



Kala Pohl. *Surfs Up*. Acrylic on canvas, 22" × 28".

Current studies of novel therapeutic agents and targets for treatment of metastatic androgen-independent prostate cancer are reviewed.

Novel Agents and Targets in Managing Patients With Metastatic Prostate Cancer

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Background: Docetaxel has recently been found to improve survival in patients with metastatic androgen-independent prostate cancer (AIPC). Chemotherapy as a first-line option leaves room for improvement, while second-line options are multiple and somewhat controversial.

Methods: Clinically relevant articles focusing on chemotherapy drugs for metastatic prostate cancer and their mechanism of action and efficacy were reviewed from January 2004 through April 2006.

Results: Docetaxel is the standard of care for AIPC. However, for doublets with docetaxel or second-line chemotherapy, multiple studies have shown interesting and promising results with calcitriol, thalidomide, bevacizumab, sunitinib, and abiraterone.

Conclusions: Docetaxel should be considered for first-line treatment of metastatic AIPC. Due to its progression-free survival of only 6 months, more effective drugs and drug combinations need to be developed to treat patients with AIPC. Combination treatments with docetaxel and other new agents are promising, but adequately powered phase III trials need to be conducted with survival as the principal endpoint for these promising drug combinations.

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Abbreviations used in this paper: AIPC = androgen independent prostate cancer, PSA = prostate-specific antigen, GM-CSF = granulocyte-macrophage colony-stimulating factor, SWOG = Southwest Oncology Group, EORTC = European Organization for Research and Treatment of Cancer.

Introduction

Prostate cancer is the most common cancer in men, with approximately 234,460 new cases and 27,350 deaths expected in 2006.¹ Patients who develop metastatic disease are often initially treated with hormone deprivation in the form of androgen suppression by medical castration or surgical castration. In advanced disease, androgen suppression alleviates symptoms in patients and produces responses in prostate-specific antigen (PSA), soft tissue metastases, and bone metastases. Since bone metastases occur in

85% of patients with prostate cancer,² a treatment strategy that targets both the bone and the disease is the optimal approach.³

Options following initial treatment include second-line hormonal therapy or systemic chemotherapy when metastatic disease develops. Chemotherapy had mixed results in the treatment of prostate cancer; in early trials, many of the chemotherapy options led to stabilization of disease and improvement of symptoms but did not increase survival.^{4,5} The PSA response rates were often between 20% and 30%, with median survival not exceeding 12 months following the development of androgen-independent prostate cancer (AIPC). Over the past years, most chemotherapy agents were at best palliative. The combination of mitoxantrone and prednisone was approved by the US Food and Drug Administration (FDA) because of its ability to provide palliation to patients with metastatic AIPC, but the combination offered no survival benefit over prednisone or hydrocortisone. This paper reviews the current recommendations for the treatment of metastatic AIPC, with docetaxel/prednisone as the standard.

Docetaxel: First-Line Chemotherapy for Metastatic AIPC

The FDA recently approved docetaxel for the treatment of metastatic AIPC. Two landmark studies — a Southwest Oncology Group trial (SWOG-9916) and the TAX-327 trial — showed survival benefit for patients with metastatic AIPC.

The SWOG-9916 trial⁶ randomized 674 patients with metastatic AIPC to receive either docetaxel plus estramustine or mitoxantrone plus prednisone. The study showed a marked improvement in survival, time to progression, and PSA response in patients who were treated

with the docetaxel and estramustine combination. The combination also was superior to mitoxantrone and prednisone in median survival (17.5 months vs 15.6 months, $P = .02$), median time to progression (6.3 vs 3.2 months, $P < .001$), and PSA declines of at least 50% (50% vs 27%, $P < .001$), with no difference in objective tumor response. Patients in the docetaxel and estramustine arm had a higher discontinuation rate (16% vs 10%), and life-threatening neutropenia was also higher with the docetaxel plus estramustine combination (5% vs 2%, $P = .01$).

