Compassionate
Oncology Medical Group

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DIPLOMATE
AMERICAN BOARDS OF INTERNAL MEDICINE
AND SUBSPECIALTIES OF
MEDICAL ONCOLOGY AND HEMATOLOGY

August 1998
December 1998
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August 2004
(Revised)

HORMONE REFRACTORY PROSTATE CANCER

Treatment with Low-Dose Weekly Taxotere/Emcyt/Carboplatinum Chemotherapy

ASTONISHING RESULTS

***Additional topics briefly discussed in the 1998 paper include Aredia, tumor flare, testosterone replacement therapy, and triple hormone blockade.**

INTRODUCTION

In May 2004, the FDA approved docetaxel (trade name Taxotere) for treating men with advanced prostate cancer. On June 7, 2004, results of two key Taxotere studies were presented at the Plenary Session of the American Society of Clinical Oncology annual meeting. Chemotherapy treatment with Taxotere compared to standard chemotherapy treatment was shown to prolong survival for men with metastatic hormone refractory prostate cancer (HRPC). These are landmark studies since this is the first time that any type of chemotherapy has been found to prolong survival for men with metastatic prostate cancer.

In August of 1998, I authored a paper describing my initial results using Taxotere for men with prostate cancer, in which I described the benefits of Taxotere as "astonishing." It has taken almost seven years for this approach to become the "new" community standard of practice. If I had waited for others to scientifically prove what was obvious to me, I would have deprived patients of the benefits of Taxotere for just shy of seven years. Most physicians are "evidence based." They will not recommend a new treatment until prospective, randomized studies prove a survival benefit for a new treatment compared to standard treatment, even if standard treatment does not prolong survival. Men with metastatic prostate cancer treated by evidence based oncologists have been treated with mitoxantrone and prednisone until the June 2004 ASCO meeting. Mitoxantrone helped to relieve pain for only 30-50% of patients, but was never shown to prolong survival. It received FDA approval because it controlled pain more often than

prednisone alone. I stopped using mitoxantrone in 1994. Although there were patients who responded to mitoxantrone, invariably within six to nine months this treatment stopped being effective.

New patients will sometimes ask if there are published medical articles that can prove that our current treatment protocols for various stages of prostate cancer are more effective than standard type treatments, or so-called "community standard of practice." Mitoxantrone/prednisone has been the community standard of practice since 1994. Most of the patients I treat for metastatic hormone refractory prostate cancer would be dead if I were an evidence based doctor who treats men only with standard of practice chemotherapy recipes. If we waited for confirmatory studies to be published that proved superiority for one of our new treatment protocols before we started to use it, then we would be just like all other community oncologists. Instead we take pride in always trying to find ways to improve treatments for each stage of prostate cancer. You come to Compassionate Oncology because we pioneer evolving state-of-the art treatment protocols. Because we are in a private practice setting, we have the flexibility to modify protocols originated by others. We never use a placebo arm. We treat each patient the way we would want to be treated if we were a layperson and had their disease. We always treat with what we believe to be the most effective treatment. That explains why we do not use a placebo controlled arm. We take pride in being outspoken patient care advocates. Our patients tell us that they come to Compassionate Oncology from literally all over the world because we are compassionate and creatively innovative. We have pioneered successful protocols for treating each stage of prostate cancer.

My original 1998 Taxotere paper follows, although I have made significant revisions to it to reflect ongoing modifications and improvements, as well as to update our results through August 2004.

One of the most important observations or contributions that I have made in our fight against prostate cancer (CaP) is to use our most effective systemic treatments "up front" for men with "early" CaP. I strongly recommend applying the same principle to men who have hormone resistant, or hormone refractory prostate cancer, metastatic prostate cancer, and/or so-called high-risk prostate cancer.

I believe it is a major mistake to "save your best weapon for later or last." The best time to attack prostate cancer cells is the first time. Right now! If you have previously been treated for prostate cancer, "up front" means the **next** time. For men being treated with hormone blockade, that means start with triple hormone blockade (THB), not monotherapy. In the 1990's, I recommended 13 months of triple hormone blockade and finasteride maintenance to treat all stages of prostate cancer, other than hormone resistant/refractory. I later revised that naive hope and reported that some stages of prostate cancer require additional therapies for best results. If it is time to consider chemotherapy, use it now, and use the most potent and effective treatment, essentially with no exceptions. If you are being treated with Casodex, never take one Casodex a day, you need three a day (all at one time). We advise simultaneous chemotherapy and hormone blockade for those who require chemotherapy treatment. We do not recommend sequential treatment (where you would first give chemotherapy, then hormone blockade, or first hormone blockade, then chemotherapy). This is our opinion, not proven fact.

We always recommend that for all stages of cancer you use your best treatments up-front. Do not wait and allow prostate cancer cells the time to mutate, become more aggressive, and spread. We know cancer cells undergo additional, molecular biological hits (mutations) that make them more resistant to treatment. Cancer cells are always trying to survive at your expense. All they want to do is to try to outsmart prostate cancer treatment. This applies to hormone sensitive and to hormone resistant prostate cancer cells. Hormone resistant cells continue to undergo additional molecular biological changes as they mutate to become hormone refractory cancer cells. Hit them hardest right now using **all** of your effective treatments simultaneously, not one at a time.

