Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Deferring treatment of some prostate cancer is feasible but is still not acceptable to most doctors and patients. ♦ Proton beam radiation devices may be the technology to watch for the future. ♦ PSA doubling time (PSADT) is starting to replace PSA measurement for detecting prostate cancer and predicting its aggressiveness, and Gen-Probe's Aptima PCA3 assay looks promising, but higher sensitivity and specificity are needed before it gets widespread adoption. ♦ Chemotherapy should be used earlier, more aggressively, and as part of a multimodal treatment approach. Of particular interest were Genentech's Avastin and epothilones, especially Bristol-Myers Squibb's ixabepilone and Novartis's ZK-EPO**.** ♦ Doctors were cautiously optimistic that Abbott's Xinlay will eventually get FDA approval, for delaying formation of bone metastases, not therapy of prostate cancer. ♦ Other agents worth watching include: Celgene's Revlimid, Novacea's DN-101 (high dose calcitriol), and OncoGenex Technologies' OGX-011 and OGX-427.

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ASCO PROSTATE CANCER SYMPOSIUM

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The 2006 Prostate Cancer Symposium was co-sponsored by the American Society of Clinical Oncology (ASCO), the American Society for Therapeutic Radiology and Oncology (ASTRO), the Prostate Cancer Foundation (PCF), and the Society of Urologic Oncology (SUO). It was a very good review of the state of research in prostate cancer, but little new data were presented.

Prostate cancer, the second leading cause of cancer death in men, is diagnosed in more men each year than lung and colon cancer combined. The American Cancer Society estimates that more than 232,000 men were diagnosed with prostate cancer in 2005, and 70% of these were age 65 or older at diagnosis. More than 30,000 men died from the disease last year. The good news is that mortality rates have been on the decline since the early 1990s, and the five-year survival rate has increased steadily to 99% for all stages combined.

The treatment options for low-intermediate risk prostate cancer are:

- External beam radiation (XRT, 3-D conformal, IMRT, IGRT, and proton).
- Brachytherapy.
- Radical prostatectomy.

Among key points made at this meeting were:

Watchful waiting or "deferred treatment." Opinion leaders were urging doctors to defer more treatments, a description they prefer to the term "watchful waiting." One source said, "You don't have to treat everyone. It is mainstream and respectable not to treat everyone." Another expert said, "What do we do with the PSA failures (post radical prostatectomy)? For the large majority the answer should be: Don't treat. Delayed treatment is recommended for men with biochemical relapse …If it is really true that you should not treat the vast majority of patients with rising PSA – and I really believe that – then we should obviously stop measuring PSA. By measuring PSA we have essentially converted people who thought they were cured to people who now know they have disease and are consumed with anxiety. You can say it is impossible to stop measuring PSA, but it isn't." A third doctor said, "The message from the meeting is to do more delayed treatment, but I don't think it will happen at least until we have the ProtecT trial results (a U.K. study evaluating treatments for localized prostate cancer, comparing radical prostatectomy, radical conformal radiotherapy, and active monitoring)."

Doctors heard this message, but they didn't appear to agree. They indicated they have no plans to increase the number of patients on watchful waiting. The main

reasons they cited for this disconnect:

1. **Patients won't accept not being treated.** A doctor said, "If you suggest watchful waiting, patients will split and go to another doctor. It is very difficult to get patients to do nothing in the U.S."
2. **The data aren't sufficient.**

Anti-androgen hormone therapy. Chemotherapy may allow hormone therapy to be tried again in hormone refractory patients. A speaker commented, "For some reason some patients, after chemotherapy, may respond a second time to hormonal therapy. In patients who've been through chemotherapy and need a drug holiday, consider doing hormone therapy again." Another said, "The quality of life issue with hormone therapy is a big deal."

However, sources estimated that use of LHRH (luteinizing hormone-releasing hormone) agonists – such as TAP Pharmaceuticals' Lupron (leuprolide acetate) – has been declining somewhat, and they predicted it would continue to decline. An expert said, "Slow-rise PSA patients are being watched, and patients with doubling PSA are getting treatment. There are more lower risk patients today, so it is harder to justify hormone use."

In all chemotherapy trials hormonal therapy is not stopped. Rather, it was continued while patients were in the trials. A speaker said, "We don't have a lot of evidence for why patients with prostate cancer must stay on hormonal therapy… That is different from breast cancer...and I see doctors who are used to breast cancer who are stopping hormonal therapy in prostate cancer."

Data were presented by European researchers on **FERRING PHARMACEUTICALS' degarelix**, a novel gonadatropin-releasing hormone (GnRH) receptor blocker. This was a one-year, open-label, multicenter, randomized study in Europe and South Africa. Researchers concluded that degarelix has an immediate onset of action with testosterone suppression to castrate levels occurring in 90% of men within three days of subcutaneous injection – with no testosterone surge. Degarelix was well-tolerated, and adverse events were similar in the various treatment groups. The optimal dosing regimen was an initial dose of 240 mg, with a 160 mg dose maintaining castrate testosterone values in 100% of men from Day 28-364.

Fatigue. Amgen's Epogen (erythropoietin alfa), methylphenidate, and Cephalon's Provigil (modafinil) all were mentioned as possible treatments for the fatigue associated with prostate cancer.

Bisphosphonates. Not all bisphosphonates are created alike when it comes to bone metastases in prostate cancer patients. A study reported that Novartis's Aredia (pamidronate) doesn't work in preventing bone mets. Other trials have shown Schering AG's Bonefos (clodronate) – which is not yet FDA approved – to be ineffective. However, AstraZeneca's Zometa (zoledronic acid), the most potent FDA-approved bisphosphonate, does appear to have value.

