumors progressing through prior cytotoxic chemotherapy.

Attempts to employ a progression endpoint as a surrogate for overall survival in HRPC continues to be challenging because of the heterogeneous nature of the disease. Accordingly, several groups are attempting to examine the predictive utility of composite progression-free survival (PFS) endpoints that incorporate multiple pathways through which HRPC is known to advance. For example, in retrospective analysis presented at ASCO 2007, Halabi and colleagues examined data from nine multicenter HRPC trials conducted by the CALGB between 1991 and 2004, evaluating a composite endpoint based on disease progression (including PSA, bone, or soft tissue progression), weight loss (defined as a $\geq 10\%$ weight decline from baseline) or performance status decline (≥ 1 level), and pain control and opioid analgesic use. If any two of the three progression components were not fulfilled, patients were considered to have experienced a clinical benefit and were placed into a “yes” category. Applying these criteria to the testing dataset, the authors reported median survival times in men who did and did not experience clinical benefit of 20.9 months (95% CI, 18.5–22.8) and 11.1 months (95% CI, 8.9–12.6) respectively (HR=0.52; 95% CI, 0.43–0.63; $P < .001$).³¹ A different but not dissimilar composite PFS endpoint was employed prospectively by investigators in the SPARC trial that was described above, and it is hoped that future analyses will evaluate the utility of this latter endpoint in predicting the survival of patients in that study.

Finally, considerable attention should be paid by investigators and regulators alike to secondary endpoints that address specifically the quality of life and level of pain experienced by men living with advanced HRPC, with such endpoints evaluated not only in the context of their potential correlation with survival but also as indicators in their own right of chemotherapeutic efficacy. This hope derives from our personal experience caring for and interacting with men living with advanced metastatic prostate cancer and having observed the degree of pain and debilitation that is inflicted on these men (and their families) by this disease. This pain was captured in an abstract presented at ASCO 2006 by Moyad and colleagues, which described the results of interviews conducted by these authors with 409 men treated at VA hospitals for HRPC. Of these men, fully 60% described experiencing bone pain “all the time or everyday.” Similarly, 68% of men reported being “very worried about pain,” and 24% said they were “very worried about mental changes” associated with pain. Even more alarming was the described impact of pain on these men’s activities of daily living: because of pain, 50% reported that they “can’t do the things I would like;” 47% said they “need medication to manage pain;” 42% said they “need to rest often;” and 32% reported feeling depression because of pain.³²

It is worth noting here that several therapies not mentioned above were approved based solely on their demonstrated impact on nonsurvival endpoints in advanced metastatic cancer. For example, both radiotherapy and bone-seeking radiopharmaceutical agents are demonstrated to relieve metastatic bone pain.^{33–41} Elsewhere, there exists evidence suggesting that fatigue, another problem cited in the survey results above, may respond to methylphenidate therapy.⁴² And finally, bisphosphonates, although again showing no impact on PFS or survival in men with HRPC, have been demonstrated to reduce the incidence among these men of fractures and other skeletal-related events they are at heightened risk for experiencing.⁴³ Endpoints beyond survival are important to patients with this disease and additional clinical trial designs incorporating endpoints that capture clinical benefit are needed.

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