For men who show the first evidence of hormone resistance (the definition of this is a rising PSA in spite of a castrate level testosterone), fight back aggressively with your best and most powerful arsenal. If your PSA rises while you are taking any of the three antiandrogens, first stop your flutamide, Casodex and/or nilutamide. Initially, these three antiandrogens (AA) kill prostate cancer cells. Over time, mutations occur and antiandrogens end up stimulating prostate cancer cells to **grow**. All men on antiandrogens who have rising PSA's with a castrate level of testosterone must immediately stop their antiandrogens and never use them again since these medications will stimulate

prostate cancer cells to grow. Once cells develop this growth stimulating (called agonist) effect from antiandrogens, we are convinced that the agonist effect is permanent. Prostate cancer cells will always grow whenever they are exposed to an antiandrogen that previously raised the PSA while the patient's testosterone was in a castrate range. The prostate cancer cells never forget. No matter how long it has been since that antiandrogen raised your PSA, if you feed them the same antiandrogen, prostate cancer cells will grow.

Invariably, a patient will remark that flutamide and/or Casodex controlled their disease for many years, and they have not taken these medicines for many years. They believe that what worked before should logically help again. It not only will not help, it will stimulate cancer growth. I call this the Benedict Arnold syndrome. Please do not yield to the temptation to try to prove that we are wrong. We have never seen an exception to this rule.

There are men who will have their PSA decline when switched to another antiandrogen. However, these responses usually last for only a few months, and only rarely cause an objective decrease in cancer volume. This is why we never use an antiandrogen a second time, even if a person does not already have hormone resistant/refractory prostate cancer. This principle applies to men whose PSA did not rise when they were previously being treated with an antiandrogen. Instead we always use either ketoconazole (Nizoral) or aminoglutethimide (Cytadren). These two medicines are adrenolytic. They block the production of androgens by the adrenal glands. The antiandrogens block androgen receptors on prostate cancer cells without reducing the amount of adrenal androgens. Androgen receptors change over time such that very low doses of testosterone cause cell growth. All men on hormone blockade still have some testosterone in their blood.

Ketoconazole or aminoglutethimide alone have an approximate 35% probability of a favorable PSA response in men with hormone refractory prostate cancer, but objective responses occur much less commonly. One article reported a 62% PSA response rate. In addition, the average duration of response lasts for months rather than years, although there are some men who respond for years. Instead of using ketoconazole or aminoglutethimide alone then later adding chemotherapy, I urge simultaneous low-dose, weekly Taxotere/Emcyt/carboplatinum chemotherapy plus either ketoconazole with hydrocortisone or aminoglutethimide

with hydrocortisone. Beginning in 2003, we have advised using ethinylestradiol instead of ketoconazole or aminoglutethimide for certain specific categories of patients. Ethinylestradiol (EE) will probably become our preferred hormone blockade treatment for men who have high-risk, aggressive metastatic hormone resistant/refractory prostate cancer. It is possible that we may begin to recommend EE to some patients who have metastatic prostate cancer even before it becomes hormone refractory. All our patients are also treated with LHRH agonist, Proscar, Celebrex, and intravenous bisphosphonates, although as of 2004, we usually do not recommend bisphosphonates every month (see our paper, "Bisphosphonates and Osteonecrosis of the Maxilla and/or Mandible (Jaw Bones)."

Although you may have hormone refractory prostate cancer, your disease will almost always respond to other non-hormone treatments -- like chemotherapy. I have been quite impressed (astonished)with our initial results utilizing Taxotere-based treatments. Later, we also showed that my Prostate Cancer Antiangiogenic Cocktail could induce responses in men with HRPC, even if they progressed on chemotherapy treatment. Compassionate Oncology is always investigating additional beneficial treatments that have the potential to help control and defeat prostate cancer. For all of our patients with prostate cancer, our goal is to have you die with prostate cancer, not from it.

T/E/D protocol:

I began using what I called the T/E/D protocol in 1997. This consists of weekly low dose Taxotere, along with Emcyt two days a week and Decadron two days a week. I treat three weeks in a row, then one week off. (Initially, I treated weekly unless a patient experienced significant side effects. In the early years, I also used a higher dose of Emcyt.)

Beginning in 1998, we always added a fourth medicine, carboplatinum 200 mg once each week, intravenous. This is our T/E/C protocol. As of August 2004, T/E/C remains our recommended chemotherapy treatment. We have made slight modifications (improvements, we believe) over these past seven years. One of my favorite original quotes is, "Those who fail to evolve are doomed to extinction."

So far, we have not seen any significant extra toxicity by adding carboplatinum, except for some mild reversible hair loss

for fewer than one in five patients. We have administered several hundred doses of carboplatinum to date. As of the August 2004 revision, we have prescribed many thousands of doses of T/E/C. In July 1998, we began using prophylactic anticoagulation with warfarin (generic), also known as Coumadin, a blood thinner to **prevent** blood clots (thrombophlebitis). Later, we recommended using low molecular-weight heparins (LMWH), such as Innohep, Lovenox, etc., rather than Coumadin, as our preferred anticoagulant. Emerging data suggests that LMWH probably have a direct antitumor effect. Compassionate Oncology believes that LMWH does have beneficial anticancer benefits including antiangiogenic properties. This is our opinion, not proven fact. We much prefer that our patients use a LMWH rather than Coumadin, but some of our patients are treated with Coumadin. Use of Taxotere/Emcyt is associated with a 25% risk for developing thrombophlebitis (blood clots in a vein), with or without pulmonary emboli (blood clots that break off and travel to the lungs). You must be treated with full-dose anticoagulation to prevent blood clots. Less than full doses of warfarin or LMWH are not protective. Anticoagulation should be continued for about two months after the last dose of chemotherapy, but for some stages of prostate cancer we treat for longer. For patients with a past history of phlebitis, we also recommend prolonged therapy. We advise tapering off anticoagulants rather than just stopping them.

