Is It Justified to Avoid Radical Cystoprostatectomy in Elderly Patients with Invasive Transitional Cell Carcinoma of the Bladder?

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Background. Although radical cystectomy is accepted by most urologists as the treatment of choice for invasive carcinoma of the bladder and age alone is not considered a contraindication for radical surgery, many consider radical major operations to be unsuitable for elderly patients.

Methods. The authors compared the results of radical cystectomy in 42 elderly patients to those in patients 69 years old or younger and to a group of 21 elderly patients, matched by stage of disease and severity of medical problems, who received alternative treatment.

Results. The overall operative mortality rate was 4.3% (seven patients). Three (4.3%) postoperative deaths in the younger group and four (9.5%) deaths among elderly patients were recorded. The operative morbidity and mortality did not differ significantly between those two groups ($P = 0.1$). Among the patients who received alternative therapy, 13 (61.9%) died within the first 6 months, and only 3 survived more than 12 months. Morbidity was encountered in 97% of these patients.

Conclusions. The authors showed that radical cystectomy is a relatively safe procedure for elderly patients. The elderly patient who is thought to be unsuitable for surgery not only is deprived of his right to definite curative therapy but also is exposed to higher morbidity and mortality and worse quality of life than are those who undergo operations. The authors conclude that it is unjustified to avoid radical cystectomy in the elderly population on the basis of age alone. *Cancer* 1993; 71:3098–101.

Key words: transitional cell carcinoma, bladder neoplasm, elderly, radical cystectomy, postoperative complications.

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Urologic cancers, mainly tumors of the prostate and the bladder, are among the most prevalent malignant tumors in the elderly population. The incidence of bladder cancer is higher in patients older than 65 years, and it increases with age. Tumor of the bladder is a leading cause of death in men older than 75 years, and death rates increase with advancing age.[1,2] Carcinoma of the bladder also has a great effect on elderly patients in terms of morbidity resulting from ureteral obstruction, local pain, irritative symptoms, and anemia caused prolonged hematuria.[2] Because bladder cancer is diagnosed most often in patients older than 65 years, it presents a major management problem. Radical cystectomy is accepted by most urologists as the treatment of choice for invasive carcinoma of the bladder and age alone is not considered a contraindication for radical surgery, but many consider radical major operations to be unsuitable for elderly patients because of the medical problems and low functional reserve of the vital organs,[3] which are thought to increase the surgical risk in such patients.

During the last 15 years, numerous studies have shown the relative safety of radical cystectomy in the older age group.[1–16] Morbidity and mortality in older patients were compared with those of patients younger than 70 years. Most authors reported acceptable morbidity and mortality that did not differ significantly between the two age groups. We present the results of radical surgery in elderly patients in comparison with results of surgery in patients 69 years old or younger and a matched group of elderly patients who received alternative treatment.

Patients and Methods

Between January 1983 and December 1989, 132 consecutive patients with invasive transitional cell carcinoma of the urinary bladder were treated at our institution. Patient age ranged from 40 to 88 years, with an average

of 65.8 years. Sixty-three (47.7%) patients were 70 years old or older (mean, 76.1 years). Fifteen of those were older than 80 years. All patients underwent routine evaluation of their functional status. Investigations of renal, cardiovascular, and pulmonary functions were done preoperatively to determine the patients' suitability to undergo major surgery under general anesthesia.

Prophylactic and therapeutic measures were instituted to treat any underlying disorder that was diagnosed through this extensive workup, including preoperative treatment of congestive heart failure, hypertension, and coronary insufficiency with medical therapy, percutaneous transluminal coronary angioplasty, or with surgery before patients underwent cystectomy. Intensive chest physiotherapy and bronchial dilators were used before and after cystectomy. Aggressive correction of anemia was attained with administration of packed erythrocyte transfusion. Postoperative monitoring of 12–24 hours in the intensive care unit was used in most patients.

Forty-two elderly patients (average age, 75.9 years; range, 70–88 years) underwent radical cystectomy. Urinary diversion to ileal conduit was performed in most patients. Twenty-one patients matched by age (mean, 77 years; range, 70–87 years), clinical stage of disease, medical history, and severity of medical problems were not considered candidates for surgery or refused surgery and received alternative treatment.

Modes of alternative treatment included any combination of radical transurethral resection of bladder tumor (TUR-BT) with or without intravesical chemotherapy, partial cystectomy with adjuvant irradiation, systemic chemotherapy, external beam radiation, urinary diversion, or observation alone.

