New drug combinations such as docetaxel and gemcitabine do not appear to increase progression-free or overall survival in patients with castrate-refractory prostate cancer. Advances may be found in the appropriate use of drug combinations that incorporate drugs with unique mechanisms of action, such as dasatinib and abiraterone acetate. Further studies will define the utility of these agents.

**Title:** Multinational, double-blind phase 3 study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial.

**Authors:** Sternberg CN, Petrylak DP, Sartor O, et al.


**Purpose:** Prostate cancer is the second most common malignancy of men worldwide. Docetaxel (Taxotere) was approved in 2004 as first-line therapy for castrate-refractory prostate cancer and is now considered the standard of care. However, all patients will discontinue the drug secondary to disease progression or drug-related toxicity. Presently, there is no second-line therapy that has significantly improved progression-free survival (PFS) or overall survival (OS). Satraplatin is a novel, oral platinum compound that has preclinical activity in prostate cancer. A phase 2 trial demonstrated activity in castrate-refractory prostate cancer with myelosuppression being the dose-limiting toxicity. This phase 3 trial was initiated to determine the efficacy and tolerability of satraplatin in men with castrate-refractory prostate cancer who had progressed following one prior chemotherapy regimen.

**Methods:** Patients with stage D2 (TxNxM1) metastatic adenocarcinoma of the prostate who had progressed following one prior chemotherapy regimen were eligible. Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2, surgical or medical castration (serum testosterone < 50 ng/dl), and adequate end-organ function. Patients were stratified based upon PS (0 or 1 vs. 2) and type of disease progression after prior therapy (tumor progression vs. prostate-specific antigen increase). Patients were randomized 2:1 to receive satraplatin 80 mg/m² or placebo orally once daily on days one through five every 35 days. All patients received prednisone 5 mg orally twice a day on a continuous basis. Crossover between treatment arms was not permitted. The primary endpoints of the study were PFS and OS. Secondary endpoints included time to pain progression (TPP) as defined by an increased present pain intensity (PPI) score of ≥ 1 point from baseline or ≥ 2 points from nadir for ≥ two consecutive weeks, or a more than 25% increase from baseline in weekly average analgesic score for ≥ two consecutive weeks.

**Results:** Nine hundred and fifty patients were enrolled, 635 receiving satraplatin and 315 receiving placebo. Patients were evenly matched in regards to age, ECOG PS, pain index, progression at study entry, and prior chemotherapy. Median PFS was 11.1 weeks (range 10.3 to 12.3 weeks) in the satraplatin arm and 9.7 weeks (range 9.3 to 10.0 weeks) in the placebo arm, which was statistically significant (p < 0.001). Median OS was 61.4 weeks for those patients treated with satraplatin and 61.4 weeks for those patients treated with placebo. This was not statistically significant. Median TPP favored satraplatin (66.1 weeks) vs. placebo (22.3 weeks) with a 36% reduction in the risk for pain progression with satraplatin therapy (p < 0.001). Tumor response, complete or partial, also favored satraplatin (8% vs. 0.7%; p = 0.002). As expected, hematologic...
Toxicities were dose-limiting in those patients treated with satraplatin. Gastrointestinal disorders were also more common.

**Conclusion:** Oral satraplatin delayed progression of disease in patients with metastatic castrate-refractory prostate cancer who experienced progression after initial chemotherapy, but it did not provide a significant OS benefit. The drug was well-tolerated.

**Managed Care Implications:** Treatment for metastatic castrate-refractory prostate cancer in patients who have failed first-line chemotherapy continues to evolve. Oral agents such as satraplatin may offer an alternative for these patients. Presently the U.S. Food and Drug Administration (FDA) is awaiting additional data on the drug in this patient population before deciding whether to approve the drug for this indication.

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**Title:** Phase 2 study of dasatinib in patients with metastatic castration-resistant prostate cancer.