We have also utilized the T/E/C protocol for men who present with either metastatic disease or “high risk,” localized prostate cancer. To date (as of December 1998), I have treated five men (by 2004, close to 100 men) who had metastatic disease, but were not hormone refractory or resistant. Most of the new patients referred to us with metastatic prostate cancer are already hormone resistant/refractory. We have treated hundreds of HRPC patients with this same protocol. Later still, we began to recommend T/E/C chemotherapy along with triple hormone blockade as our recommended initial, up-front treatment for men who present with one or more high-risk, negative prognostic factors without any known metastatic disease (for details, please see my March 2004 videotaped lecture). High risk is defined as PSA greater than 20; Gleason 4+3 or higher; clinical stage T2b or higher on digital rectal exam, or finding prostate cancer cells in 50% or more of the total number of biopsy samples examined by the pathologist. The presence of any one of these is considered high-risk disease.

Responses to T/E/C, the decline of these PSA's are just astonishing -- see Table 1.

Responses are not just declines in PSA (that would be a biochemical response). Prior to therapy, a number of these men had large masses on CT scans (these represented big islands of prostate cancer cells in lymph glands). This is a type of metastatic disease and is referred to as adenopathy. Others have had metastases to their liver and/or lungs. When masses shrink more than 50%, you call that a partial response. If the mass goes away entirely, you call this a complete response. A 25-50% decrease is a minor response, and less than 25% shrinkage is considered stable disease. We have seen partial and complete responses with our Taxotere-based chemotherapy. All of the men with bone pain prior to Taxotere were completely pain free and off all pain medicines, usually within one week of starting treatment, even if they required morphine prior to starting chemotherapy. In February 1999, an 81-year-old patient presented with a PSA of over 6,272, and a bone scan that showed over 100 metastases. He came to the office in a wheelchair and on a morphine patch. He was told by his Louisiana urologist that he had one to two months to live. After one dose of chemotherapy he was pain free within two days and off all pain medications. He was walking within a few days. He tolerated his chemotherapy perfectly. He never had nausea or vomiting. In 2003, he celebrated his 85th birthday at Hooters, and we saw the happy pictures. As of June 2004, he is being treated with high-dose testosterone replacement therapy (TRT). His PSA is in single digits. He has not required pain medications since prior to his first dose of chemotherapy.

One other patient deserves special elaboration:

He presented in February 1995 with a PSA of about 2400. He had obvious metastases to bone and lung. He was treated with 13 months of triple hormone blockade, then about 18 months of Proscar, 5 mg once a day, so-called finasteride maintenance® therapy. His PSA was unmeasurable when we stopped triple blockade, and slowly rose on Proscar alone to 23.51. He was treated with triple hormone blockade, Aredia, Taxotere/Emcyt/Decadron low-dose weekly, which is an easily tolerated chemotherapy regimen, and his PSA became unmeasurable again. At present (as of December 1998), his only medicines are once a month Aredia and daily Proscar maintenance therapy. He is OFF triple blockade; and has been off Taxotere since

December 4, 1997. His PSA is still unmeasurable, and his testosterone level is returning to normal. (As of June 2004, he is on another cycle of hormone blockade, and recently completed a short course of chemotherapy). His PSA as of July 2004 is less than 0.1. He is still hormone responsive, and has been off hormone blockade more than 50% of the time between 1995 and 2004.)

As of my August 1998 original version of this paper, I had treated about 20 patients with this Taxotere-based protocol.

The most impressive part of this treatment is that patients do not experience any significant side effects from this Taxotere regimen. The most common side effect is fatigue after many doses. Some fluid retention which may require an occasional diuretic (water pill) is not uncommon. Most of the men have <u>not</u> had noticeable hair loss; many have not lost any hair. In 1997-1998, I treated men weekly; then changed to three weeks on, one week off.

My usual goal is to use only 15 doses of Taxotere-based chemotherapy. For men with localized disease, we only use 12 doses. On occasion (see chart) I have given more. One extraordinary, slowly responding patient has received 40 doses and continues to show declining PSA's (over 97% so far). Later, I concluded that we should almost never treat beyond 15 (rarely up to 18) doses. I consider these Taxotere results spectacular and extraordinary. At least four of these chemotherapy patients receive some of their chemotherapy doses by local doctors since they live some distance from my office. By 2004, 95% of our patients on chemotherapy receive some of their chemotherapy doses from their local oncologist. We are very much appreciative and thankful for their continuing help. Our patients receive one dose in our office, then two doses by a local oncologist, and then one week off. As of July 2004, we have had local oncologists from all over the USA and many parts of the world help us treat our men. We have treated more than 50 patients from Germany alone. Please seen Table 1 for a chart showing our early experience with Taxotere. A number of these men have volunteered to talk to patients considering this treatment. You can get their names and phone numbers by calling my office.

DEFINITION OF HORMONE RESISTANT vs. HORMONE REFRACTORY PROSTATE CANCER

If your PSA rises in spite of a castrate level of testosterone, then you have hormone resistant prostate cancer. If your PSA rises in spite of **all** hormone blocking agents (including medicines like Nizoral, aminoglutethimide, and estrogen), then you have HRPC (hormone **refractory** prostate cancer).

AREDIA, THE NON-CHEMOTHERAPY INTRAVENOUS WONDER DRUG

I also urge liberal use of Aredia (pamidronate). In 2003, we advised against monthly IV bisphosphonates -- see our paper on "Bisphosphonates and Osteonecrosis of the Maxilla and/or Mandible (Jaw Bones)." This is also discussed on my March 2004 videotaped lecture that can be ordered from our office.