In the TAX-327 trial,⁷ 1,006 men with metastatic AIPC received 5 mg of prednisone twice daily and were also randomized to one of three arms: (1) mitoxantrone every 3 weeks, (2) docetaxel once weekly for 5 weeks on a 6-week cycle, and (3) docetaxel once every 3 weeks. Patients who received docetaxel once every 3 weeks showed significant improvements over those receiving mitoxantrone in survival (18.9 months vs 16.5 months, $P = .009$), pain control (45% vs 32%, $P = .01$), quality of life (22% vs 13%, $P = .009$), and PSA response (45% vs 32%, $P = .001$), with no significant difference in objective tumor response in any of the three arms of the study. Those patients receiving weekly docetaxel showed no significant difference in survival (17.4, $P = .36$), borderline pain response (31%, $P = .08$), quality of life (23%, $P = .005$), or PSA (48%, $P = .001$) compared with those in the mitoxantrone group. Adverse side effects were more common in the group receiving docetaxel every 3 weeks. Neutropenia in this group was 46% compared with 32% in the weekly docetaxel arm and 22% in the mitoxantrone arm.

These studies have confirmed a 20% to 24% reduction in mortality in patients with metastatic AIPC treated with docetaxel and prednisone. Although the SWOG-9916 trial combined docetaxel with estramustine, this combination did not add any survival advantage when compared to the docetaxel/prednisone arm in the TAX-327. Therefore, most oncologists do not use estramustine/docetaxel combination in clinical practice. There is also an increased risk of thrombosis with this combination. Based on these trials, overall survival should be the standard endpoint for subsequent trials in metastatic AIPC. It is important to note that PSA response did not correlate with survival in the TAX-327 trial and that objective tumor response did not correlate with survival in both trials (Table).

Novel Agents

Despite improved survival shown with docetaxel/prednisone, the benefit is at best 2 months compared to mitoxan-

Data From Phase II/III Trials in Androgen-Independent Prostate Cancer: Overall Survival, PSA Response/Survival, Objective Response, and Time to Progression*

	Overall Survival (mos)	PSA Response Correlation With Survival	Objective Response	Time to Progression (mos)
Mitoxantrone/prednisone	16	N/A	7% TAX 327 11% SWOG 9916	3
Docetaxel/prednisone	18.5	SWOG-9916: yes TAX-327: no	11% SWOG 9916 7% TAX327 No difference	6
Satraplatin/prednisone	14	N/A	N/A	5.2
Docetaxel/calcitriol	23	no	No difference	N/A
Docetaxel/thalidomide	25	yes	N/A	5.9
APC8015 (Provenge)	25.9	N/A	N/A	N/A
GVAX	26.2	N/A	N/A	N/A

*Pooling of data, not head-to-head comparison.
N/A = data not available or not included in the study.

trone plus prednisone, and the progression-free survival is short (6 months). Therefore, there is a need to further improve on these results. Several novel agents with different mechanisms of action and less toxicity are being studied in combination with docetaxel. These combinations (doublets) have shown promising results.

Docetaxel/Calcitriol

Vitamin D receptors are present in most prostate cancer cell lines. Exposure to 1,25-dihydroxyvitamin D₃ induces differentiation as well as decreased proliferation and invasiveness in these cell lines. Preclinical studies have shown that calcitriol, an oral form of vitamin D, enhances cell death in several prostate cancer cell lines. However, commercially available formulations of calcitriol were not designed for cancer therapy, so a high concentration of calcitriol (DN-101) was formulated for use in the clinical trials.

In a phase II study of docetaxel plus calcitriol, patients with AIPC had an 81% PSA response rate (more than a 50% decrease in the PSA).⁸ Median time to progression was 11.4 months. A subsequent phase III study, the Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT) trial,⁹ consisted of two arms: docetaxel plus calcitriol and docetaxel plus placebo. Docetaxel at 36 mg/m² weekly for 3 out of 4 weeks was used in the trial instead of 75 mg/m² every 3 weeks, which was the dose and frequency approved by the FDA. On an interim analysis at 18 months, there was no significant improvement of PSA response between the two arms. Overall survival was 16 months for the docetaxel/placebo arm, but in the combination arm the overall survival was not yet reached (estimated survival was 23 months). Toxicity was similar in both arms. Since this study with 250 patients was underpowered to give survival results, a second phase III trial has been initiated and will be powered appropriately.

