

Hoosier Oncology Group Randomized Phase II Study of Docetaxel, Vinorelbine, and Estramustine in Combination in Hormone-Refractory Prostate Cancer with Pharmacogenetic Survival Analysis

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Abstract Purpose: To determine the safety and efficacy of two docetaxel doublets in hormone-refractory prostate cancer (HRPC) patients and to examine the prognostic role of polymorphisms in host genes important to docetaxel metabolism and transport.

Experimental Design: Sixty-four chemotherapy-naïve patients with HRPC were randomized to docetaxel and vinorelbine (D, 20 mg/m² i.v. days 1 and 8; V, 25 mg/m² i.v. days 1 and 8) or docetaxel and estramustine phosphate (D, 60-70 mg/m² i.v. day 1; E, 280 mg oral thrice daily days 1-5) administered q21d. Primary end point was clinically significant toxicity. A pharmacogenetic analysis of host genes was done in patients who received at least one cycle of docetaxel therapy.

Results: Grade 3/4 toxicity occurred in 15.6% of DV patients and in 28.6% DE patients. Neither arm exceeded the threshold of clinically significant toxicity. In the DV arm, objective response rate was 33%, prostate-specific antigen response rate was 20%, and median survival was 16.2 months. In the DE arm, objective response rate was 67%, prostate-specific antigen response rate was 43%, and median survival was 19.7 months. Pharmacogenetic analyses showed a significant association between survival beyond 15 months and the ABCG2 421 C>A (Q141K) polymorphism compared with the wild-type (C/C) genotype (66% versus 27%; *P* = 0.05).

Conclusions: DV and DE doublets are active with a tolerable toxicity profile in patients with HRPC; however, efficacy does not seem superior to standard single-agent docetaxel. The ABCG2 421 C>A (Q141K) polymorphism may be an important predictor of response and survival in HRPC patients treated with docetaxel-based chemotherapy.

Prostate cancer afflicts 234,000 men yearly and results in >27,000 deaths (1). Recent trials have shown a survival benefit for men with hormone-refractory prostate cancer (HRPC) treated with a docetaxel-based regimen (2, 3).

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Vinorelbine is a *Vinca* alkaloid that inhibits the microtubular apparatus in malignant cells and has documented activity in HRPC (4-6). Vinorelbine and docetaxel inhibit different portions of the microtubule apparatus in a synergistic manner in preclinical *in vitro* prostate cancer models (7-9). With this in mind, the Hoosier Oncology Group conducted a randomized phase II trial of weekly docetaxel and vinorelbine (DV) with docetaxel and estramustine phosphate (DE) as a parallel reference arm.

This study also included a pharmacogenetic analysis of host genes with critical roles in docetaxel drug transport and metabolism. Clinical studies suggest that variant alleles in the thiopurine methyltransferase gene can identify patients at risk of severe hematologic toxicity after azathioprine, 6-mercaptopurine, or related agents (10). Similar toxicity associations are seen with dihydropyrimidine dehydrogenase gene mutations and 5-fluorouracil therapy (11) and with UGT1A1 mutations and irinotecan (12). Single-nucleotide polymorphisms (and other genetic variants) have also been observed, which affect docetaxel metabolism and transport. These include alterations in the degradation pathway (cytochrome P450 3A4 and 3A5; refs. 13-15), microtubule associated proteins (MAP4 and MAPT; ref. 16), and drug transport proteins [multidrug resistance 1 (ABCB1) and breast cancer resistance protein (ABCG2); refs. 15, 17]. Polymorphisms in these genes

were assessed to identify genetic variants that predict for toxicity and efficacy of docetaxel-based chemotherapy.