**Authors:** Yu EY, Wilding G, Posadas E, et al.


**Purpose:** Prostate cancer that is not cured with local therapy results in metastases, primarily to bone, to which second-line hormonal therapies usually result in brief responses in less than half the patients treated. Docetaxel (Taxotere) chemotherapy has been shown to extend survival in men with metastatic castration-resistant prostate cancer (CRPC) but is associated with significant adverse events including myelosuppression, neuropathies, and fatigue. Dasatinib (Sprycel) is an oral tyrosine kinase inhibitor with activity against SRC family kinases (SFK), which are commonly overexpressed in prostate cancer lines. The drug is also known to have activity vs. BCR-ABL, platelet-derived growth factor receptor, and c-KIT. SFKs also play a significant role in osteoclast and osteoblast function. Inhibition of SFKs has been shown to delay the appearance of bony metastases in murine models of breast cancer. Dasatinib has been shown in preclinical trials to inhibit the proliferation of prostate cancer cells, decrease prostate-specific antigen (PSA) levels, and increase bone mineral density. This phase 2 study was conducted to evaluate the efficacy and safety of dasatinib in patients with metastatic CRPC and increasing PSA levels.

**Methods:** This open-label study was conducted at 10 centers in the U.S. and Europe. Patients had to have histologically or cytologically proven prostate cancer and radiologic evidence of metastatic disease. Progressive disease was mandatory and defined as two serially increasing PSA levels obtained more than one week apart with castration serum testosterone levels of < 50 ng/dl. Exclusion criteria included those patients with central nervous system metastases, patients with preexisting pleural or pericardial effusions, and
patients who had received previous or ongoing therapy with cytotoxic chemotherapy or glucocorticoids. Patients were initially administered dasatinib 100 mg orally twice a day. After 25 patients received dasatinib at that dose, the dose was reduced to 70 mg orally twice a day due to clinical observation that the drug was equally effective but less toxic at the lower dose. The primary objective of the study was a composite response rate defined as either confirmed ≥ 50% PSA decline, stable disease (SD), complete response (CR), partial response (PR), or confirmed disappearance of lesion(s) by radionuclide bone scan assessment. Secondary endpoints included investigator assessment of changes in the bone scan, PSA, and bone turnover marker urinary N-telopeptide (uNTX). Safety of dasatinib in this patient population was also assessed.

**Results:** Forty-seven patients were enrolled in the study; 25 initially received dasatinib 100 mg orally twice a day, and 22 initially received dasatinib 70 mg orally twice a day. The predefined endpoint of composite response/stable disease was achieved in 13 of 47 patients, or 28% (95% confidence interval, 16% to 43%). This exceeded the minimum expected response of 10%. Lack of progression was noted in 20 patients (43%) at week 12 and nine patients (19%) at week 24. Response rates were similar in both dosing arms. Of 41 evaluable patients, 21 (51%) achieved a ≥ 40% reduction in uNTX by week 12, and 33 (80%) had some reduction during the study. Of 40 patients evaluated, bone alkaline phosphatase was reduced in 24 patients (60%) at week 12, and 25 patients (63%) achieved some reduction while on the study. The most common adverse events were diarrhea (62%), nausea (47%), and fatigue (45%). The incidence of pleural effusions (any grade) was reported in 51% of those treated while pericardial effusions (grade 1 only) were noted in 23% of patients. There was no significant difference based upon daily dose of dasatinib received.

**Conclusion:** This study provides initial evidence of dasatinib activity in patients with metastatic CRPC and bone disease. The therapy is reasonably well-tolerated in this chemotherapy-naive patient population.

**Managed Care Implications:** Drug therapy with new mechanisms of action, such as dasatinib, may be a new option for patients with metastatic CRPC. Additional studies including combination therapy with dasatinib will further identify the role of this agent.

**Title:** Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of CRPC.

**Authors:** Attard G, Reid AHM, A’Hern R, et al.


**Purpose:** Patients who experience relapse from hormone-refractory or androgen-independent prostate cancer may respond to further hormonal treatments, but response rates are modest. There is evidence that CRPC remains hormonally driven using by adrenal hormones or through intracrine synthesis. CYP17 is a key to androgen and estrogen synthesis. Weak, nonspecific inhibitors of CYP17, such as ketoconazole (Nizoral), have shown some antitumor activity in CRPC. A more potent, selective, and irreversible inhibitor of CYP17, abiraterone, has shown promising activity in chemotherapy-naive patients with CRPC.