Docetaxel/Vinorelbine

Vinorelbine is a microtubulin inhibitor that affects polymerization of the microtubules. In a phase II study,¹⁰ 19 men with AIPC received a regimen of docetaxel 25 mg/m² and vinorelbine 20 mg/m² intravenously for 6 consecutive weeks followed by a 2-week rest. The regimen continued repeatedly until disease progression. An objective response rate was observed in 2 of 9 men with measurable disease (22%). Side effects included neutropenia and neuropathy. In another trial,¹¹ 40 patients with progressive metastatic disease were given docetaxel at 60 mg/m² on day 1 and vinorelbine at 15 mg/m² on days 1 and 8 of a 21-day cycle. A decrease in PSA of more than 50% was reported in 19 patients (37%) with no prior chemotherapy and in 21 patients (29%) who had received one or more prior chemotherapy treatments.

Docetaxel/Capecitabine

Capecitabine is an oral thymidine synthetase inhibitor. The combination of docetaxel and capecitabine included the convenience of an oral drug with a different mechanism of action, although capecitabine as a single agent has limited activity in prostate cancer.¹² A recent study reported 77 men with AIPC who were given docetaxel intravenously at 60 mg/m² and capecitabine orally at 1,000 mg/m² twice a day for 14 days on a 21-day cycle.¹³ The PSA response rate was 36%, and the median progression free-survival was 5.1 months. Common side effects included mucositis, fatigue, and hand-foot syndrome.

Docetaxel/Thalidomide

Thalidomide was initially thought to have antiangiogenesis activity, but to date its mechanism is poorly understood. It is believed to have an immunomodulatory effect on the tumor microenvironment. As a single agent, thalidomide has a PSA response rate of 15%. In a randomized phase II study¹⁴ consisting of two arms, docetaxel plus thalidomide and docetaxel alone, a response rate of 53% was seen in the combination arm compared with 37% in the docetaxel-only arm. The median progression-free survival was 5.9 months for the combination and 3.7 months for docetaxel alone. Toxicities in both groups were manageable after administration of prophylactic low-molecular-weight heparin in the combination group due to thrombosis. Major toxicities included thrombosis, constipation, and neuropathy. Updated results of the study showed a survival of 25.9 months for the combination arm and 14.7 months for docetaxel-alone arm.¹⁵

Docetaxel With Bevacizumab Plus Estramustine

Angiogenesis is a critical step in proliferation, growth, and metastasis. Vascular endothelial growth factor (VEGF) is an angiogenesis factor that is markedly increased in men with metastatic prostate cancer. Bevacizumab is a humanized monoclonal antibody that targets VEGF and has recently been reported to improve survival in patients with colon, breast, and lung cancer. A phase II trial by the Cancer and Leukemia Group B (CALGB) evaluated the activity of bevacizumab in hormone-refractory prostate cancer. Docetaxel combined with bevacizumab plus docetaxel showed a PSA response rate of 77% and a median progression-free period of 10 months.¹⁶ The CALGB is currently conducting a phase III study using docetaxel/prednisone with and without bevacizumab.

Docetaxel/Imatinib Mesylate

Platelet-derived growth factor (PDGF) has been implicated in the progression of prostate cancer and bone metastasis, and it is expressed in 80% of AIPC lesions.¹⁷ Preclinical trials have found that imatinib mesylate, a PDGF inhibitor, is active in prostate cancer cell lines. In

a multi-institutional phase II trial¹⁷ of imatinib as a single agent in 17 patients with hormone-refractory prostate cancer after PSA progression, 6 patients (35%) demonstrated stable disease. In a modular phase I trial of 21 patients with AIPC and bone metastases,¹⁸ a decline in PSA of more than 50% was observed in 8 patients (38%). Dose-limiting toxicities included fatigue (35%) and nausea (20%).