Materials and Methods

Eligibility criteria. The protocol was approved by the institutional review boards of all participating centers. Key eligibility criteria are listed in Fig. 1. In addition, all patients had progressive disease after at least one hormonal therapy (orchiectomy, estrogens, luteinizing hormone-releasing hormone therapy, etc.) with castrate levels of testosterone (<30 ng/dL). Progressive disease was defined as one of the following: an increase in prostate-specific antigen (PSA) >50% over nadir on hormonal therapy measured on two successive occasions at least 2 weeks apart (18) and/or objective evidence of progressive disease on computed tomography scan and/or new symptomatic bone metastases. Patients treated with an antiandrogen must have also progressed after the antiandrogen had been discontinued for at least 4 weeks (or for 6 weeks for antiandrogens with a longer half-life, such as bicalutamide) and have continued evidence of disease progression (at least a 25% increase in PSA after discontinuing). There was no maximum number of hormonal therapies allowed.

Patients were excluded if they had new or unstable central nervous system metastases, had received external beam radiation therapy to >25% of their bone marrow, or had a history of grade ≥ 2 peripheral neuropathy. Patients with active cardiac disease defined as active angina, symptomatic congestive heart failure, or myocardial infarction within the previous 6 months were excluded. Patients with a history of deep venous thrombosis, pulmonary embolism, or cerebrovascular attack within the last 6 months were also excluded. Patients who had received external beam radiation or samarium injection <4 weeks before enrollment and patients who had received a strontium injection <6 weeks before enrollment were ineligible. Patients with a history of prior malignancy <5 years disease-free with the exception of curatively treated basal and squamous skin cancers were excluded. Patients were excluded if they had received PC-SPEs within 4 weeks before enrollment. In addition, the use of saw palmetto or lycopenes was not allowed.

Treatment. Patients were randomized to one of two regimens. Patients on the DE arm received 280 mg of oral estramustine phosphate thrice daily 1 to 2 hours after a meal from days 1 to 5 with dairy products restricted on those days. Patients received i.v. infusion of docetaxel over

60 minutes at a dose of 60 mg/m² on day 2. If no grade 3 or 4 toxicities occurred in the first cycle, docetaxel was increased to 70 mg/m² for all subsequent cycles. Patients received 8 mg dexamethasone orally every 12 hours for five doses beginning the night before chemotherapy. From day 1 until 2 weeks after discontinuation of estramustine phosphate, patients received 325 mg of enteric-coated aspirin as prophylaxis for arterial thrombosis and 2 mg of oral warfarin.

Patients randomized to the DV arm received i.v. vinorelbine over 6 to 10 minutes at a dose of 20 mg/m² on days 1 and 8. Patients also received i.v. docetaxel over 30 minutes at a dose of 25 mg/m² on days 1 and 8. All patients received 4 mg dexamethasone orally every 12 hours for 3 days beginning the day before treatment. In patients with a prior history of external beam radiation, vinorelbine and docetaxel were reduced to 15 and 20 mg/m², respectively. In both DE and DV arms, treatments were repeated on a 21-day cycle up to a total of six cycles or until disease progression or dose-limiting toxicity.

Patient evaluation. All patients had a history, physical exam, and PSA within 1 week before treatment. Other laboratories (complete blood count, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, testosterone, PSA, and coagulation studies) were done within 2 weeks before treatment. All radiologic studies (bone scan, abdomen and pelvis computed tomography scan, and chest X-ray) were done within 4 weeks before treatment.

Before each cycle, a case report form, complete blood count, hepatic panel, PSA, and coagulations laboratories were recorded. Radiographic studies were repeated before each odd-numbered cycle and in follow-up for patients with documented objective responses to therapy.

Disease assessment. Patients with measurable disease were assessed for response to therapy according to standard Response Evaluation Criteria in Solid Tumors criteria. Patients with an elevated PSA were assessed for a serologic PSA response. PSA complete response was defined as an undetectable PSA if prior prostatectomy and <4 ng/mL if prostate in place (after irradiation, no local therapy, etc.) on two consecutive measurements 3 weeks apart. PSA partial response was defined as a decline of PSA value by >50% for two consecutive determinations at least 3 weeks apart. PSA stabilization was defined as a <50% increase or decrease in PSA over a period of 3 months if baseline PSA >20 ng/mL. PSA progression was defined as an increase in PSA to >50% above baseline on two consecutive measures at least 3 weeks apart. PSA relapse was defined as a >50% increase in PSA over the minimum value recorded during a response as evidenced on three successive determinations.