These patients belong chronologically to the early years of the study. Because of the retrospective nature of the study and in view of our current approach, it is impossible to define specifically why radical surgery was avoided in some of these patients. In addition, it is possible that according to our current policy, most of these patients would have undergone operations. Operative mortality was defined as death within 1 month after surgery or within the period of hospital stay after cystectomy. Late mortality was defined as death occurring after hospital discharge and within the first year after discharge. Statistical analysis was done by unpaired Student *t*, chi-square, and Fisher exact tests, when appropriate.

Results

The most common medical problems that were encountered preoperatively among the patients who underwent surgery included cardiovascular disease, chronic pulmonary disease, and diabetes mellitus. A history of problems was associated with increased surgical risk, especially when two or more problems were present simultaneously, which was found to be the most important single cause of significantly increased morbidity and mortality among the patients who underwent operations. However, their prevalence did not differ significantly between the older and younger patients (70% and 64%, respectively; $P = 0.4$).

The overall early mortality among the group of patients who underwent operations was 6.3% (seven patients). There were three (4.3%) postoperative deaths in the younger group and four (9.5%)deaths among patients older than 70 years. Nonfatal morbidity and operative morbidity also were more common among the older patients. However, the operative morbidity and mortality did not differ significantly between the two groups ($P = 0.1$). Early postoperative death, in both age groups, was related primarily to cardiovascular emergencies (five of the seven patients who died postoperatively). Two other postoperative deaths were caused by sepsis. In addition, five patients (two patients older than 70 years and three younger than 70 years), died within the first year after hospital discharge. Four of the late deaths were associated with progression of the primary disease. One 69-year-old patient died of cardiac arrest 2 months after hospital discharge. Four (19%) patients who received alternative treatment died within 7–30 days after initiation of treatment. In addition, 11 (52.4%) died within the first 6 months after the start of alternative treatment, and another 5 (23.8%) died within 12 months.

Morbidity was encountered in 97% of these patients. Sepsis was the direct cause of death in nine (50%) patients. It was related to obstructed urinary tracts and to compromised immunity caused by adjuvant radiation and chemotherapy. Cardiovascular problems were the direct cause of death in another five (27.8%) patients; two patients died of renal failure; and another two died of metastatic disease (Table 1). The most common postoperative nonfatal complications included respiratory and cardiovascular problems and urinary tract infection. Other less common complications were wound infection, wound dehiscence, ureteral obstruction, urinary fistula, deep vein thrombosis, pulmonary emboli, prolonged ileus, sepsis, and liver function test disturbances.

Discussion

Radical cystectomy is accepted as the optimal treatment and the most common approach for invasive carcinoma of the urinary bladder. Several other modes of therapy are available in the urologist's armamentarium against invasive bladder tumor and are used in selected patients with invasive transitional cell carcinoma, primar-

Table 1. Patient Characteristics

	Young group (operated on)	Elderly group (operated on)	Alternative treatment group
No. of patients	69	42	21
Median age (range) (yr)	62.8 (40–69)	75.9 (70–88)	77 (70–87)
Mortality (%)	$P > 0.05$	$P < 0.05$	
Early*	3 (4.3)	4 (9.5)	4 (14.0)
Late†	3 (4.3)	2 (4.7)	14 (66.7)
Overall	6 (8.6)	6 (14.2)	18 (85.7)
Cause of death (%)			
Cardiovascular‡	3 (50)	3 (50)	5 (27.8)
Sepsis	1 (16.7)	1 (16.7)	9 (50.0)
Metastasis	2 (33.3)	2 (33.3)	2 (11.1)
Renal failure			2 (11.1)

* Deaths occurring during postoperative hospital stay or within 1 month after surgery.

† Deaths occurring after hospital discharge or after 1 month and within 1 year.

‡ Acute myocardial infarction, acute heart failure, fatal arrhythmias, pulmonary emboli, and cerebrovascular accidents.

ily as adjuvant treatment in addition to radical surgery. These alternative modes of therapy often serve as the only therapy in elderly patients, regardless of their medical and functional status. The issue of safety of radical cystectomy in patients older than 70 years was discussed by many authors and was confirmed almost uniformly.[1–16]

Morbidity and mortality after radical cystectomy in elderly patients were reported to be comparable to the results found in younger age groups. However, despite the solid data showing the safety of cystectomy, the concept that older people are not suitable for major radical surgery is a common fallacy. Many urologists are reluctant to perform radical cystectomy in older patients and prefer a conservative approach based on alternative modes of therapy and avoiding such surgery. This approach is clearly demonstrated by Zincke's statement[8] that cancer of the bladder in the elderly patient is preferably treated conservatively. He reserves radical treatment to a selected group of elderly patients who have tumors that are unresponsive to conservative measures, those who have severe symptoms, or those who have both. The enigma of the appropriate management of the older patient with invasive tumor of the bladder is growing more perplexing in view of the steady increase in the mean age of the population and the increased incidence of bladder cancer in patients older than 65 years.[1–2]