Novel Targets

Ixabepilone

Ixabepilone (BMS-247550), a synthetic epothilone B analog, is a novel microtubulin inhibitor. Epothilones are a new class of chemotherapeutic agents that exhibit activity in taxane-resistant animal models.¹⁹ A study of ixabepilone²⁰ with or without estramustine revealed a PSA response of 69% in the combination arm and 48% in the ixabepilone-alone arm. A phase II study as first-line single-agent treatment²¹ showed a PSA response rate of 39%. The major dose-limiting toxicity of this agent was peripheral neuropathy. Neutropenia and peripheral neuropathy were the most common side effects. A single-agent study of BMS-247550 demonstrated a PSA response of 34%.²¹ Unfortunately, 29% of the participants developed significant neuropathy. The objective response rate was 16%.

Satraplatin

Satraplatin is an oral platinum analog that has significant inhibitory activity in platinum-resistant tumor models. A phase II study²² showed that 10 of 39 participants had a PSA response. A phase III study²² including 50 patients consisted of two arms: satraplatin and satraplatin/prednisone. The planned accrual of this study was 380 participants, but the study was prematurely closed since patients in the satraplatin-only arm had significant improvement in progression-free survival compared to those in the combination arm (5.2 months and 2.5 months, respectively), and PSA response was also superior (33% vs 9%). The EORTC is conducting an ongoing trial with two arms, satraplatin/prednisone and prednisone, as second-line agents in patients with metastatic AIPC.

Vaccines

The immune process is significantly altered in cancer. Vaccines are being developed to stimulate the immune system that in turn improve the function of antigen presentation and stimulate dendritic cells. Proteins expressed in prostate cancer including PSA, prostatic acid phosphatase, and prostate membrane antigens have been used as targets for developing immunotherapy.²³

The APC8015 vaccine (Provenge) consists of autologous dendritic cells that have been exposed to a

recombinant protein of prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor (GM-CSF). A phase III trial²⁴ compared placebo and the vaccine in patients with AIPC. Time to progression, the primary endpoint, was not met but on further analysis at 36 months, a median survival advantage was seen in the patients who received the vaccine (25.9 vs 21.4 months on the placebo arm).

GM-CSF-GVAX is a vaccine composed of whole tumor cells including two allogeneic prostate cancer cell lines that have been genetically modified to secrete GM-CSF. GM-CSF is a cytokine that regulates proliferation and differentiation of myeloid cells and also increases the efficiency of tumor antigen presentation and subsequent activation of tumor-specific cytotoxic T lymphocytes.²⁵ A study in patients with metastatic AIPC²⁶ reported a median survival of 26.2 months compared to 19.5 months (based on the Halabi nomogram, a predictive nomogram to predict individual survival). A phase III placebo-controlled clinical trial is underway with the primary endpoint of showing a significant overall survival difference.

Bone-Targeted Treatment

Several bone-targeted treatments have been developed over the past years. These treatments are aimed at palliating bone metastasis, which is the most common site of metastases and morbidity.

Bone-targeted radioisotopes are indicated for pain due to bone metastases. The radiopharmaceuticals currently available include phosphorus-32, strontium-89, and samarium-153. A review of four placebo-controlled trials²⁷ showed evidence of a small benefit on pain control. Mild myelosuppression was the predominant toxicity with the bone-seeking radiopharmaceuticals.

Chemotherapy has been combined with radiopharmaceuticals. In preliminary studies in which strontium-89 was combined with doxorubicin, survival improved when given to stable or responding patients with metastatic disease. However, the regimen is cumbersome to administer and is associated with significant toxicity.²⁸

Zoledronic acid is approved by the FDA to prevent skeletal events in patients with bone metastases. In animal studies, it has shown an inhibitory effect on both osteolytic and osteoblastic bone.²⁹ Zoledronic acid can cause osteoclast apoptosis resulting in a decrease in osteoblastic lesions. In a placebo-controlled trial,³⁰ zoledronic acid decreased the amount of skeletal events by 36%. Common toxicities included myalgia, bone pain, and occasionally renal insufficiency.