Pharmacogenetic evaluation. All patients who received at least 1 day of docetaxel therapy on either trial arm were eligible for inclusion in the companion pharmacogenetic study. Participation in the pharmacogenetic study was not required for participation in the treatment portion of the trial. After a separate informed consent was obtained, a single 5-mL blood sample collected in an EDTA tube was drawn from each patient. Samples were stored at 2°C to 8°C for ≤ 5 days and shipped to Washington University (St. Louis, MO) for analysis. DNA was extracted from whole blood using the Gentra PureGene kit (Gentra Systems, Inc., Minneapolis, MN) following the manufacturer's instructions. Eight polymorphisms in six genes associated with taxane metabolism (CYP3A4*1B and CYP3A5*3C), transport (ABCB1 3435 C>T and ABCG2 421 C>A), and microtubule assembly (MAP4 68 G>A, MAP4 1280 C>A, MAPT-13 G>A, and MAPT 3674 A>G) were assessed using PCR and Pyrosequencing technology as described previously (19–22).

Statistical analysis. The primary end point of the study was the incidence of clinically significant toxicity defined as any significant adverse event, which required reporting or need for RBC or platelet transfusion that was thought to be related to treatment. Events that required reporting were serious adverse events or reactions that were at least possibly related to therapy and resulted in death, or were life threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability.

Age > 18
KPS ≥ 70
Life expectancy ≥ 3 months
Histologically confirmed adenocarcinoma of the prostate
Written informed consent provided by patient
(Metastatic disease) or (Symptoms in the absence of metastatic disease with analgesic requirements ≥ 10 mg Morphine equivalents or Pain ≥ 2 out of 10) or (Asymptomatic in the absence of measurable disease with a PSA > 20 ng/ml)
Creatinine < 2 mg/dl
Total bilirubin WNL
SGOT/SGPT < 2.5 x ULN if alkaline phosphatase < ULN
Alkaline phosphatase < 4.0 x ULN if SGOT/SGPT < ULN
Absolute neutrophil count > 1500
Hemoglobin ≥ 8.0 g/dl
Platelets $\geq 100,000$
No prior chemotherapy
Not actively on anticoagulation, and no contraindication to starting anticoagulation or low dose aspirin

Fig. 1. Key eligibility criteria.

Secondary end points included objective, PSA, and clinical response rates, time to progression, and pharmacogenetic analyses. Patients were stratified based on baseline performance status, pain requiring opiates, and presence of measurable disease. There was no intention to statistically compare the two arms.

Eighteen patients were treated on each arm in the first stage. A study arm was to be terminated if ≥ 5 patients, among the first 18, experienced clinically significant toxicity. This did not occur in either arm; therefore, 14 additional patients were assigned to each arm in stage II. If ≥ 6 patients, among the total 32 of each arm, experienced clinically significant toxicity, the arm was to be considered not worthy of further testing. These numbers were determined by the Simon two-stage phase II design and provided the study with 90% power to detect a true toxicity rate of 30% with a 5% type I error rate. Confidence intervals for clinically significant toxicity rates of each arm were obtained using Jennison and Turnbull (1983) method. Confidence intervals for response rates were obtained using an exact method. Curves for time to progression and overall survival were estimated using Kaplan-Meier method. Toxicity grades were summarized using contingency tables. Pharmacogenetic polymorphism frequencies were analyzed in relation to clinical benefit, PSA response, and overall survival using χ^2 proportional analyses. For the survival analysis, a cutoff of 15 months was chosen to approximate the expected median survival in study subjects.