Viral link. Cleveland Clinic and University of California, San Francisco, researchers reported using gene array technology to find a virus associated with genetic susceptibility to prostate cancer. The researchers emphasized that they have not found a direct link between the XMRV virus and prostate cancer, but they called it an important research discovery.

The XMRV virus was found 30 times more frequently in men with a specific mutation in HPC1, the gene that produces the RNaseL protein, causing it to stop functioning normally. Of the 20 men with two mutated copies of the HPC1 gene, 45% had the XMRV gene compared to only 1.5% of the 66 men with one or no copies of the mutated gene.

Some other viruses have already been linked to cancer. For example, human papilloma virus (HPV) has been associated with cervical cancer, and hepatitis B and C viruses have been blamed for liver cancer. Dr. Erick Klein of the Cleveland Clinic said, "This could be the first evidence that a virus is linked to prostate cancer…The hypothesis is that infection leads to chronic inflammation of the prostate, which ultimately leads to cancer." He speculated that the XMRV virus could be sexually transmitted, similarly to HPV.

Researchers now plan to test hundreds more prostate patients, and they are developing a diagnostic tool to test for the XMRV virus in the blood. They also want to determine how widespread the virus is in humans and whether it is exclusive to prostate patients. They are planning an epidemiological study to look at the association between sexual history, personal and family medical history, viral infection, and prostate cancer.

Surgeon experience. Practice may not make surgeons perfect, but it does make them better. A study found that – at least among surgeons at academic centers – the number of prostatectomies a surgeon does is associated with the rate of biochemical recurrence (BCR) in patients. A source estimated that 50,000-60,000 men a year develop BCR, and it is an underserved market, but it is a hard endpoint to measure. Researchers said 54% of the observed difference in BCR can be explained by genuine differences in surgical technique and approach, not just chance alone.

Referral patterns. Experts claimed that referral patterns are changing, that urologists are referring more patients to medical oncologists and radiation oncologists, and they are doing it sooner. However, speakers called for improved collaboration among these three specialties.

Quality of life is becoming more important in determining treatment decisions.

RADIOTHERAPY (RT)

The rate of change in PSA following RT is predictive of survival. Men with a very short doubling time (<3 months) die in six years, on average.

IMRT and IGRT. A speaker estimated that at least 50% of centers are doing IMRT, though perhaps not for every patient. Another expert said, "We don't have IGRT yet, but we are on the cusp. Now we can bill for IGRT, and there will be a tidal wave of use." A third source commented, "The technology is great, but it is seductive and expensive."

Questions have been raised about the risk:benefit ratio of IMRT in younger men (40s and 50s), and several experts said they will not do IMRT in men in that age group. One commented, "I'm very worried about IMRT in young patients. Inducing cancer with radiation is a small but real risk." Another expert said, "I generally don't refer patients in their 40s and 50s for RT. I offer them the option, but most men prefer surgery." A speaker said, "The good news is that (IMRT) is highly conformal. The bad news is that there are hot spots within the target volume which are of clinical significance. And there is low dose spread, and the consequences of that in 10-30 years is unknown…There is no question IMRT allows a very creative use of radiotherapy, but it is also very well reimbursed and allows some creative billing nationally. Many urologic practices are now opening IMRT centers, and you have to wonder about the quality that will be delivered at those centers."

Dosing. Researchers are challenging the idea that more small doses of radiation are the best approach in prostate cancer. Speakers suggested that less fractionation and more dose per day may be a better strategy.

Proton beam therapy. This also is highly conformal, but the beam is not as sharp at the prostate depth. Five sites in the U.S. (one each in California, Texas, Florida, Ohio, and Massachusetts) currently have proton beam radiation devices. An expert said it is good for pediatric and CNS tumors but of less clear benefit in prostate cancer. He said, "Watch proton beam over the next 10 years…And watch for combined IMRT and proton technology…It could be there is no clinically significant advantage to this high technology…but over the next 3-5 years, we will be looking at quality of life with proton beam, 3-D, and IMRT." Another expert said, "Protons are costly to install. You need cyclotrons, but they are very sharp and very accurate…There is a perception that it may be better, and that is driving installation. But the value is not proven." The two companies with proton beam devices are Belgium-based Ion Beam Applications (IBA) and a Japanese company.

Cost-effectiveness of Proton Beam Therapy for a 70-year-old Male

Measurement	5 years	10 years	15 years
Proton beam: expected mean cost	$59,656	$61,383	$62,872
IMRT: expected mean cost	$28,947	$32,910	$36,100
Incremental cost-effectiveness ratio	$613,780/QALY	$111,250/QALY	$66,930/QALY

Reportedly the Japanese vendor will put in the accelerator based only on per-use charges.

A study by researchers at Fox Chase Cancer Center in Philadelphia found that protons can approach cost-effectiveness (≤$50,000/QALY), but only over a long period of time (>15 years).

Stereotactic radiotherapy. This should only be done in a trial, a speaker emphasized, warning that it would prove valuable or be a catastrophic disaster in prostate cancer.

RT and VEGF inhibitors. How will anti-angiogenic therapy integrate with RT? A speaker said it could help or it could make tumors resistant to radiation.