Aredia belongs to a family of medicines known as bisphosphonates. Bisphosphonates treat osteoporosis and can prevent the loss of calcium from bones for men on hormone blockade. Hormone blockade causes bone loss which can eventually result in osteoporosis. Bisphosphonates can prevent and even usually reverse osteoporosis.

However, I also recommend using Aredia for its potential anticancer effect.

The lead (feature) article and the ensuing editorial in this past week's *New England Journal of Medicine*, Volume 339, Number 6, August 6, 1998, reported the striking, beneficial anticancer effects of bisphosphonates.

Aredia has already been widely used in breast cancer and in multiple myeloma. It is my strong belief, prejudice and prediction that Aredia will become much more widely utilized in prostate cancer. We already have proof that IV bisphosphonates relieve pain in men with hormone refractory prostate cancer (HRPC), and we have seen some PSA responses. (In 2002, Zometa, the second IV bisphosphonate, was approved.)

Bisphosphonates are the most potent medicines we have to treat osteoporosis. They have antitumor effects including inducing

apoptosis (programmed cell death of tumor cells), as well as turning off the blood supply to prostate cancer cells (antiangiogenic effect).

Bisphosphonates are thought to reduce the tumor burden in bone by altering the microenvironment (bone) in which the tumor cells grow.

Imagine that cancer cells are seeds. All chemotherapy and hormone therapy work against the seeds, trying to kill or alter those (cancer) seeds. Bisphosphonates work on the soil. The prostate cancer cell **seeds** need the right **soil** in which to grow and multiply. Aredia makes the soil (the bones) inhospitable to cancer cells.

From an editorial in the *New England Journal of Medicine*, Volume 330, Number 6, August 1998: "The evidence that bisphosphonates can reduce the tumor burden in bone is exciting news for patients with cancers that spread to bone."

Obviously prostate cancer spreads to bone. There is no form of cancer that more frequently spreads to bone than prostate cancer.

Aredia is very well tolerated; it is **not** chemotherapy. The most frequent side-effects are low grade fever, chills, body aches, muscle aches (may feel like the flu). I <u>believe</u> these symptoms occur because the chemicals in your immune system are being activated. The symptoms usually last 24-36 hours and usually go away after the first one to three doses. Less than 10% of patients ever have this type of reaction. These side effects always go away for all patients.

A small percentage of patients may experience temporary bone pain with the first one or two doses (probably in areas of bone metastases). I try to explain this by telling a man to picture the prostate cancer cells swelling before they burst and die (my simplistic explanation). Other side-effects are much less common, but these and other potential side-effects should be discussed with your treating doctor.

This medicine is <u>not</u> chemotherapy. There is no nausea, vomiting or hair loss. It must be given intravenously, usually over 90-120 minutes, once a month. See Appendices A, B, and C for Aredia response.

TUMOR FLARE

In breast cancer, we often see that when successful systemic treatment is started, there may be a temporary "surge" or transient rise in breast cancer blood tumor markers.

With T/E/D, and then often with the addition of carboplatinum, we may see PSA increases for the first few weeks. Then the PSA plummets. This represents tumor flare. We also have observed that if a bone scan is obtained on a man successfully being treated with T/E/C, it often looks like the abnormal bone scan spots are more intense compared to pre-T/E/C treatment. This type of scan is usually read by the radiologist as progressive disease. This is another example of tumor flare, not progressive disease. When bone is healing, the "spots" become more "hot;" they are more intense as a result of bone healing. Any growth of new bone causes an abnormal bone scan. Teenagers have abnormal bone scans in the parts of bone that are growing. A bone scan can become abnormal whenever there is healing of bone resulting from successful chemotherapy treatment. These are examples of false positive bone scans. It is important to remember this or else you might believe your disease is progressing when it is actually improving and going into remission.

Another example of tumor flare was in a man whose PSA prior to T/E/C was 239; it rose to 368, 15 days later, but all of his bone pain was gone within 12 hours of his first dose of this chemotherapy. It took seven weeks to get back to 231, but his PSA is now about 7 (in 1998).

PSA's rarely decline every single measurement. It is common to see PSA's bounce up one week, every now and then, even as the PSA's pursue their long, impressive decline.

I do not have a good explanation for this, except to advise not measuring PSA's each week of chemotherapy, but a falling PSA is such positive feedback, and results in uplifting spirits, that it takes will power not to want to measure it each week of Taxotere.

I love watching those PSA's fall almost every week. I find this process releases endorphins, boosts morale and helps to answer a question often posed to me:

"How can you be a cancer doctor? Isn't it depressing?

TESTOSTERONE REPLACEMENT THERAPY

I am now treating three different men with testosterone replacement therapy (in 1998).

All three were previously surgically castrated. All had unmeasurable PSA's; hence, they were hormone sensitive.

All three wanted to be on intermittent androgen blockade, but lacked the necessary equipment to produce their own testosterone.

When I reviewed the information available on why it is generally felt that testosterone replacement is contraindicated in a man with metastatic prostate cancer, I concluded that this statement is accurate for most men with hormone resistant or hormone refractory disease.

If, however, you are still hormone sensitive, then testosterone may not be harmful (my opinion for these three men only). Do not apply this rationale to your situation; this has the potential to worsen your prostate cancer and hasten complications and/or even death.