Progression-free survival was defined as the time from enrollment on study until either measurable progressive disease was noted, 50% increase in PSA from nadir was observed and confirmed at least 4 weeks later, or clinical deterioration (decline in Karnofsky performance score of ≥ 20 points from baseline, an increase in opiate requirements of 10 mg i.m. equivalents, or death due to any cause) was noted. Overall survival was defined as the time from enrollment on study until death due to any cause.

Results

Patients. From March 21, 2002 to April 21, 2004, 64 patients were randomized, 32 to each arm. The median age was 72 years. Median pretreatment PSA level was 136. The median Karnofsky performance score was 90 with a median pain score of 2 and median i.m. morphine equivalent opiate use of 0 mg/d. A total of 38 (59.4%) patients had measurable disease at baseline. Baseline characteristics are summarized in Table 1 for the entire group and each arm individually. There were no significant differences in any of the baseline stratification factors.

Toxicity. In general, treatment was well tolerated. Nine of 32 (28.1%) patients [95% confidence interval (95% CI), 6.4-39.8] experienced grade 3 or 4 toxicity in the DE arm. Grade 3 toxicities included diarrhea, febrile neutropenia, hypoglycemia/hypokalemia, increased lacrimation, hypersensitivity reactions,

typhlitis, urinary retention, and elevated transaminases (one patient each). Grade 4 toxicities included hematuria, hyperglycemia/fatigue, stroke, and elevated transaminases (one patient each). Five of 32 (15.6%) patients (95% CI, 5.0-32.0) experienced grade 3 or 4 toxicity in the DV arm. Grade 3 toxicities included bone pain, edema, hyperglycemia, venous catheter-associated infection, and recurrent urinary tract infections (one patient each). Grade 4 toxicity was limited to a single episode of hypocalcemia. Neither arm exceeded the prespecified limit of six clinically significant toxic events as previously defined.

Chemotherapy administration. A total of 164 cycles of DE chemotherapy was given to patients. Of these, 87.2% of cycles were given without dose reduction or delay. The most common reasons for dose reduction or delay were infectious (2.4%; cellulitis, fever, neutropenic fever, and herpes zoster; all one patient each), hematologic (2.4%; four patients with neutropenia), unknown (1.8%; three patients), and gastrointestinal toxicity (1.2%; hepatotoxicity and nausea/emesis; one patient each).

In the DV arm, 150 cycles of chemotherapy were administered, 76.0% without dose reduction or delay. The most common causes for reduction or delay were prior radiotherapy (10.7%; 16 patients, mandated at baseline per treatment plan), hematologic (8.7%; 11 patients with neutropenia, 2 patients with thrombocytopenia), and infectious (2.7%; 4 patients with febrile neutropenia).

Response and survival. Among patients with measurable disease in the DE arm, six of nine (66.7%) patients had a partial or complete response. A partial PSA response was observed in 42.9% of patients. Median progression-free survival was 5.7 months (95% CI, 5.1-7.1), with an overall survival of 19.7 months (95% CI, 12.0; not reached).

In the DV arm, 4 of 12 (33.3%) patients with measurable disease had a partial or complete response. A partial PSA response was observed in 20.0% of patients. Median progression-free survival was 6.2 months (95% CI, 5.0-8.0), with an overall survival of 16.2 months (95% CI, 13.1-25.2). Kaplan-Meier curves for progression-free survival and overall survival are summarized for both DE and DV arms in Figs. 2 to 3.