Although the current reports of radical surgery in the older population are favorable, none of the available studies reviewed the outcome of the conservative approach with regard to perioperative morbidity and mortality in comparison with radical surgery in patients older than 70 years. We attempted to clarify the issue of whether or not conservative treatment modalities are an acceptable alternative when the more aggressive radical modality seems to be inappropriate. This can be true because surgery is considered too risky because of patient age or chronic medical problems or because the patient refuses radical cystectomy based on its mutilating implications. In the current report, the overall mortality and the age group specific mortality compare favorably with the mortality reported by other authors.[1–16]

Although mortality and morbidity were higher in patients older than 70 years, the difference was not statistically significant. This trend also was noted in previous studies, and its relevance should be evaluated. Analysis of causes of death among the group of patients who underwent surgery showed that medical cardiovascular mortality, as a whole, was the main cause of postoperative death.

Among the patients who received alternative treatment, death was related primarily to sepsis and only secondarily to cardiovascular complications. The frequent occurrence of septic complications, less common cardiovascular problems, and the association of sepsis primarily with oncologic treatment or ureteral obstruction differentiate this group from patients who underwent operations. Adverse effects of adjuvant treatment were the major source of morbidity and mortality among the patients who received alternative treatment.

Preoperative radiation therapy was shown by several authors to increase the incidence of perioperative complications.[4,11,14] Complication rates in older patients undergoing salvage cystectomy are reported to be especially high,[1,12] so we think that radiation does directly affect the operative risk in the older age group. Irradiation as a single curative modality in elderly patients is reported to be associated with increased morbidity and mortality, low survival rates, and pelvic recurrence rates of 40–70%, with only a minority of the patients being suitable for salvage surgery.[1,16] The postoperative fatal and nonfatal complication rate correlated with the presence of active medical problems diagnosed before surgery. Such chronic systemic diseases are considered important risk factors and should be weighted more seriously with the biologic age, instead of the absolute chronologic age, when the surgeon is calculating the operative risks.[8]

The performance status according to the Karnofsky performance status is another important factor reported by Orihuela and Cubelli[1] to significantly influence the postoperative results in elderly patients. The incidence of preoperative medical problems did not differ significantly among patients who underwent operations and in the group of 21 patients selected for conservative treatment, although it was slightly higher in older patients. The presence of two or more concomitant prob-

lems was the most important single cause of significantly increased surgical risk. Similarly, occurrence of one complication led to other complications and to increased mortality among the patients who underwent operations.[14]

Preoperative screening and evaluation of potential problems followed by prophylactic and therapeutic measures is essential to enable safe radical surgery in older patients. In a selected group of high-risk patients, preadmission to intensive care units for additional evaluation and monitoring may be indicated. This concept was developed and reported in several studies of cystectomy in the elderly.[8,14] Because postoperative complications are directly related to the active medical problems encountered in such patients, we can not overemphasize the importance of preoperative characterization and intensive treatment of the potential problems to control or to reduce their influence. Because of understandable ethical reasons, it was impossible to form a control group for the assessment of the statistical significance of preoperative treatment.

The type of procedure performed was shown to influence the rates of morbidity and mortality. Several authors reported better results with less perioperative complications when cystectomy was performed in association with transureteroureterostomy and cutaneous ureterostomy. The advantages over ileal conduit or ureterosigmoidostomy are that the technique is less demanding, requires less operation time, and does not interfere with bowel continuity; the procedure also is not associated with metabolic complications.[5–6,8] We performed cystectomy and urinary diversion to ileal conduit in most elderly patients without complications specifically related to the procedure and with acceptable morbidity and mortality equal to or better than those reported after cutaneous ureterostomy.[5–6,8] Radical cystectomy with complete bladder substitution in a highly selected group of elderly patients was not associated with increased morbidity and mortality. The results did not differ from the results of urinary diversion to ileal conduit in patients older than 70 year or bladder substitution in younger patients. Miller et al.[16] reported a markedly decreased ability to achieve complete continence among patients older than 70 years who underwent bladder substitution. In our study, old age did not seem to affect daytime or nighttime continence. The functional results of cystectomy and bladder substitution in both age groups were satisfactory.