**Methods:** All patients were chemotherapy-naive with a diagnosis of progressive CRPC and had an ECOG performance status of 0 or 1. Patients were required to have documented progressive disease and a minimum washout period of four weeks after hormonal therapy (except luteinizing hormone-releasing hormone) and six weeks after stopping bicalu-
tamidine (Casodex) or nilutamide (Nilandron). Patients who had received previous cytotoxic chemotherapy or radiopharmaceuticals for treatment of their prostate cancer were excluded. One thousand milligrams of oral abiraterone acetate powder were administered once daily, continuously, to fasted patients in 28-day cycles. Computed tomography scans were performed every 12 weeks, and circulating tumor cell (CTC) enumeration was also performed. The primary objective of the study was the number of patients with a ≥ 50% decline in their PSA level after 12 weeks of therapy with abiraterone acetate. A secondary endpoint was drug safety.

Results: Forty-two patients were enrolled in this phase 2 open-label, single-arm study. A decline in PSA of ≥ 50% was observed in 28 of 42 patients (67%), and declines of ≥ 90% were noted in eight (19%) patients. Radiologic responses were reported in nine (37.5%) patients. All were PRs. The median time to PSA progression (TTPP) was 225 days (range 162 to 287 days). The median TTPP for patients who had a ≥ 50% decline in PSA was 253 days (median 122 to 383 days) and 393 days in those patients with a ≥ 90% decline in PSA (range 252 to 533 days). Decreases in CTC counts from ≥ 5 to < 5/7.5 ml were noted in 10 of 59 (59%) patients, and 12 of 17 (70%) patients had a decline of ≥ 30% after the start of treatment. Abiraterone acetate was well-tolerated. Secondary mineralocorticoid excess was noted in a majority of patients, manifested by hypokalemia, hypertension, and fluid overload. It was managed by the use of the oral-selective aldosterone blocker eplerenone (INSPRA).

Conclusion: CYP17 blockade by abiraterone acetate results in declines of PSA and CTC counts as well as radiologic responses as first-line therapy in the treatment of patients with metastatic CRPC. This confirms that CRPC commonly remains a hormone-driven disease.

Managed Care Implications: New oral drug therapy with agents such as abiraterone acetate may have an important role to play in patients with metastatic CRPC. Additional studies will help to identify the exact role of such agents.

Title: Integrated data from two randomized double-blind, placebo-controlled phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer.

Authors: Higano CS, Schellhammer PF, Small EJ, et al.


Purpose: Prostate cancer is the most common solid tumor and second leading cause of cancer-related deaths in men in the U.S. Many men will experience disease control after primary therapy, but 20% to 40% of these patients will have a disease recurrence. While androgen deprivation will usually control these relapses, these patients will progress most likely to bone and/or regional lymph nodes. Management of androgen-independent prostate cancer (AIPC) is challenging. New agents with acceptable toxicity spectrums are needed. Sipuleucel-T is an autologous active cellular immunotherapy designed to stimulate an immune response against prostate cancer. It consists of autologous peripheral blood mononuclear cells, including antigen-presenting cells (APCs), which have been activated in vitro with a recombinant fusion protein. This protein is composed of prostatic acid phosphatase (PAP), an antigen linked to granulocyte-macrophage colony stimulating factor (GM-CSE, Leukine), an immune cell activator. Phase 1 and 2 studies show sipuleucel-T to be well-tolerated and to provide PSA responses as well
as several objective responses. The purpose of these phase 3 trials was to validate those results.

**Methods:** Data from two identically designed randomized, double-blind, placebo-controlled studies were combined to evaluate the safety and efficacy of sipuleucel-T. Patients had to have histologically proven adenocarcinoma of the prostate with radiologic evidence of metastases, serum testosterone level of < 50 ng/dl, and a life expectancy of at least three months. Also required were an ECOG PS of 0 or 1, (+) immunohistochemical for PAP in at least 25% of the tumor cells, adequate end-organ function, and a CD4+ T count of > 400/µL. Any prior therapy (chemotherapy, hormonal, radiation, or herbal) had to be discontinued at least four weeks before the start of the study. The only exception was luteinizing hormone-releasing hormone antagonists. Radiopharmaceuticals could not have been administered within 12 months of the trial. Patients were randomized in a 2:1 ratio to receive sipuleucel-T or placebo. After randomization, both groups underwent three leukapheresis procedures at weeks zero, two, and four with infusion of sipuleucel-T or placebo two days following the last leukapheresis. The primary objective of the study was to compare time to disease progression in patients with asymptomatic metastatic hormone-refractory prostate cancer between the two groups. Secondary endpoints included OS and drug safety.