DIAGNOSTICS

PSA velocity (PSAV) and PSA doubling time (PSADT)

PSA is not considered a great test; it misses an estimated 30% of cancers, and about two-thirds of men have elevated PSA due to non-cancerous reasons. An expert said, "PSA is no better than a coin flip."

As a result, interest is growing in how fast PSA rises rather than just the PSA level, and several new studies were presented on the use of PSAV and PSADT for detecting cancer and predicting its aggressiveness. However, most experts are not yet convinced that either of these measures should dictate treatment decisions yet, and one source suggested PSADT may need to be adjusted for both age and Gleason score. Another expert said, "The jury is still out (on how to use PSADT)."

Probability that Rising PSA after RT Will Lead to Death

Measurement	PSADT <3 months	PSADT >3 months
5 year mortality	31%	1%

A study of 113 patients found that PSADT was ***not*** predictive of a positive bone scan, suggesting that other factors or symptoms may be more appropriate for when to image for recurrent or metastatic disease. Researchers found no PSADT cut-off value predictive of a positive bone scan or positive CT scan. An investigator said, "We may no longer base scans just on PSADT but on a conglomeration of factors, especially symptoms."

GEN-PROBE'S Aptima PCA3

PCA3 is a marker that Gen-Probe is working on to improve the sensitivity and specificity of prostate cancer tests. PCA3 is a non-coding prostate-specific mRNA that is highly up-regulated in prostate cancer. Like PSA, PCA3 is isolated from urine specimens. PCA3 is basically another prostate-centric gene, and the Gen-Probe assay compares the relative expression

patterns (mRNA) of both PSA and PCA3 to boost the prognostic value of PSA alone. The doctor does a digital rectal exam (DRE) before collecting the urine sample and sending it off to the lab. The urine sample is analyzed for relative expression of PSA and PCA3.

A poster presented at ASCO Prostate reported on a study of urine samples from 491 North American men who were scheduled for biopsy or prostatectomy. Researchers reported that the specificity was higher than for serum PSA in all subgroups tested, with the benefit most evident in men with ≥1 prior negative biopsy, while the serum PSA assay had essentially no diagnostic value in this population.

A Gen-Probe researcher said the key findings in her poster were: "Hopefully, PCA3 will help guide physicians in what to do in men with rising PSA who have had one negative biopsy. Should they do another biopsy or delay an additional biopsy?" She said the company is working on improving the assay, "Two labs are evaluating our ASR product (test) to create their own PCA3 assay, and we are working on our own assay. PSA is our normalizer. The PCA3 number alone doesn't tell you anything. A patient could have a high normal or a low cancer level, so there is a need for the PSA to normalize it. I'm not saying the assay gives a diagnosis of cancer or not, but it is an additional tool in making treatment decisions. It is an improvement over the specificity of PSA."

Doctors commenting on the outlook for this assay generally wanted to see higher sensitivity and specificity before they would adopt it. There were no other assays that they thought were more promising, but they were very reserved about the Aptima PCA3. They said:

- "There is a suggestion that the test is telling us something that is real but not significant. It is not better than PSA, but it is better than guessing."
- "It's promising. The question is what to do with the information and when to change your biopsy practice based on markers. The question is what you miss if you don't get the correct diagnosis. They need to standardize the number of cores in a biopsy for validation studies. They also need more work and studies where it is controlled for follow-up and for biopsy procedures."
- "I just don't know what to make of it. I prefer PSADT."

PCA3 Sensitivity and Specificity

Men	PCA3		PSA	
	Sensitivity	Specificity	Sensitivity	Specificity
All	50%	75%	50%	57%
With 1 prior negative biopsy (n=119)	50%	78%	---	---
With ≥2 prior negative biopsies (n=64)	50%	83%	---	---
With ≥1 prior negative biopsy (n=188)	50%	80%	50%	50%

- "PCA3 is promising, but the specificity needs to be ≥90%, and the sensitivity needs to be ≥75%. Only then would I consider using it."
- "Sensitivity and specificity both need to be ≥90%. But you still can't replace a biopsy because the Gleason score remains the most important prognostic factor."

JOHNSON & JOHNSON/VERIDEX/IMMUNICON'S CellSearch

This is starting to get traction in breast cancer, and new data presented at ASCO Prostate suggested measuring circulating tumor cells (CTCs) may have utility in prostate cancer as well. A study of 18 patients with >15 circulating tumor cells per 7.5 mL of blood showed that the androgen receptor gene was amplified by FISH analysis in a significant number of patients who all failed hormone therapy. In comparison, none of these patients had amplification of HER2. An investigator said, "Molecular profiling of CTCs obtained by immunomagnetic selection is feasible in a significant percentage of patients with metastatic prostate cancer."

ASCO guidelines say that specialized techniques to detect isolated tumor cells are not a required part of sentinel lymph node evaluation at this time. Experts predicted that eventually CTC measuring will be more routine, but most do not believe use of this test will increase substantially over the next year.

ALGETA'S Alpharadin (radium-223)

In a Phase I trial, this external beam radiation (XRT) sensitizer showed minimal toxicity. It is currently in a multicenter, European Phase II trial in patients with bone metastasis from prostate cancer. Although the company has data on 100 patients in Europe, a source said the FDA is demanding additional ***preclinical*** data before it will approval a U.S. clinical trial in humans.

Preliminary (16-week) biomarker data from the Phase II study was presented at ASCO Prostate. After receiving palliative XRT, HRPC patients were randomized to 4 IV injections of Alpharadin or saline, repeated at four-week intervals. Researchers concluded that Alpharadin had:

- Minimal bone marrow toxicity after repeated administration.
- Strong effect on bone micro-environment (show with bone-ALP and other markers of bone turnover).
- Favorable SA response.