We showed that radical cystectomy is a relatively safe procedure for elderly patients with invasive transitional cell carcinoma of the urinary bladder. Our data suggest that radical cystectomy is much safer than the alternative therapy modalities available for management of invasive transitional cell carcinoma of bladder. The insignificant increase in the operative risk in older patients is by far less than the major effects of alternative treatment and the associated morbidity and mortality. Death caused by undertreated cancer is much more common than is death related to intercurrent medical diseases, and the quality of life during survival time is strongly affected.[11]

Thus, the elderly patient who is found unsuitable for surgery is deprived not only of his right to definite curative therapy but also is exposed to significantly higher morbidity and mortality and worse quality of life than are patients who undergo operations.

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Final Medical Team Leader Comments on NDA 20,892

AD-32 (Valstar) for CIS of the Urinary Bladder
September 16, 1998

See the attached review by Dr. Odujinrin. I concur with his recommendation that Valstar be approved for the limited indication described below.

Questions to ODAC

The following text and questions given to the Oncologics Drugs Advisory Committee summarize the updated data and analyses:

"The NDA for AD32 (Valstar) includes data from 90 patients in Studies 9301 and 9302 who had received at least 2 prior intravesical therapies for carcinoma *in situ* (CIS) of the bladder, including at least one course of BCG; 70% had received at least 2 courses of BCG and 30% had received one course of BCG. Of the 19 complete responses (CR) claimed by the applicant, baseline CIS was documented at multiple biopsy sites (i.e., there was multifocal disease at baseline) in only 7 patients. In many of these patients, however, multiple sites of CIS had been documented in the past. Baseline cytology was positive in only 11 of the 19 patients.

"After patients were treated by intravesical administration of AD32, the applicant found that 19 of 90 (22%) patients had a complete response. The FDA classified 9 (10%) patients as having "definite CR" according to strict protocol criteria and 7 (8%) patients as having "potential CR." Such patients with "potential CR" had either single lesions with negative or inadequate baseline cytologies (3 patients) or only one follow-up biopsy documenting complete response instead of the two sequential biopsies designated by protocol (4 patients). Median duration of response from start of treatment varied according to the method of analysis, from 13.5 months (measured to time of last documented negative bladder biopsy) to 21 months (measured to time of documented recurrence).

"Two additional analyses have been submitted as supporting evidence that the 19 complete responses identified by the applicant represent clinical benefit. First, time to cystectomy was shown to be longer in the complete responders than in the non-responders. Second, in the complete responders, time to recurrence of disease after treatment with AD32 was shown to be longer than time to recurrence after previous courses of intravesical therapy.

"**Question 1** These data demonstrate that intravesical treatment with Valstar produces durable complete responses and delays time to cystectomy in some patients with BCG-refractory CIS of the urinary bladder. Given the new supportive analyses, the Division believes that the overall FDA CR rate

("definite CR" plus "potential CR") is an appropriate measure of patient benefit in this population. In this study the overall FDA CR rate was 18%. Do you agree that these data demonstrate efficacy of Valstar in this setting?

"After treatment with AD32, 7 of the 90 patients in these trials maintained a complete response until the time of data cutoff and 4 were lost to follow-up. Of the remaining 79 patients, 22 (28%) received additional intravesical therapy and 44 (56%) underwent cystectomy. Of the 44 patients who underwent cystectomy, six demonstrated stage progression to deeply-invasive disease (T3), with lymph node involvement in one patient. Four patients who did not undergo cystectomy are reported to have died with metastatic bladder cancer. Therefore, of the 90 patients treated, at this time there is documentation that 11% (10 patients) have developed metastatic or deeply-invasive bladder cancer. It is difficult to ascertain to what extent the development of advanced bladder cancer in these patients was due to the delay in cystectomy required to receive treatment with AD32 (generally 3 months) since cystectomy was often delayed or was never performed after failure of treatment with AD32. In the 10 patients documented to have invasive bladder cancer or metastatic disease, the delay between recurrence of CIS (when cystectomy should have been performed) and cystectomy or documentation of advanced bladder cancer was a median of 17.5 months (1,6,9,11,13,22,22,25,26, and 36 months).

"Toxicities of intravesical AD32 were limited to the bladder and consisted of mild to moderate cystitis, bladder pain, and dysuria.

"**Question 2** There may be some risk associated with even a 3 month delay of cystectomy. It is not possible to estimate the size of that risk, but it is thought to be small. It is certainly much smaller than would arise from the more prolonged delays seen here. Consider this as you weigh the risks and benefits of Valstar (AD32) in the following populations.

a. Should Valstar (AD32) be approved for intravesical therapy in the general population of patients with BCG-refractory CIS ?

b. In patients with a medical contraindication to cystectomy, treatment with AD32 is not associated with an additional risk of delaying cystectomy; therefore, the benefit to risk ratio of treatment with AD32 is increased in this group. Given the evidence of a reasonable complete response rate and no added risk, the Division believes the case for approval is strong for this population. Do you agree?