**Results:** Two hundred and twenty-five patients were randomized between the two studies. One hundred and forty-seven were treated with sipuleucel-T and 78 with placebo. Baseline characteristics were comparable between the two groups. Five patients treated with sipuleucel-T had a PSA reduction of ≥ 50%, and two patients had a PSA reduction of ≥ 25% for an overall PSA response rate of 4.8%. No patients in the placebo group had a confirmed PSA reduction of 25% or more. The median survival was 23.2 months for the sipuleucel-T vs. 18.8 months for those receiving placebo, showing a 21% reduction in the risk for disease progression (HR, 1.26; p = 0.111) and a 33% reduction in the risk for death in patients treated with the immunotherapy (HR, 1.50; p = 0.011). The percentage of patients alive at 36 months was 33% and 15%, again favoring the group treated with sipuleucel-T. The most common adverse events associated with treatment were chills, pyrexia, headache, dyspnea, vomiting, and tremor. These events were primarily grade 1 and 2 and usually lasted less than two days.

**Conclusion:** The study demonstrates a survival benefit for patients treated with immunotherapy in comparison to placebo. That coupled with a modest toxicity profile suggests a favorable risk-benefit ratio for sipuleucel-T in patients with advanced prostate cancer.

**Managed Care Implications:** Immunotherapy may be another option for patients with AIPC. Given its favorable toxicity profile, sipuleucel-T in combination with other form(s) of therapy may be possible.

**Title:** Changes in alkaline phosphatase levels in patients with prostate cancer receiving degarelix or leuprolide: results for a 12-month comparative phase 3 study.

**Authors:** Schroder FH, Tombal B, Miller K, et al.

**Reference:** Br J Urol Int [published online ahead of print November 13, 2009].

**Purpose:** The bone is the most frequent site of metastases in men with prostate cancer. Bone formation and resorption are both altered in this patient population. Bone matrix components are released into the circulation during bone formation and resorption. Markers for bone formation include serum osteocalcin, procollagen I extension peptides, total serum alkaline phosphatase (S-ALP), and bone-specific alkaline phosphatase (B-ALP). Elevated S-ALP and B-ALP levels have been associated with progression of skeletal metastases in patients with prostate cancer and have been shown to be predictors of early death. Androgen-deprivation therapy (ADT) is commonly used in patients with advanced prostate cancer and bony mets. The most commonly used agents to treat the disease are GnRH receptor agonists that achieve castrate testosterone levels, ≤ 0.5 ng/dl in nearly all patients. However, ADT with GnRH receptor agonists is associated with a decrease in bone mineral density and an increased risk for fracture. GnRH receptor blockers are a new class of hormonal therapy
that induces a faster suppression of serum testosterone without causing a testosterone surge. Degarelix (Firma-gon) is a GnRH receptor blocker that has shown activity in patients with prostate cancer who require ADT. This study compares the changes in S-ALP in patients with prostate cancer when treated with degarelix or leuprolide (Lupron).

**Methods:** Men ages 18 and older with a histologically confirmed diagnosis of adenocarcinoma of the prostate for whom endocrine treatment was indicated were eligible. Patients were required to have a screening testosterone level of > 1.5 ng/dl and an ECOG PS of ≤ 2. Patients considered to be candidates for curative therapy were excluded. Patients were randomized to receive degarelix at a starting dose of 240 mg SQ, followed by monthly maintenance doses of 80 mg SQ (arm 1) or 160 mg SQ (arm 2) or leuprolide 7.5 mg IM monthly (arm 3). Therapy continued for 12 months. Antiandrogens were allowed in the leuprolide treatment for the prevention of a testosterone flare reaction at the discretion of the treating physician. S-ALP and PSA levels were measured at baseline and periodically during the study. The primary objective of the trial was to determine which drug suppressed S-ALP levels most effectively. Results focused on the comparison of degarelix 240/80 mg with leuprolide 7.5 mg, which were the doses approved by the FDA and European Medicines Agency.