If testosterone were harmful for all men with prostate cancer, then no one should ever be allowed to stop hormone blockade, since stopping blockade almost always results in your testosterone rising to prehormone blockade levels. Intermittent hormone blockade would not be allowed if all doctors believed that testosterone is harmful to all men with prostate cancer.

The first patient has been on testosterone replacement for about one and one-half years. His PSA is about 0.26 and <u>not</u> rising. He feels much better; much stronger; and hits his golf ball 25 yards further than pre-testosterone days.

The second patient has been treated with testosterone for over one year and has a stable PSA of 0.4 (by a different PSA assay). He also feels much better and has improved his golf game.

The third patient has only been on treatment a few months and still has an unmeasurable PSA. He does not play golf.

I must stress that any decision to consider testosterone replacement therapy (TRT) must be made on an individual basis, and I urge never trying it if you are hormone resistant at all. Your PSA will rise if you do.

I have recently begun treating a fourth patient.

(I advise reviewing a March 2004 videotaped lecture for updated information and follow-up. As of August 2004, we have treated between 100 and 200 patients with high-dose testosterone replacement therapy.)

THE BEST LOCAL TREATMENT IS SYSTEMIC TREATMENT

Triple Hormone Blockade

In almost every field of medicine, the fewer the facts, the stronger the opinions. Every honest prostate cancer specialist admits that no study has ever proven that any form of radical local therapy (including radical prostatectomy, radiation therapy, seeds and/or cryotherapy) is both necessary and effective.

I hope that any promising prostate cancer treatment that is developed is immediately shared. Tell everybody what works best for your patients.

I treat men who have so-called clinically localized prostate cancer with triple hormone blockade® for 13 months, followed by Proscar, 5 mg once a day, so-called finasteride maintenance® therapy. This treatment is noninvasive; treats prostate cancer cells throughout the body, and has side effects that are almost always completely reversible.

I have not had to retreat a single patient. My charts are being audited so I can submit the data for publication. (Our results were published in a peer reviewed medical journal: Leibowitz, R.L., Tucker, S.J.: Treatment of Localized Prostate Cancer With Intermittent Triple Androgen Blockade: Preliminary Results in 110 Consecutive Patients. *The Oncologist*, Vol. 6, pp. 177-182, April 2001.) As of the date we submitted our manuscript, no patient required a second cycle of hormone blockade. As of March 2004, we had retreated 13 patients from our series of 185 patients presenting with previously untreated

clinically localized prostate cancer. We have had one death from prostate cancer which gives us a 99.5%, five-year, prostate cancer cause specific survival. This patient had a very rare and aggressive form of prostate cancer named endometrioid or ductal prostate cancer. Under the microscope the cells resemble cells found in a woman's uterus (also known as endometrium).

Since none of these patients had any local treatment (no R.P., no radiation, no seeds, no cryotherapy), they all still have their prostate glands.

When they go off triple hormone blockade, their testosterone levels rise to above their pretreatment baseline levels (since finasteride maintenance® raises testosterone levels). Testosterone will, of course, stimulate their normal prostate gland cells to make PSA. Therefore, they have to have measurable PSA while on maintenance finasteride (Proscar).

But, so far, all of their PSA's have reached a plateau, and are <u>not</u> rising. (Later, I find most men exhibit what I call a roller-coaster PSA pattern.)

My highest plateau is about 4 for one patient; my next highest plateau is about 3 (as of 12/98). (See March 2004 video for update on the first 185 patients treated with triple hormone blockade/Leibowitz protocol.)

Since I have never had to retreat a patient with clinically localized prostate cancer, who was treated with 13 months of triple hormone blockade followed by finasteride (Proscar) maintenance (as of January 2000), none of these patients can be hormone resistant or hormone refractory (HRPC). None are. As of August 2004, the one patient who died from prostate cancer had developed HRPC; one other patient has hormone resistant prostate cancer.

Does this mean that <u>so</u> <u>far</u> my success rate seems too good to be true?

Yes, it does.

Then find any patient that I have treated for clinically localized prostate cancer whose initial PSA is 60 or less, who was treated with 13 months triple blockade followed by Proscar maintenance, and who has had to be retreated by me, and you can

prove me wrong (as of the original version of this paper). Until you find any such patient, you can choose to either believe my results or not. Believe them; they are true. (Several years after this paper was written, Drs. Strum and Scholz claimed on an Internet site that they had treated some "failures" of mine. When they reviewed their records, they found that the patients they were referring to had not been treated with triple hormone blockade®/Leibowitz protocol. These patients had previously failed radical local therapy and/or prior hormone blockade.)

You can see our updated treatment results by ordering a copy of our most recent videotaped lecture. Lectures from Dr. Bob and Dr. Tucker are available.