Preliminary Alpharadin Phase II Biomarker Data

Measurement	Alpharadin n=31	Placebo n=28	p-value
Patients getting 4 injections	28 patients	21 patients	---
Confirmed PSA responder	32%	18%	.243
PSA responder	48%	18%	.0263
Confirmed PSA progressor	16%	36%	.133
PSA progressor	19%	57%	.004

CHEMOTHERAPY

Chemotherapy for prostate cancer got a huge boost at this meeting, not only from a review of the numerous experimental agents in development but also new uses for older drugs like Celgene's Thalomid (thalidomide). Treatment of prostate cancer was repeatedly compared to breast cancer. An expert said, "We need to use the breast cancer model more. Urologists, medical oncologists, and radiation oncologists need to work together. And we need to see a role in using chemotherapy earlier, after surgery but before metastatic disease develops instead of referring patients too late in their disease." Another doctor said, "For every one prostate cancer patient in a trial, there are four in breast cancer trials, and the populations in the two cancers is about the same."

A speaker suggested that current Phase II trial designs in chemotherapy may not be the best approach. Another speaker said none of the current experimental agents is likely to show more than a marginal improvement in survival, "These are not a home run, so we don't need to compare them to each other but to keep working on new agents."

SANOFI-AVENTIS'S Taxotere (docetaxel).

Taxotere remains the standard of care in first-line treatment of metastatic hormone-resistant prostate cancer (mHRPC), but second-line chemotherapy is clearly an unmet need. A doctor said, "What to do in docetaxel failures is a question, and that is a growing population. And second-line is a less crowded field, but a second-line drug can't be really toxic. Second-line is a more attainable registration process.

Interesting findings relating to Taxotere that were reported at the meeting include:

- Treatment every three weeks with Taxotere improves quality of life more effectively than Ares Serono's Novantrone (mitoxantrone) in hormone refractory metastatic prostate cancer (22.3% vs. 13%).
- Another study found that pain relief is correlated with better survival (18.2 months with Taxotere vs. 12 months with Novantrone). Earlier studies found that Taxotere increases survival. A researcher said, "Patients experiencing a reduction in pain during treatment can expect to live an average of six months longer compared to patients without pain reduction."
- Adjuvant Taxotere should be started earlier, soon after surgery. An expert predicted there will be an increase in this approach. Another expert said, "Even in patients with minimal symptoms, there is a benefit to starting chemotherapy early."
- In elderly patients, lower dose weekly Taxotere can often be a substitute for standard Q3W dosing. A speaker said, "There are more nail changes, and the toxicity is different (with weekly dosing), but my experience is that elderly patients not able to tolerate Q3W docetaxel can take it weekly – and if they do poorly, you can stop it easily."
- A speaker reassured doctors that it is not unethical to withhold Taxotere in asymptomatic HRPC patients, but an expert in the audience respectfully disagreed, making it clear that even the opinion leaders don't agree on this.

Novel therapies

More than 25 different novel and experimental therapies for prostate cancer were discussed at this meeting. Dr. Maha Hussain of the University of Michigan said several agents are exciting, but she pointed to the epothilones and targeted therapies as among the most promising, "Some of the targeted agents may have activity if we can figure out how to measure response, and they are promising in combination with chemotherapy."

The agents experts were most excited about include:

➢ **GENENTECH'S Avastin (bevacizumab).** This is probably the agent considered to have the most promise of all the experimental agents, but in combination with docetaxel, not as monotherapy. Dr. Hussain said, "By itself, Avastin does not appear to have measurable objective activity in a variety of tumors, but when added to chemotherapy it has shown survival advantages." Another doctor said, "Avastin is an easy trial to get patients in because it is a large trial and so many places are participating. The smaller Phase I and II trials are harder to get patients in because they are more regional-dependent. Avastin is the only cooperative group Phase III trial open in HRPC…If the Avastin trial is positive, it will set the bar for FDA approval of other agents."

Asked about the use of anti-angiogenic agents (like Avastin) upfront earlier, a speaker said, "Patients are continuing on hormonal therapy, so the difficulty in an earlier setting is that unless you have some evidence of assessing disease beyond PSA, it will be difficult to test the contribution of the agent vs. PSA reduction with hormone therapy…Putting experimental agents upfront will be difficult to assess in a single arm trial."

➢ **Epothilones**, especially **BRISTOL-MYERS SQUIBB'S ixabepilone (BMS-247550)** and **NOVARTIS'S ZK-EPO.** An expert said, "Ixabepilone is a drug worth putting up against docetaxel to see if it is better than docetaxel…There is also interest in it second- and third-line. (In trials) there was a disappointing PSA response second-line (17%), which may dampen enthusiasm as a second-line single agent, but potential combinations should be considered (including with mitoxantrone)."

A poster reported on Phase II results with ixabepilone in HRPC patients who progressed on docetaxel. There was one death from neutropenic sepsis. An investigator said, "I was surprised mitoxantrone did as well as it did, and that ixabepilone didn't do better…We need to pick the patients better."

The next Phase I/II trial, which will combine ixabepilone and mitoxantrone, is expected to start in the next couple of months in second-line, taxane-experienced patients (patients who have

progressed either on or off docetaxel, rather than only docetaxel-refractory patients).