**Results:** Baseline characteristic and demographics were comparable between the three treatment arms. Six hundred and ten patients were included with a median age of 73 years and a median PSA level of 19.0 ng/dl. Two hundred and seven patients were treated with degarelix 240/80 mg and 201 with leuprolide 7.5 mg. Baseline S-ALP levels were high in patients with metastatic disease due to the presence of skeletal metastases and highest in patients with metastatic disease and hemoglobin levels < 13 g/dl at baseline. S-ALP levels were suppressed below baseline with degarelix but were maintained around baseline with leuprolide. A late rise in S-ALP was noted in the leuprolide-treated patients that was not noted with those treated with degarelix. The pattern of S-ALP response was similar in patients with a baseline PSA ≥ 50 ng/dl.

**Conclusion:** Patients with metastatic prostate cancer with a baseline PSA ≥ 50 ng/dl and requiring ADT had a greater reduction in S-ALP levels and requiring ADT had a greater reduction in S-ALP levels when treated with degarelix than leuprolide. S-ALP suppression was noted throughout the study period in those treated with degarelix, which was not noted in patients treated with leuprolide. This suggests that degarelix may offer better S-ALP control and prolong control of skeletal metastases in this patient population.

**Managed Care Implications:** GnRH receptor blockers, such as degarelix, may become the drugs of choice when treating patients with prostate cancer requiring ADT. Additional studies to verify these results are needed.

**Title:** Docetaxel-based chemotherapy with zoledronic acid and prednisone in hormone refractory prostate cancer: factors predicting response and survival.

**Authors:** Nayyar R, Sharma N, and Gupta NP.


**Purpose:** Androgen-deprivation therapy is the first-line treatment for metastatic prostate cancer with an average duration of response of 18 to 24 months. Treatment of hormone-refractory prostate cancer (HRPC) remains palliative. Docetaxel (Taxotere) is a potent inhibitor of microtubular depolymerization and has been
shown to be active in the treatment of HRPC. The combination of docetaxel/prednisone has shown a survival advantage over mitoxantrone (Novantrone)/prednisone in a multicenter trial. Zoledronic acid (Zometa) is a bisphosphonate that reduces pain and skeletal complications associated with bone metastases. It has several mechanisms of action, including inhibition of osteoblastic proliferation, inhibition of bone destruction through osteoclasts, and inhibition of production of prostaglandins E2 and interleukin 1. The purpose of this study was to combine docetaxel, prednisone, and zoledronic acid in patients with HRPC and identify prognostic factors predicting response to chemotherapy and improved survival.

**Methods:** Men ages 45 to 85 with a histologically confirmed diagnosis of adenocarcinoma of the prostate with radiologic evidence of metastatic disease and disease progression after prior hormonal therapy were eligible. Patients were also required to have a Karnosky performance status (PS) of 60% to 100% and adequate end-organ function. A baseline physical exam, blood tests including PSA, radiologic imaging, and a bone scan were obtained. A baseline pain score was also documented using a numeric pain intensity scale. Docetaxel 75 mg/m² IV and zoledronic acid 4 mg/m² IV were administered every three weeks until disease progression or unacceptable toxicity. An 8 mg dose of IV dexamethasone was given with the chemotherapy, and prednisone was prescribed at a dose of 5 mg orally twice a day for the next five days. The primary endpoints of the study were either death of the patient or disease progression. Secondary endpoints included a reduction in pain score as defined by a minimum two-point decline in pain score from baseline without an increase in analgesics, or a reduction of ≥ 50% in analgesic intake without an increase in pain score and toxicity or the regimen.

**Results:** Forty-four patients were enrolled and received a total of 274 cycles of chemotherapy (mean 6.3; range 2 to 21). The average PSA at baseline was 171.2 ng/dl (median 40.5 ng/dl; range 5.8 to 1,422.7 ng/dl). Good PSA response, more than 50% fall from baseline, was seen in 26 of 44 cases (59.1%) and partial response (25% to 50% fall in PSA) in 11 of 44 cases (25%). Those responses were maintained for a median of 10.6 months. Patients who received more than four cycles of chemotherapy had improved survival (p < 0.01). Median OS was 62.4 weeks, with patients with a good and partial PSA response achieving the best OS. A more than 75% reduction in pain score was noted in 31 of 44 patients (70.5%) with a more than 75% decrease in analgesic intake reported in 28 of 44 cases (63.6%). A more than 50% reduction in the activity of the bone scan was noted in 32 of 44 cases (72.7%). The most significant factors predicting survival via univariate Cox regression analysis were a Gleason score < 7 and the number of cycles of chemotherapy received. Adverse reactions were considered acceptable and consisted of myelosuppression, nausea, vomiting, diarrhea, and rash.