Pharmacogenetic analysis. Samples for pharmacogenetic analyses were available for 51 patients. In this pilot analysis, it was noted that 4 of 6 (66%) patients with the ABCG2 421 C>A (Q141K) polymorphism were alive past 15 months compared with only 12 of 44 (27%) patients with wild-type (C/C; $P = 0.05$). Polymorphisms in other candidate genes (CYP3A4, CYP3A5, ABCB1, MAPT, and MAP4) were not

Table 1. Baseline patient demographics

	All patients		Arm DV		Arm DE	
	n	Median (range)	n	Median (range)	n	Median (range)
Age	67	72 (41-85)	35	70 (41-85)	32	72 (55-82)
PSA	64	136.2 (7.3-1,881.0)	33	146.9 (7.3-1,881.0)	31	126.6 (10.1-1,333.9)
KPS	64	90 (70-100)	33	90 (70-100)	31	90 (70-100)
Mean pain score	61	2.0 (0.0-9.0)	32	2.2 (0.0-9.0)	29	2.0 (0.0-5.7)
Median opiate use*	61	0 (0-50)	32	0 (0-50)	29	0 (0-24)

Abbreviation: KPS, Karnofsky performance score.

*I.m. morphine equivalents.

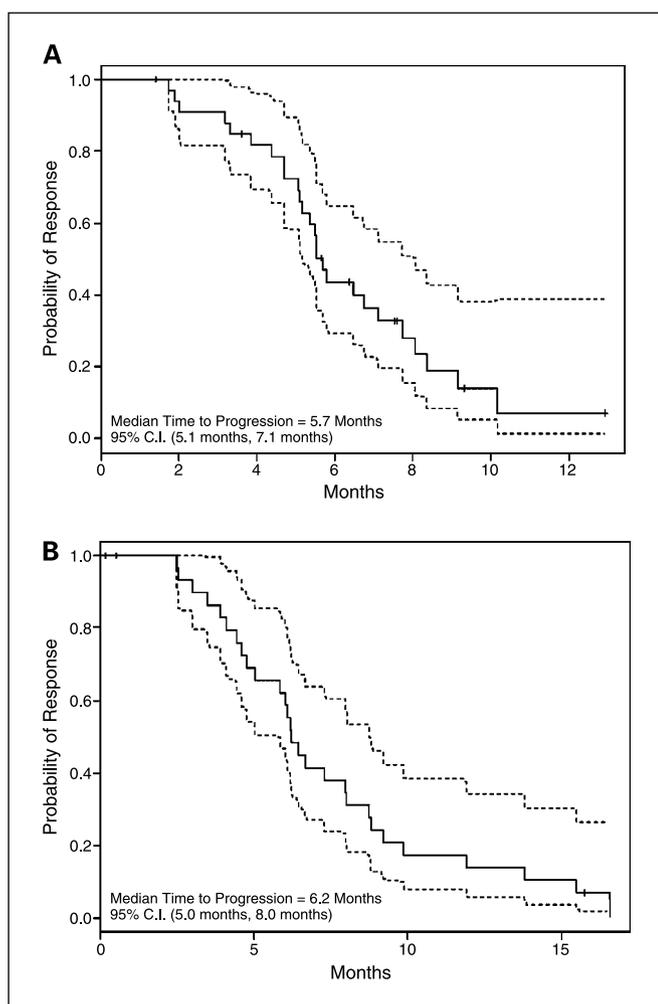


Fig. 2. A, progression-free survival for DE arm. B, progression-free survival for DV arm.

associated with an increased chance of being alive beyond 15 months (Table 2). Pharmacogenomic analyses of toxicity or PSA response revealed no additional significant associations (all $P > 0.05$).

Discussion

Metastatic HRPC remains the third leading cause of cancer-related mortality among men in the United States. In 2004, Petrylak et al. (2) and Tannock et al. (3) reported results of two separate randomized controlled trials confirming a survival advantage for docetaxel-based chemotherapy. However, the potential toxic effects of chemotherapy remain a valid consideration as we evaluate new combinations.

In previous studies combining estramustine phosphate and docetaxel in the treatment of HRPC patients, objective response rates of 6% to 50% were observed, with most responses characterized as partial responses. PSA responses range from 45% to 82%. Major toxicities include myelosuppression, fatigue, and nausea. Grade 3 or 4 neutropenia is seen in up to half of patients. With therapy, overall survival ranges between 12 and 20 months with variations depending on patient characteristics at baseline (23–26).