Phase II Ixabepilone in HRPC Docetaxel-Refractory Patients

Measurement	Ixabepilone n=41	Mitoxantrone + prednisone n=41
Primary endpoint: PSA decrease >50%	17%	20%
Unconfirmed PSA decline >50%	1 patient	0
PSA decline 25%-50%	12%	12%
PSA decline <25%	12%	10%
No PSA decline	54%	56%
Mean number of cycles	3.6	4.2
Objective response	<3%	<3%
Estimated survival data	12-13 months	12-13 months
Safety		
Total adverse events	23 patients (64 events)	27 patients (66 events)
Treatment-related Grade 3-4 neutrophilia	17 patients	23 patients
Deaths	1 patient from neutropenic sepsis	0

➢ **AMERICAN PHARMACEUTICAL PARTNERS' Abraxane (ABI-007).**

➢ **CYTOKINETICS' ispinesib (SB-715992)**, a mitotic kinesin spindle protein (KSP). In Phase I trials the MTD of this novel small molecule was 18 mg/m^2 on a Q21 day schedule, with neutropenia the dose-limiting toxicity, but no neuropathy or significant GI toxicity. A SWOG Phase II trial is evaluating this agent in taxane-resistant androgen-independent prostate cancer (AIPC) and second-line therapy. Altogether, nine Phase II trials and five Phase I/Ib monotherapy and combination therapy trials are underway in a variety of cancers besides prostate cancer.

➢ **Halichondrin B analogs,** such as **EISAI'S E-7389**.

Other agents worth watching include:

ABBOTT'S Xinlay (atrasentan). Sources at this meeting were cautiously optimistic that this oral, QD, selective endothelin-1 (ET_1) antagonist eventually will get FDA approval in prostate cancer. In September 2005, an FDA Advisory Committee unanimously voted against approval for the treatment of mHRPC. Abbott had submitted Xinlay to the FDA based on a retrospective of subgroups in a failed Phase III trial and a failed Phase II trial. An Abbott official said, "We tried to argue that mHRPC is an unmet medical need." The panel concluded Xinlay showed some activity but needs to be studied further in a prospective trial – to determine how it works, identify which subgroups might be most likely to benefit, and better characterize potential cardiovascular safety risks. (In the Phase II trial, there was a four-fold increase in CV-related deaths vs. placebo).

The FDA wanted more data, and Abbott currently has another Phase III trial underway in early stage, non-metastatic prostate cancer with the goal of delaying formation of bone metastases. This is an event-driven trial which could be completed in 3Q06 or 4Q06, but the data may not be presented until ASCO Prostate 2007. A researcher said, "Atrasentan may work where Zometa failed." He said the FDA will be looking at the magnitude of the treatment effect and the robustness of the data, "If the benefit is marginal, that may not be enough. But if the results show a good treatment effect and a strong statistical positive then this one additional trial may be enough for approval."

Abbott also is in the planning stage with SWOG for a study of docetaxel + prednisone ± Xinlay in hormone refractory prostate cancer patients with bone metastases. Survival is the endpoint. An official said, "We know there isn't a profound effect in killing cancer cells. PSA will continue to rise. This is a bone-targeted drug. Unpublished animal data show that docetaxel + atrasentan is better than docetaxel alone in terms of tumor burden."

A speaker at the ASCO Prostate meeting said that one of the lessons from the rejected Xinlay trials was that baseline PSA and PSADT need to be matched between the arms of a trial. PSA was significantly higher in the Xinlay arms, and baseline PSADT was shorter in the Xinlay arm. He said, "We argue that you should stratify the population at the time of randomization...You should control for PSA and PSADT at randomization…with at least three values at least 12 weeks apart."

Preliminary data were presented on 27 of 38 proposed patients in a Phase I/II study of docetaxel + atrasentan in metastatic HRPC. Preliminary PK data showed that atrasentan doesn't affect the clearance of docetaxel. An investigator said, "Stable disease may be the role for this. There is no dramatic effect on PSA, but maybe it is good for stabilization. But we still need to look at bone mets and bone turnover markers…If it is approved, I'd use it like Zometa – in mHRPC patients for stabilization of disease."

A retrospective analysis of 690 patients with baseline bone metastases from the 809-patient MOO-211 trial was also presented.

Doctors asked about the outlook for this agent were cautiously optimistic. Among their comments were:

- *(Investigator #1):* "I'm not optimistic."
- *(Investigator #2):* "I think the trial is likely to be positive, and if it is approved, I would use it in combination with docetaxel first-line. This is not a single agent."

- *(Investigator #3):* "I'm optimistic. I think the FDA will approve it if there is one good trial, and then it would be used in HRPC patients with a rising PSA and no objective metastases, which is a two-year window. All men on hormone therapy eventually fail. The label will be for use ahead of docetaxel, but you could give them at the same time…There is no evidence docetaxel given earlier vs. later affects survival."
- "If it gets approved, it would only be a second-line therapy, after docetaxel."
- "It is a classic trial design issue. I think we've been doing trials in reverse – focusing on objective response rather than lack of response. Atrasentan won't necessarily kill a lot of tumor burden. Patients were mandated off the study when they developed new bone lesions (that was the definition of progression), but the new bone mets may not have been clinically meaningful…If the new trials are positive and it is approved, it will be widely used because it is directed at a fundamental issue. If it prevents bone mets in high risk patients, the benefit probably extends down. But use also depends on safety issues, and it appears safe, with only some runny nose and muscle aches."