**Conclusion:** The combination of docetaxel/prednisone/zoledronic acid is both safe and effective in the management of HRPC. Patients with a Gleason score < 7, a PSA decline of > 50%, and those who receive at least four cycles of chemotherapy have significantly better survival.

**Managed Care Implications:** Early identification of patients with lower
Gleason scores and significant declines in PSA is essential in determining long-term survival in patients with HRPC treated with this new drug combination.

Title: Phase 1/2 study of docetaxel, gemcitabine, and prednisone in castrate-refractory metastatic prostate cancer.

Authors: Buch-Hansen TZ, Bentzen L, Hansen S, et al.

Reference: Can Chemo Pharm [published online ahead of print October 31, 2009].

Purpose: Most men with prostate cancer have disease that is initially responsive to hormonal therapy, although the majority become insensitive to this type of therapy over time. Chemotherapy then becomes the treatment of choice. Castrate-refractory metastatic prostate cancer (CRMPC) is defined as clinical disease progression and/or an increase in PSA in spite of castrate levels of plasma testosterone. Patients with CRMPC often suffer from skeletal pain, fractures, and spinal cord compression, thus making palliation an important parameter of treatment. Docetaxel (Taxotere) has demonstrated improvement in OS and quality of life in this patient population and has become the cornerstone for chemotherapy regimens. The combination of docetaxel, gemcitabine (Gemzar), and prednisone has been shown to be active in other solid tumors including breast cancer and non-small cell lung cancer. The purpose of this study was to assess the efficacy and toxicity of a fixed dose of docetaxel and prednisone with escalating doses of gemcitabine (DGP) in patients with CRMPC.

Methods: This was an open-label multicenter phase 1/2 study. Eligible patients had histologically documented adenocarcinoma of the prostate with either radiologic or clinical evidence of metastatic disease and castrate levels (< 0.5 nmol/L) of testosterone. CRMPC was defined as clinical and biochemical progression despite castration. PSA levels had to be at least 10 µcg/l, and no previous treatment with estrogen or steroids for metastatic disease was allowed. End-organ function was required to be adequate, and patients had to have an ECOG PS of ≤ 2 and a life expectancy of at least three months. In phase 1, 15 patients were included, three at each dosing level of DGP. All received docetaxel 75 mg/m² IV every three weeks and prednisone 5 mg orally twice a day continuously. The maximum tolerated dose of gemcitabine was 1,000 mg/m² IV days one and eight of an every-21-day cycle. The primary endpoint of the phase 2 portion of the study was PSA response as defined as a ≥ 50% reduction in PSA from baseline, verified by a second measurement at least four weeks later. Secondary endpoints were time to progression (TTP) and toxicity. Results: Fifty patients were entered in the phase 2 portion of the trial. Thirty-seven patients (74%) achieved a biochemical response with a reduction in PSA by ≥ 50%. A major PSA response, as defined as a ≥ 75% reduction in PSA, was seen in 23 patients (46%). Single-agent docetaxel studies in the same patient population have shown 50% PSA response rates to range from 30% to 70%. The TTP was 7.9 months, and the OS was 13.9 months. OS in the single-agent docetaxel study, TAX 327, was 18.9 months. Twenty-four patients had measurable disease, with 12 (50%) achieving a partial response and five (21%) having stable disease. Neutropenia was the most common adverse event and developed in 74% of patients treated. Nonhematologic toxicity was mild.

Conclusion: The PSA response rate was promising with the DGP combination, and adverse events were manageable. However, OS rates were comparable to single-agent docetaxel.

Managed Care Implications: New chemotherapy regimens for the treatment of men with CRMPC are needed. The combination of DGP should not be considered since the PSA response rates and OS are similar to those achieved with single-agent docetaxel.