In the present study, 9 of 32 (28.1%) patients (95% CI, 6.4–39.8) treated with DE experienced grade 3 or 4 toxicity. An objective response rate of 66.7%, a PSA response rate of 42.9%, and a median overall survival of 19.7 months were observed. These results compare favorably with the pivotal phase III randomized trials described above in terms of efficacy of every 3-week docetaxel and toxicity of the docetaxel and estramustine combination.

Vinorelbine is a semisynthetic *Vinca* alkaloid that has shown activity against solid organ malignancies, including lung, breast, and germ cell tumors. Its preclinical synergism when combined with docetaxel in prostate cancer cell line experiments was a basis for its inclusion in this trial (27). Furthermore, as a single agent, it is tolerable in elderly patients with metastatic HRPC (28–31).

In the present study, 5 of 32 (15.6%) patients (95% CI, 5.0–32.0) treated with DV experienced grade 3 or 4 toxicity and 1 had clinically significant toxicity per the protocol. An objective response rate of 33.3%, a PSA response rate of 20.0%, and a median overall survival of 16.2 months were observed. Koletsky et al. (32) have reported the only other phase II data combining vinorelbine and docetaxel to date. In the Koletsky study, 74% of patients experienced grade 3 or 4 neutropenia. One case of acute respiratory distress syndrome

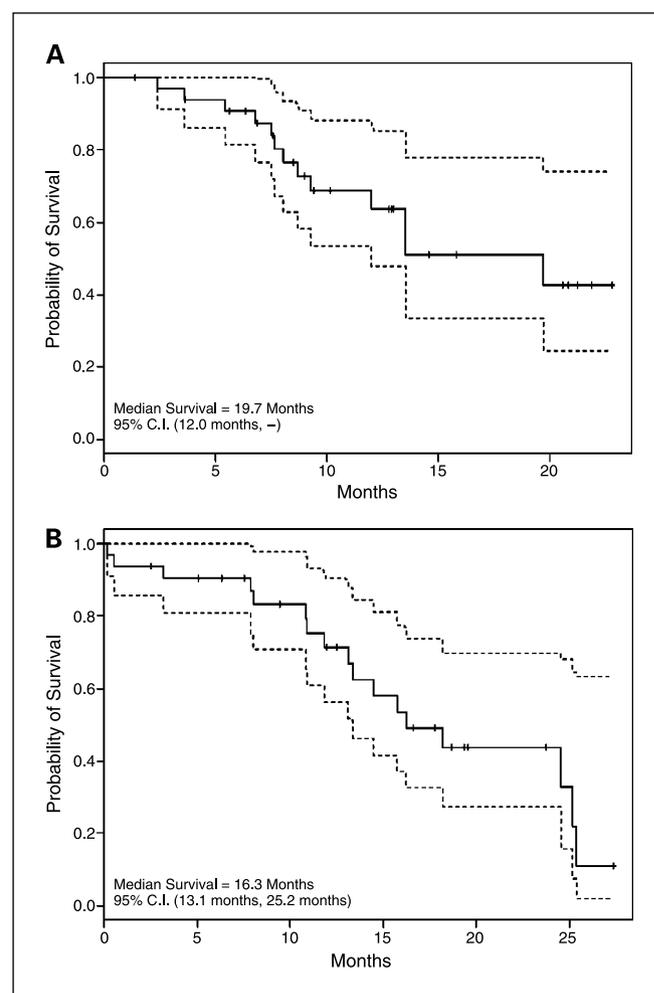


Fig. 3. A, overall survival for DE arm. B, overall survival for DV arm.