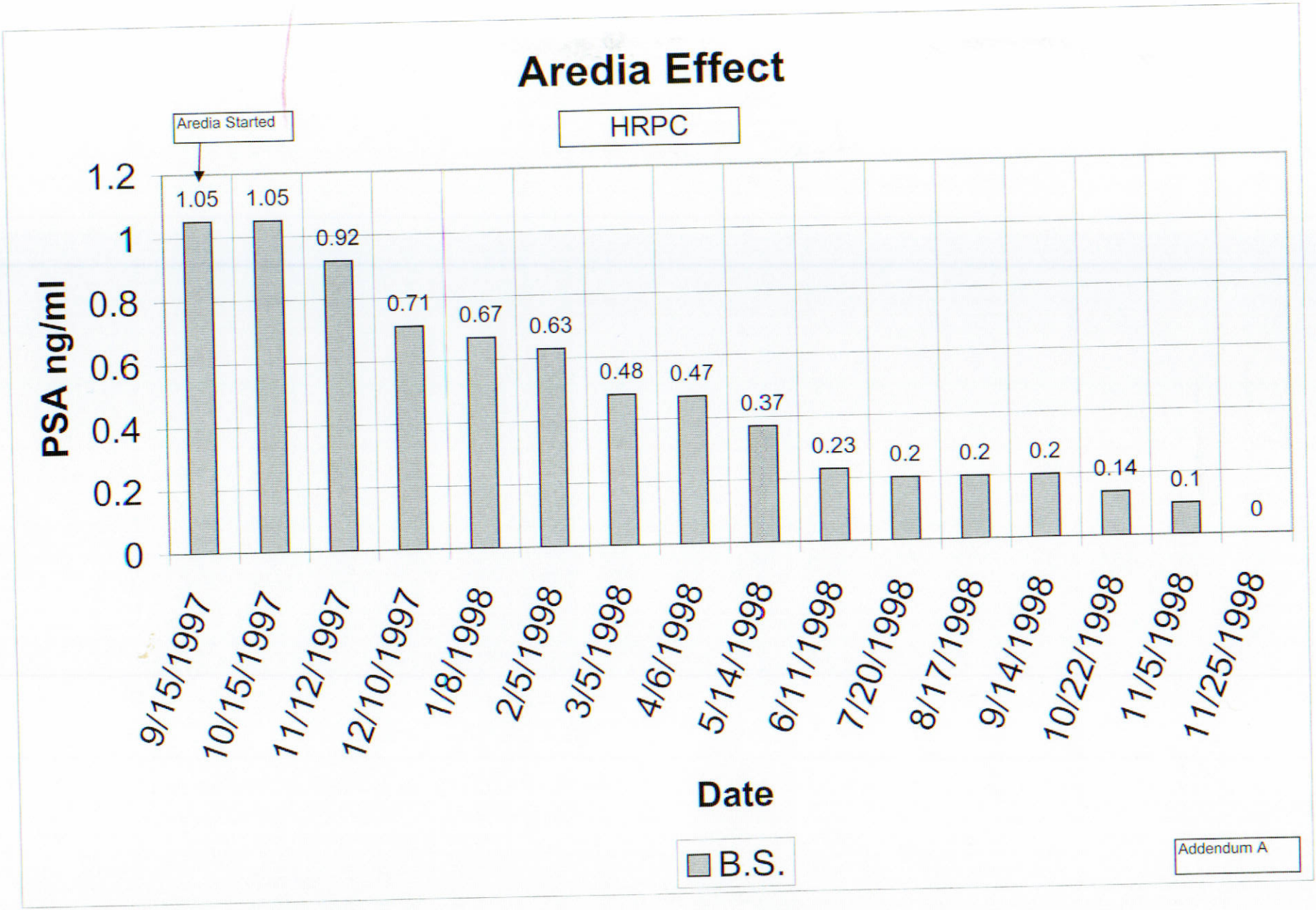
You can order a copy for $25.00 for a videotape and 35.00 for a DVD, including shipping and handling, by calling us at (310) 229-3555. If the tape is returned, we will refund $10.00. I urge you to please watch a tape; you will learn many new insights regarding the treatment of all stages of prostate cancer. We believe we have the best treatment outcomes literally in the world for treating all stages of prostate cancer.

And as always --
Be happy,
Be well,
Live long and prosper,

BOB LEIBOWITZ, M.D. AKA Dr. BOB

****** None of the above should be construed as medical advice or consultation, and anything discussed in this paper is meant for information only. All medical treatments, consultations, decisions and recommendations can only be made by the patient and his/her treating physician.