Atrasentan

Endothelin-1 (ET-1) is a potent vasoconstrictor that modulates cell growth in prostate cancer. It has been implicated in progression and osteoblastic metastasis.³¹

Several phase II and phase III studies³² have shown only a trend toward improvement in time to progression; however, in a meta-analysis of data, atrasentan significantly prolonged time to progression 19% ($P = .002$), decreased alkaline phosphatase ($P = .001$), and improved quality of life ($P = .003$), time to onset of bone pain, and biochemical time to progression.³³ Common adverse effects included rhinitis, peripheral edema, and headache. The SWOG-S0421 trial is testing this further in patients with metastatic AIPC to the bone in a randomized phase III trial to compare the efficacy of docetaxel and prednisone with or without atrasentan. This trial will evaluate whether combination of chemotherapy and a bone-targeted drug such as atrasentan will provide an improvement in progression-free survival as the primary endpoint.

Conclusions

Currently, the standard of care for patients with metastatic AIPC is the combination of docetaxel and prednisone. Because of its progression-free survival of only 6 months, more trials are needed to either study novel therapeutic agents in combination with docetaxel or discover novel therapeutic targets through the available technologies in the form of genomics and proteomics. Since the standard for determining therapeutic efficacy is overall survival, the goal of treatment should focus on using the least toxic drugs to produce the maximum control and possibly a cure in the future. To succeed in this endeavor, it is imperative that the urologist, radiation oncologist, and medical oncologist work as a team to achieve this goal for their patients.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin*. 2006;56:106-130.
2. Koeneman KS, Yeung F, Chung LW. Osteomimetic properties of prostate cancer cells: a hypothesis supporting predilection of prostate metastasis and growth in the bone environment. *Prostate*. 1999;39:246-261.
3. Baweja M, Tan W. Bone metastases from prostate cancer: known and novel targets for palliation. *Support Palliat Cancer Care*. 2005;1:47-58.
4. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol*. 1996;14:1756-1764.
5. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone refractory prostate cancer: result of the Cancer and Leukemia group B 9182 study. *J Clin Oncol*. 1999;17:2506-2513.
6. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004;351:1513-1520.
7. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351:1502-1512.
8. Beer TM, Eilers KM, Garzotto M, et al. Weekly high-dose calcitriol and docetaxel in metastatic androgen independent prostate cancer. *J Clin Oncol*. 2003;21:123-128.
9. Beer TM, Ryan CW, Venner PM, et al. Interim results from ASCENT: a double-blinded randomized study of DN-101 (high-dose calcitriol) plus docetaxel vs placebo plus docetaxel in androgen-independent prostate cancer (AIPC). *J Clin Oncol*. 2005;23(16S, Pt 1):4516. Abstract.
10. Di Lorenzo G, Pizzia C, Autorino P, et al. Weekly docetaxel and

vinorelbine (VIN-DOX) as first line treatment in patients with hormone refractory prostate cancer. *Eur Urol*. 2004;46:712-716.