Table 2. Pharmacogenetic polymorphism analysis in patients surviving >15 months

Gene	Polymorphisms			P
ABCB1 3435	C/C, 4/10 (40%)	C/T, 7/29 (24%)	T/T, 6/12 (50%)	0.24
ABCG2 421	C/C, 12/44 (27%)	C/A, 4/6 (67%)	A/A, 0/0 (0%)	0.05
CYP3A4*1B	A/A, 16/43 (37%)	A/G, 0/5 (0%)	G/G, 1/2 (50%)	0.10
CYP3A5*3C	A/A, 1/2 (50%)	A/G, 0/5 (0%)	G/G, 16/44	0.10
MAP4 68	G/G, 14/46 (30%)	G/A, 3/5 (60%)	A/A, 0/0 (0%)	0.18
MAP4 1280	C/C, 7/25 (28%)	C/A, 5/18 (28%)	A/A, 3/5 (60%)	0.37
MAPT-13	G/G, 0/3 (0%)	G/A, 7/18 (39%)	A/A, 10/29 (34%)	0.26
MAPT 3674	A/A, 10/30 (33%)	G/A, 6/17 (35%)	G/G, 0/3 (0%)	0.29

was also observed. An objective response was seen in 60% of patients with a PSA response in 60% of patients also. Patients in the Koletsky study had a significantly lower median PSA level at baseline (116 ng/mL) compared with our study population (242 ng/mL), which may account for the somewhat decreased response rates seen in our experience. Insufficient antitumor activity associated with weekly docetaxel dosing must also be considered. The weekly dosing of both docetaxel and vinorelbine in our trial was based on prior results of a phase I dose escalation study in non-small cell lung cancer patients, which revealed a maximally tolerated dose of 20 mg/m²/wk of vinorelbine and 25 mg/m²/wk of docetaxel without scheduled treatment breaks (33).

The total number of patients experiencing clinically significant toxicity with the combination of vinorelbine and docetaxel did not exceed our prestudy threshold. However, the efficacy results do not suggest an advantage compared with single-agent docetaxel. As such, we would not recommend further study of the combination regimen at this dosing schedule. However, clinicians should be reminded of the single-agent tolerability of vinorelbine, particularly in elderly patients often encountered with metastatic HRPc.

The companion pharmacogenetic study assessed germ-line polymorphisms in genes known to play important roles in chemotherapy drug transport, metabolism, and mechanism of action. Analysis of candidate genes showed a significantly greater proportion of patients surviving beyond 15 months with docetaxel-based therapy in the presence of the ABCG2 421 C>A polymorphism. Previous studies of the ABCB1-associated

P-glycoprotein-mediated drug efflux pump have shown minimal, if any, effect on docetaxel plasma concentrations when an inhibitor of this pump is administered (34). The effect of ABCG2 polymorphisms on docetaxel pharmacokinetics is unknown. The increased survival seen in individuals with an ABCG2 421 C>A polymorphism may suggest a less functional drug efflux pump, leading to increased intracellular (intratumoral) docetaxel concentrations and improved cytotoxic activity. This hypothesis should be interpreted cautiously due to the small patient sample size and potential confounding variables. In addition, this exploratory analysis was not subject to a multivariate analysis. Therefore, at most, these data are hypothesis generating and will be used as preliminary data for future large-scale studies. Nonetheless, the study shows the ability to successfully conduct translational pharmacogenetic studies in a community setting, such as the Hoosier Oncology Group.

In summary, this randomized phase II study of two docetaxel-based regimens showed a tolerable toxicity profile with a weekly docetaxel and vinorelbine regimen. However, the efficacy data do not support evaluation in the phase III setting. A pharmacogenetic analysis of germ-line DNA showed that patients with an ABCG2 421 C>A genotype had an increased chance of being alive beyond 15 months if treated with docetaxel-based combination chemotherapy. This study shows that modern translational efforts can be accomplished beyond the confines of large tertiary academic medical centers and should serve as a model for future trial design.

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