8/04


Aredia Effect
Aredia Started
HRPC
PSA ng/ml
1.2
1
0.8
0.6
0.4
0.2
0
1.05
1.05
0.92
0.71
0.67
0.63
0.48
0.47
0.37
0.23
0.2
0.2
0.2
0.14
0.1
0
9/15/1997
10/15/1997
11/12/1997
12/10/1997
1/8/1998
2/5/1998
3/5/1998
4/6/1998
5/14/1998
6/11/1998
7/20/1998
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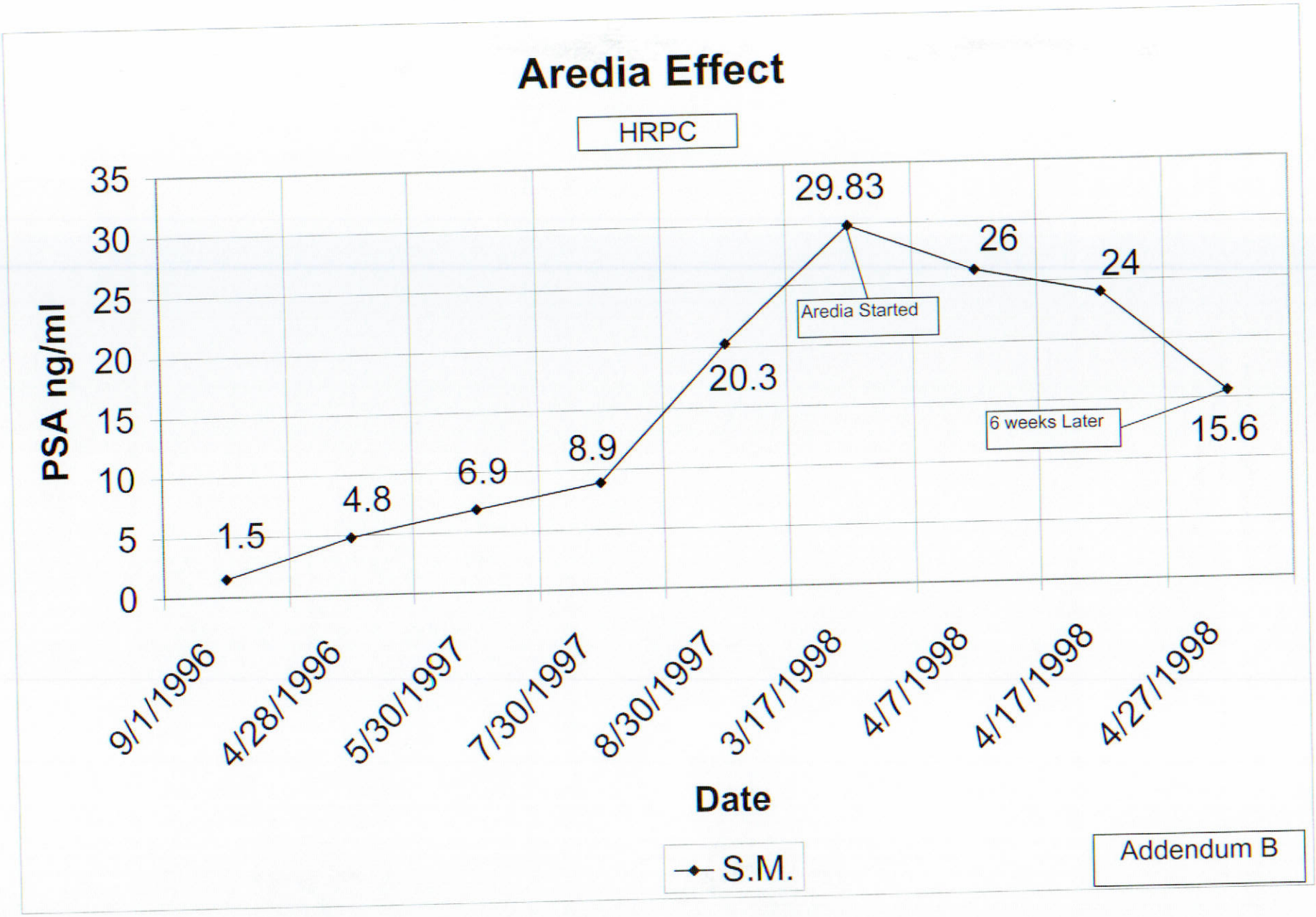
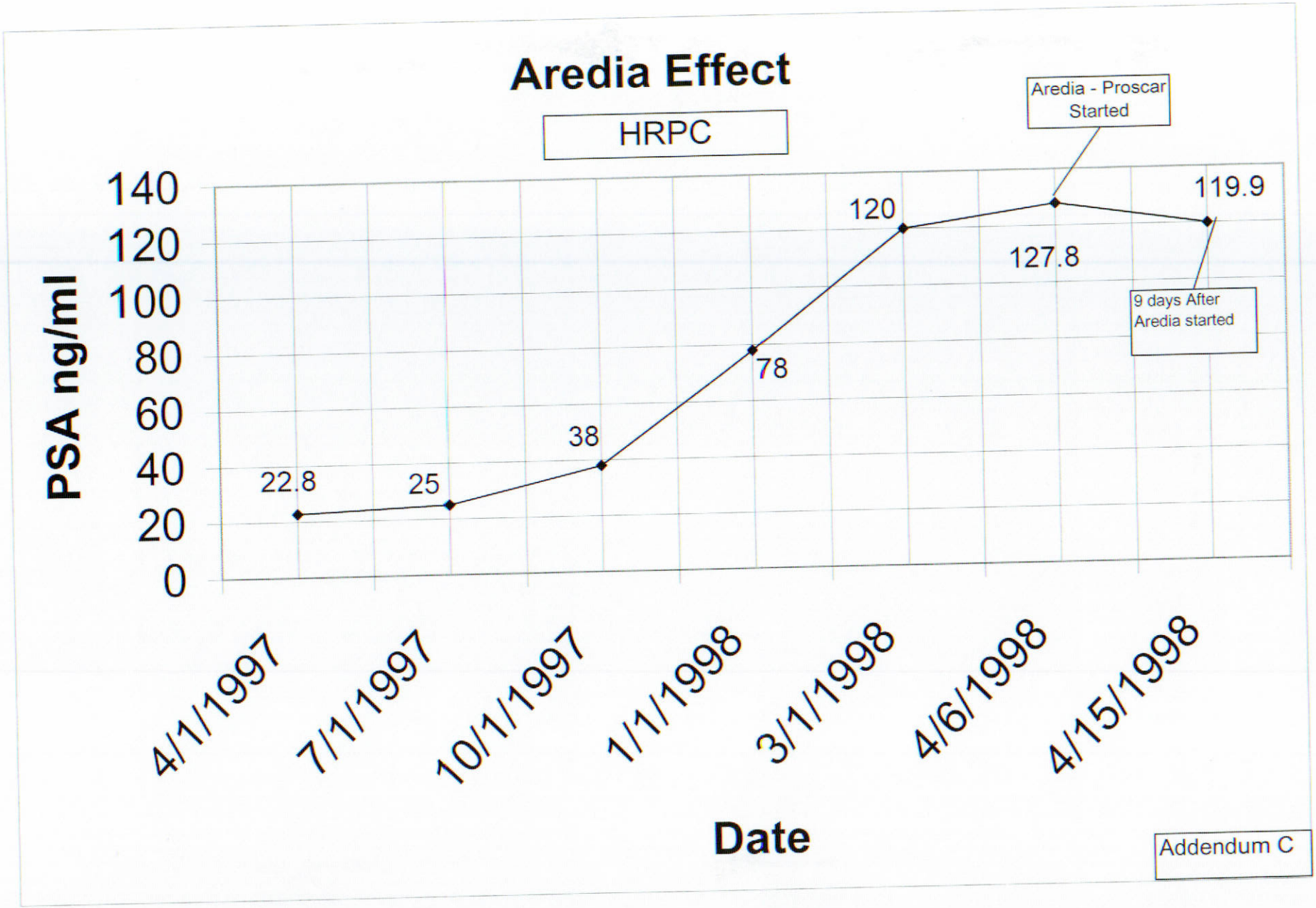
9/14/1998
10/22/1998
11/5/1998
11/25/1998
Date
B.S.
Addendum A