Retrospective Analysis of Bone Pain in MOO-211 Atrasentan Trial in HRPC

Measurement	Placebo n=335	Atrasentan 10 mg n=355	p-value	Risk reduction
Time to disease progression	N/A	N/A	0.016	Down 19% (HR 0.813)
Radiographic progression	61.5%	59.7%	0.080	Down 15% (HR 0.846)
Clinical progression (events)	27.5%	20.0%	0.014	Down 32% (HR 0.68)
First new opiate analgesic or pain progression	54.9%	43.6%	0.004	Down 85 days (HR 0.72)
Bone pain	62.7%	54.1%	0.021	Down 20% (HR 0.795)
Median days to bone pain	77 days	117 days	---	Down 40 days
Mean change in PSA	~250	~125	<.05	---

Phase I/II Trial of Docetaxel + Atrasentan in mHRPC

Measurement	60 mg/m^2 atrasentan + docetaxel n=8	70 mg/m^2 atrasentan + docetaxel n=15	75 mg/m^2 atrasentan + docetaxel n=3	Overall n=26
TTP median	14 weeks	14 weeks	17 weeks	14.8 weeks
TTP maximum	29 weeks	Not reached	22.5 weeks	Not reached
Overall survival at 12 months	---	---	---	63%
Overall survival at 24 months	---	---	---	13%
Stable disease	5 patients	11 patients	1 patient	17 patients
≥50% PSA reduction	1 patient	2 patients	2 patients	5 patients
≥80% PSA reduction	1 patient	2 patients	1 patient	4 patients
Progressive disease	2 patients	2 patients	0	4 patients
Adverse events				
Adverse event	Grade 1-2	Grade 3	Grade 4	---
Neutropenia	8%	38%	15%	---
Febrile neutropenia	0	0	12%	--
Anemia	85%	0	0	---
Fatigue	96%	4%	0	---
Alopecia	38%	0	0	---

ASTRAZENECA:

➢ **Iressa (gefitinib).**

➢ **AZD-2171.** A 14-patient, Phase I study of QD dosing found the MTD to be 20 mg/day. There were no objective responses during this study, but 4 patients had stable disease by RECIST. Trials are continuing as combination therapy with chemotherapy and as single agent monotherapy in mHRPC and in docetaxel-refractory patients.

BAYER'S Nexavar (sorafenib, BAY-43-9006). An NCI-sponsored study reported that PSA continues to rise during treatment with sorafenib, but bone scans improve despite that. A researcher said, "PSA may be an inadequate biomarker for monitoring efficacy… There is activity, but we don't know how much or how long it lasts. Two of 22 patients in this study had a strong response, and one patient cleared 12 bone lesions in two months despite a rising PSA… And this is an oral agent that is well-tolerated."

However, it is not clear yet how long the effect will last, but sorafenib could, potentially, be given in addition to Zometa. NCI researchers have plans to do bone scans every 3-6 months, depending on the PSADT."

CELGENE:

➢ **Revlimid (lenalidomide).** Data on Revlimid in prostate cancer are expected at ASCO 2006. A doctor at ASCO Prostate reported on his experience with one patient on the combination of Taxotere (Q3W) and Revlimid who had a very good response. He said, "Revlimid is worth testing in a Phase II trial."

➢ **Thalomid (thalidomide).** A doctor said data show thalidomide is active, but he doubted that it will ever be used because Revlimid is more likely to be used instead. Two thalidomide studies were presented at ASCO Prostate:

1. A Phase II open-label, single-arm, single institution study at the Cleveland Clinic of thalidomide + GM-CSF in patients with localized prostate cancer. Researchers reported that neoadjuvant therapy with this combination was well-tolerated and did not appear to impact on peri-operative morbidity while inducing PSA declines in 79% of patients. Administration of the

combination appeared to induce T-cell, macrophage, and PTEN over-expression in prostate tumor tissue vs. a historical untreated control.

2. An open-label, single center study by the National Cancer Institute is looking at the effect of docetaxel + thalidomide + prednisone + Avastin in metastatic androgen-independent prostate cancer (mAIPC). A poster was presented on preliminary data from 22 of 33 planned patients (accrual is continuing). Researchers reported that the combination resulted in a high durable response in PSA (86%) with acceptable toxicity. All patients were given 1 mg/kg/day enoxaparin (Sanofi-Aventis's Lovenox) for thrombosis prevention. All patients remain on trial with no progression after a median of 7 treatment cycles, and disappearance of lesions was seen on multiple bone scans. The febrile neutropenia was seen until pegfilgrastim was added. No thrombosis was seen.

NCI Study of Taxotere + Thalomid + Avastin + Prednisone in mAIPC

Measurement	Combination n=22
PSA reduction >50%	19 patients
Median duration of >50% PSA reduction	6 cycles
PSA reduction >90%	11 patients
Grade 4 toxicity	11 patients with neutropenia
Grade 3 toxicity	3 patients with febrile neutropenia 3 patients with non-neutropenic infection

CELL THERAPEUTICS' Xyotax (paclitaxel polyglumex, PPX). In a currently-accruing trial in AIPC, a dose of 150 mg/m^2 was reported to have "acceptable tolerability." Grade 3 neuropathy occurred in 3 of 9 patients after 27 weeks of therapy using a Q3W cycle, so the protocol was amended to dosing Q4W. So far, patients on the trial have received a median of five cycles, with 2 PR in previously treated patients.