11. Goodin S, Rao KV, Kane M, et al. A phase II trial of docetaxel and vinorelbine in patients with hormone-refractory prostate cancer. *Cancer Chemother Pharmacol*. 2005;56:199-204.
12. Spicer J, Plunkett T, Somaiah N, et al. Phase II study of oral capecitabine in patients with hormone-refractory prostate cancer. *Prostate Cancer Prostatic Dis*. 2005;8:364-368.
13. Kolodziej M, Neubauer M, Pluenecke R, et al. Results of a phase II trial of capecitabine and docetaxel in hormone-refractory patients. *Proc Annu Meet Am Soc Clin Oncol*. 2005;286. Abstract.
14. Dahut WL, Gulley JL, Arlen PM, et al. Randomized phase II trial of docetaxel plus thalidomide in AIPC. *J Clin Oncol*. 2004;22:2532-2539.
15. Retter A, Ando Y, Price DK, et al. Follow-up analysis of a randomized phase II study of docetaxel and thalidomide in androgen-independent prostate cancer: updated survival data and stratification by CYP2C19 mutation status. *Proc Annu Meet Am Soc Clin Oncol*. 2005;265. Abstract.
16. Picus J, Halabi S, Rini B, et al. The use of bevacizumab with docetaxel and estramustine in hormone refractory prostate cancer: interim result of CALGB 90006. *Proc Annu Meet Am Soc Clin Oncol*. 2005;1578. Abstract.
17. Ko YJ, Small EJ, Kabbavar F, et al. A multi-institutional phase II study of SU101, a platelet-derived growth factor receptor inhibitor, for patients with hormone-refractory prostate cancer. *Clin Cancer Res*. 2001;7:800-805.
18. Mathew P, Thall PF, Jones D, et al. Platelet-derived growth factor receptor inhibitor imatinib mesylate and docetaxel: a modular phase I trial in androgen-independent prostate cancer. *J Clin Oncol*. 2004;22:3323-3329.
19. Goodin S, Kane MP, Rubin EH. Epothilones: mechanism of action and biologic activity. *J Clin Oncol*. 2004;22:2015-2025.
20. Galsky MD, Small EJ, Oh WK, et al. Multi-institutional randomized Phase II trial of the epothilone B analog ixabepilone (BMS 247550) with or without estramustine phosphate in patients with progressive castrate metastatic prostate cancer. *J Clin Oncol*. 2005;23:1439-1446.
21. Hussain M, Tangen CM, Lara PN Jr, et al. Ixabepilone (epothilone B analogue BMS-247550) is active in chemotherapy-naïve patients with hormone-refractory prostate cancer: a Southwest Oncology Group trial SWOG0111. *J Clin Oncol*. 2005;23:8724-8729.
22. Sternberg CN, Whelan P, Hetherington J, et al. Phase III trial of satraplatin, an oral platinum plus prednisone vs prednisone alone in patients with hormone refractory prostate cancer. *Oncology*. 2005;68:2-9.
23. Fong L, Small E. Immunotherapy for prostate cancer. *Curr Urol Rep*. 2006;7:239-246.
24. Small EJ, Chelhammer PF, Higano C, et al. Immunotherapy (APC8015) for androgen independent prostate cancer: final survival data from a phase 3 randomized placebo-controlled trial. *Proc Annu Meet Am Soc Clin Oncol*. 2005;284. Abstract.
25. Roth MD, Gitlitz BJ, Kiertscher SM, et al. Granulocyte macrophage colony-stimulating factor and interleukin-4 enhance the number and antigen-presenting activity of circulating CD14+ and CD 83+ cells in cancer patients. *Cancer Res*. 2000;60:1934-1941.
26. Small J, Higano C, Smith D, et al. A phase 2 study of an allogeneic GM-CSF gene-transduced prostate cancer cell line vaccine in patients with metastatic hormone-refractory prostate cancer (HRPC). *Proc Annu Meet Am Soc Clin Oncol*. 2006;254. Abstract.
27. McEwan AJ. Use of radionuclides for palliation of bone metastases. *Semin Radiat Oncol*. 2000;10:103-114.
28. Tu SM, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomized phase II trial. *Lancet*. 2001;357:336-341.
29. Coleman RE. Bisphosphonates: clinical experience. *Oncologist*. 2004;9(suppl 4):14-27.
30. Saad F, Gleason DM, Murray R. Long-term efficacy of zoledronic acid for prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004;96:879-882.
31. Carducci M, Nelson JB, Saad F, et al. Effects of atrasentan on disease progression and biological markers in men with metastatic hormone-refractory prostate cancer: phase 3 study. *Proc Annu Meet Am Soc Clin Oncol*. 2004;4508. Abstract.
32. Vogelzang NJ, Nelson JB, Schulman C, et al. Meta-analysis of clinical trials Atrasentan 10 mg in metastatic hormone refractory prostate cancer. *Proc Annu Meet Am Soc Clin Oncol*. 2005;4563. Abstract.
33. Sleep DJ, Nelson JB, Petrylak DP, et al. Clinical benefit of atrasentan for men with metastatic hormone-refractory prostate cancer metastatic to bone. *J Clin Oncol*. 2006;24:18S. Abstract 4630.