Aredia Effect
HRPC
PSA ng/ml
35
30
25
20
15
10
5
0
1.5
4.8
6.9
8.9
20.3
29.83
26
24
15.6
Aredia Started
6 weeks Later
9/1/1996
4/28/1996
5/30/1997
7/30/1997
8/30/1997
3/17/1998
4/7/1998
4/17/1998
4/27/1998
Date
S.M.
Addendum B


Aredia Effect
HRPC
Aredia - Proscar Started
9 days After Aredia started
PSA ng/ml
140
120
100
80
60
40
20
0
22.8
25
38
78
120
127.8
119.9
4/1/1997
7/1/1997
10/1/1997
1/1/1998
3/1/1998
4/6/1998
4/15/1998
Date
Addendum C

T/E/C for Hormone Sensitive Met. Ca

Patient Intl.	Age	Initial PSA	Recent PSA	# of Doses	Mos.	% Decline
D.W.	54	681	0.17	16	7	99.90%
T.T.	56	33.28	0.7	14	6	98.10%
J.B.B.	57	993	2.93	21	8	99.70%
A.C.	67	239	<0.05	14	10	100%
R.W.	56	2372	<0.05	16	15	100%

HRPC WEEKLY T/E/D ± Carbo as of 9/99

Patient's Initials	Age	Initial PSA	End PSA	Doses T/E/D	Date Started	Date Stopped	# of Months on Treatment	# Doses w/Carbo	% Decline	# of Prior Hormone Regimens	Prior R.T.[2]	# of Prior Chemo Regimens	Notes[1]	Most Recent PSA
JK	59	36.65	3.11	22	Apr-98	Sep-98	6	14	91.5%	6	No	No	F, L, O, C, PcS, N, C+P	6.90
RR	63	31.5	3.13	21	May-98	Sep-98	5	9	90.1%	3	1	No	L, C, F	1.99
RN	76	228	10.65	17	Apr-98	Aug-98	5	5	95.3%	4	No	No	O, F, AG, PcS	16.00
RB	66	15.8	13.55	19	Apr-98	Oct-98	7	7	14.2%	4	No	1	CX, DES, L+C, KC	26.67
EK	76	77	2.60	20	Jan-98	Jul-98	6	0	96.6%	4	1	No	Z, F+P, C, KC, N, AG	85.90
SM	79	15.5	7.31	17	Apr-98	Sep-98	5	9	52.8%	3	2	No	L+F, P, ME, R, ME	86.00
TI	71	120	2.98	22	Apr-98	Aug-98	5	8	97.5%	3	No	No	O, F, C, FW	0.62
KR	69	16.28	1.53	11	Jan-98	Apr-98	3	0	90.6%	3	No	No	Z+C+P, F	0.15
CFH	59	0.84	0.34	12	Mar-98	May-98	2	0	59.5%	2	No	No	FW, TRIPLE BLOCKADE	39.80
AP	69	239	7.01	48	Sep-97	Oct-98	13	15	97.1%	3	1	No	L, RI, C, F, P	47.53
JP	58	13.42	0.04	14	Jul-98	Nov-98	5	5	99.7%	3	1	No	L+C, F+P	0.26
CR	74	2.54	0.66	14	Jul-98	Oct-98	4	0	74.0%	3	No	No	O+F, C+P	2.10
DM	73	53.8	5.20	16	Jul-98	Oct-98	4	15	90.3%	3	No	No	L+F, C+P	1.05
LB	69	25.87	1.50	16	Aug-98	Dec-98	4	8	94.2%	3	No	No	L+F+C+P	0.97
NS	55	4.58	5.80	6	Oct-98	Dec-98	2	2	0%	2	1	No	L+F+P	14.97

Analysis

Mean PSA for patients off treatment-	**4.36**
% of patients with ≥ 50% Decline-	**76.5%**
% of patients with ≥ 90% Decline-	**58.8%**

Mean Number of Months off R_x - **#REF!**

Prior R.T.[2]

Code	Description
1=	R

Notes[1]

Code	Description	Code	Description
AG	Aminoglutethimide	N	Nizoral
C	Casodex	O	Orchiectamy
CX	Cytoxan	P	Proscar
D	Decadron	PcS	Pc Spec
Des	Estrogen	R	Spot Radiation
E	Emyct	RI	Radiation Isotope
F	Flutamide	RT	Radiation Therapy To Prostate
FW	Flutamide withdrawal	T	Taxotere
KC	Ketoconazol	TX	Taxol
L	Lupron	V/E	Velban/Emcyt
M	Mitoxantrone	Z	Zoladex
Me	Megace		