NOVACEA'S DN-101 (high dose calcitriol). Experts were fairly enthusiastic about this active form of vitamin D. DN-101 was studied in ASCENT, a multicenter, randomized, double-blind Phase II/III trial in 232 patients with AIPC in the U.S. and Canada, and those efficacy results were presented at ASCO 2005. At ASCO Prostate an exploratory analysis of thromboembolic events (defined as DVT, pulmonary embolism, cerebrovascular accident, arterial thrombosis, and MI) was reported. In that analysis, DN-101 patients had fewer thromboembolic events (TEs).

Thromboembolic Event Analysis of ASCENT Trial

Measurement	Placebo + Taxotere 36 mg/m^2 n=125	DN-101 45 µg on Day 1 + Taxotere 36 mg/m^2 IV on Day 2, repeated weekly 3 of 4 weeks n=125	p-value
Patients entering the trial on an antithrombotic agent	16%	10%	---
History of prior thrombosis or atrial fibrillation	15.2%	7.2%	---
Serious adverse events	41%	27%	.02
Serious adverse event TEs	7.2%	1.6%	.03
Grade 3-4 TEs	8.0%	1.6%	.02
All grade TEs	8.8%	1.6%	.01
All DVT/PE	6/1	1/1	---
All CVA/MI/AT	2/1/1	0/0/0	---

ONCOGENEX TECHNOLOGIES/ISIS PHARMACEUTICALS' OGX-011 and OGX-427. These cytoprotective chaperones were cited by several sources as promising. One speaker said responses with OGX-011 have been observed in prostate, lung, and ovarian cancer patients. The OGX-011 dose chosen for Phase II trials is 640 mg QW, and three Phase II trials are now underway. Clinical trials of OGX-427 are due to begin later this year in solid cancers, including mHRPC and lung.

PROCYON BIOPHARMA'S PCK-3145. This synthetic peptide is in early clinical trials to treat mHRPC. Researchers reported on eight patients added to the first clinical study of this drug. The results confirmed the safety and tolerability of PCK-3145. The majority of adverse events were clinically non-significant and unrelated to the study medication. Overall tumor response measured by CT scans showed stable disease in three patients. Some PSA reduction was observed in two patients, but it was not significant enough (>50%) to be considered a definitive response. A U.S. pilot study is ongoing to determine the optimal treatment schedule and to select the appropriate patient population. This will be followed by a Phase II trial looking at PFS.

SPECTRUM PHARMACEUTICALS' satraplatin. A Phase III trial of satraplatin as second-line therapy in 912 HRPC patients is fully enrolled, and the results are expected in 2007. An expert predicted that satraplatin would become "the de facto second-line therapy" if the trial is positive.

A poster at ASCO Prostate reported on PK data from a Phase I study, which found that there is an effect of food on the C_{max} of satraplatin – ~20% reduction in plasma ultrafiltrate (PUF) following a high fat meal – but AUC was unchanged. The clinical significance of the decrease in C_{max} is not known, but researchers recommended that satraplatin be administered to patients 1 hour before or 2 hours after a meal.

WYETH'S Rapamune (rapamycin). An investigator with a poster on this agent said he thought it may have a role as combination treatment. He plans to put together a Phase III trial as salvage therapy in HRPC after docetaxel.

DES (diethylstilbestrol). University of Washington researchers had DES specially made for their trial, but there reportedly are companies that are trying to bring this drug back. DES is a synthetic

estrogen that was prescribed in the 1950s-1970s to prevent miscarriage but also for pregnancy complications such as diabetes and high blood pressure. It was withdrawn from the market after it was discovered to cause a rare vaginal cancer in women and their daughters. An investigator said, "DES is more economical than an LHRH agonist, and it doesn't have a first pass through the liver, so it may have a lower thrombosis risk."

17-AAG. Dr. David Solit of Memorial Sloan Kettering Cancer Center (MSKCC) said, "Phase I studies showed the toxicity is schedule-dependent…If you gave 17-AAG steadily, there would be liver toxicity, but it is more tolerable on an intermittent schedule…Formulation and toxicity issues made this difficult to move forward." MSKCC is conducting a study of 17-AAG in combination with Taxotere, with 52 patients enrolled so far, and Dr. Solit said, "We've seen responses in lung and prostate cancer, so there are clearly early hints of activity…But the greatest activity is in combination with Herceptin in Herceptin-refractory breast cancer patients…The major problem with this and other targeted therapies is measuring effect and how long the effect lasts. We don't know much about durability yet…We are trying to develop an imaging probe for expressions of Hsp90 proteins."

Future directions include:

- Novel 17-AAG formulations.
- Novel ansamycin (17-DMAG). Ten of 50 patients have been enrolled at MSKCC in a trial of this agent.
- Novel scaffolds. Several companies, including Serenex, Conforma, and Vernalis/Novartis are working on less toxic orals, and Dr. Solit said, "These probably have great promise."

HDACs (or HiDACs). A Phase I trial of HDAC + XRT has been proposed, and an ECOG trial of HDAC + AstraZeneca's Casodex (bicalutamide) in patients with rising PSA has been proposed. A speaker said, "HDAC has shown preliminary results so far, but we need to identify the optimal dose, schedule, and duration of treatment. Combinations are the next challenge."

Several companies have an HDAC in development, including:

- **MERCK'S SAHA,** which has not shown a decline in PSA. A Phase II study by the DOD consortium and a pre-prostatectomy study are planned. A combination trial in post-docetaxel patients also is being considered.
- **NOVARTIS'S LBH-589** and **NVP-LAQ824**.
- **SCHERING AG'S MS-275** – which has not shown a decline in PSA.
- **METHYLGENE/PHARMION'S MGcd0103**, which also has not shown a decline in PSA.
- **GLOUCESTER PHARMACEUTICALS' depsipeptide (FK-228).** Interim results of a Phase II trial of this HDAC in HRPC were presented on 16 patients from Stage 1 and 8 patients from Stage 2. Enrollment continues with a goal of 24 evaluable patients.

Phase II Results with Depsipeptide in HRPC

Measurement	Depsipeptide n=24	
Mean duration of treatment	62.8 days for patients who completed or discontinued treatment 51.4 days for patients still on treatment	
Status of patients	3 patients completed 6 cycles 5 patients ongoing 16 patients discontinued treatment	
Primary endpoint: % of patients with objective disease response	17.6%	
Confirmed radiological PR for 6 months	1 patient of 17	
Confirmed SD	2 patients of 17	
PSA response rate (decline ≥50%)	11%	
Safety		
	Grade 1-2	**Grade 3**
Any adverse event	100%	20.8%
Fatigue	75.0% *	0
Nausea	66.7%	8.3%
Anorexia	62.5%	0
Vomiting	54.2%	8.3%
Constipation	45.8%	0
ECG changes	29.2%	8.3%
Diarrhea	25.0%	0
Dyspepsia	25.0%	0
Discontinuations		
Due to objective disease progression	33% (8 patients)	
Due to adverse events/toxicity	20.8% (5 patients)	
Due to PSA progression	8.3% (2 patients)	
Withdrawal of consent	4.2% (1 patient)	

* Resolved within 72 hours post-infusion in the majority of patients.

IMMUNOTHERAPY

In a talk on immunotherapy, Dr. Eric Small of the University of California, San Francisco, predicted immunotherapy products will be shown to unambiguously prolong life and will be approved, with the greatest effect in combination therapy. He highlighted these vaccines and other immunotherapies:

➢ **BRISTOL-MYERS SQUIBB'S Orencia (ipilumimab, CTLA4-Ig).** Dr. Small said, "This is one of the most exciting areas in immunotherapy today…Much to our pleasant surprise, we found PSA responses in a few patients after a single dose…It appears safe, and there is preliminary evidence of modest single agent activity…Combination therapy (with GM-CSF, androgen deprivation, chemotherapy, vaccination, etc.) is almost certainly the way to go…Ipilumimab has biologic effect and has tremendous potential for the future."

➢ **CELL GENESYS'S GVAX.** Dr. Small said, "This was tested in several Phase II trials. There are provocative data suggesting a dose response survival benefit…GVAX has a biologic effect, can affect PSA, and has shown provocative retrospective survival data."

In a poster presented at the meeting, higher dose vaccine was used in two trials, which both showed prolonged survival with GVAX (26.2 months vs. 19.5 months in one trial, and >29.1 months vs. 22.0 months in the other). An investigator said, "All we've done in Phase II is show we have something worth testing in Phase III."

Two Phase III trials – VITAL-1 and VITAL-2 – are now underway. Both are randomized, open-label studies of Taxotere with prednisone ± GVAX in mHRPC patients.

- **VITAL-1** is in patients who are asymptomatic for cancer pain. There are two arms: Arm 1 is immunotherapy in 13 bi-weekly injections over 24 weeks, followed by monthly immunotherapy injections for life or until a new treatment for prostate cancer begins. Arm 2 is Taxotere administered every 21 days and prednisone daily over 9 cycles.
- **VITAL-2** is in patients with cancer-related pain. Again, there are two arms: Arm 1 is immunotherapy in combination with Taxotere every 21 days over 27 weeks, followed by monthly immunotherapy injections alone for life or until a new treatment for prostate cancer begins. Arm 2 is Taxotere administered every 21 days and prednisone daily over 10 cycles.

➢ **DENDREON'S Provenge (APC-8015).** Dr. Small said the failure of a randomized Phase III clinical trial to show a statistically significant difference in TTP (p=.061) was probably due to the small (127-patient) sample size and was not likely due to an imbalance in prognostic features and not to an imbalance in chemotherapy use following Provenge treatment. He also thought the survival benefit trumped everything (34% vs. 11% alive at 36 months, p=.01), "TTP may not be the appropriate endpoint. I firmly believe the appropriate endpoint is overall survival…We did a blinded analysis in a subset of patients (n=49) and found a 16-17-fold increase in immune response with Provenge vs. placebo…Provenge has a biologic effect, can affect PSA, has shown an occasional objective response, and provocative survival data, but it is a small sample size. This is the first and only time we've seen a survival advantage with an immunologic agent in prostate cancer."

➢ **Pox viral vaccines.** Dr. Small noted that these have been shown to be safe, and strategies to improve potency include adding a stimulatory molecule, GM-CSF, etc. He said, "ProstVac (vaccinia-PSA vaccine) has a biologic effect, can affect PSA, has shown an occasional objective response, and may prolong TTP (PSA)."

➢ **Granulocyte/Macrophage-Colony Stimulating Factor, (GM-CSF).** Dr. Small said, "GM-CSF has a biologic effect, lowers PSA, and decreases PSADT, but there is no survival data."

Open Phase III trials include:

- An ECOG study of Vaccinia-PSA/TRICON.
- VITAL-1 of docetaxel + prednisone ± GVAX in asymptomatic patients.
- VITAL-2 of docetaxel + prednisone vs. docetaxel + GVAX in symptomatic patients.
- Provenge D-9902B Phase III trial.

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