"Cystectomy has a significant effect on quality of life and some patients are very reluctant to undergo it. The applicant proposes that Valstar (AD32) be approved for intravesical therapy in patients with BCG-refractory CIS of the urinary bladder who refuse cystectomy. If this approval were contemplated, a patient package insert could be

created to inform patients of the risk of delaying cystectomy and of the limited efficacy demonstrated for AD32. Should Valstar (AD32) be approved for intravesical therapy in patients with BCG-refractory CIS of the urinary bladder who refuse cystectomy?"

Final comments

The applicant's evidence for the efficacy of Valstar was strengthened by the submission of supplemental analyses. The FDA's original count of definite CRs increased to 9 with an analysis which included patients who recurred with only Ta GI-II disease but not CIS as complete responses. Furthermore, the analyses described in the following paragraphs convinced this reviewer that the 7 patients previously classified by the FDA as "potential complete responses" could be considered definite complete responses. This gives an FDA CR rate of 18%.

The first supportive analysis was an analysis of time-to-cystectomy in the full population of study patients. This clearly demonstrates that the group of 19 patients deemed by the applicant to have complete responses underwent cystectomy later than those not deemed to have a CR. This is expected: if investigators considered a patient to have a CR, an immediate operation would not be likely. If this analysis had not suggested a difference, then clearly one could not even consider approval for this indication. However, proving the association between CR and lack of cystectomy does not prove that AD-32 caused the CR or that AD-32 caused the delay in cystectomy. The applicant examines the baseline prognostic factors and finds them balanced. This is helpful. Taken together, these analyses lend some credence to the applicant's assertion that treatment with AD-32 was an independent factor in this analysis, and that treatment with AD-32 caused the delay in cystectomy. Finally, such analyses can seldom be definitive; in a non-randomized study, one can never be certain that unidentified and untested prognostic factors might not be responsible for the association between response and other outcomes such as time to cystectomy.

A second supportive analysis, performed on the group of 19 patients deemed by the applicant to have CRs, compares an individual's duration of response to previous therapies with the individual's duration of response to AD-32. Although one should be cautious about making statistical claims in retrospective exploratory analyses, the duration of response to AD-32 was longer than the duration of response to previous treatments. If anything, this analysis seems likely to have been biased against AD-32; this protocol called for frequent and careful follow-up which would have minimized the response duration of AD-32, whereas previous courses of therapy may not have had such frequent or rigorous follow-up. If one accepted the results of this analysis as definitive, then several of the underlying criticisms which led to a lower Agency response rate would have been addressed. One might reclassify the 7 "possible responses" as definite complete responses, yielding an Agency response rate of 18%.

The applicant's support for the existence of a group of patients with medical contraindications to cystectomy was not strong. However, the committee felt that the

existence of such a group of patients was self evident, as demonstrated by the committee's unanimous vote for approval of Valstar in patients with medical contraindications to cystectomy. It was the consensus of the committee that the determination of medical risk versus benefit was an individual decision to be made by patient and physician. After discussions which have included the Acting Division Director and the Office Director, the following indication is proposed:

> Valstar is indicated for intravesical therapy of BCG-refractory CIS in patients with medical conditions associated with unacceptable morbidity or mortality from immediate cystectomy.

/S/

MD 9/16/98

Grant Williams. M.D.
Medical Team Leader

CC: Orig. NDA - 20-892
Div File
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Medical Team Leader Comments on AD-32 (Valstar) NDA Submission (Edited 9/15/98)
Prepared for September 1st, 1998 meeting of ODAC

See the attached review by Dr. Odujinrin of the most recent amendments submitted by the applicant. The applicant presents two new arguments which are discussed in the following sections.

AD-32 in Patients for Whom Cystectomy is Contraindicated

At the suggestion of the Agency, the applicant attempts to demonstrate that there exists a population of patients for whom cystectomy is contraindicated and for whom the clinical benefit of having a chance at experiencing a complete response (whether that chance is 7%, 14%, 19%, or 29% as suggested by various analyses) outweighs the risk of treatment (especially the risk of developing advanced bladder cancer as a result of delaying cystectomy for treatment with AD-32). This reviewer is willing to consider this approach to approval since the major risk from treatment identified during review was the risk associated with delaying cystectomy: the risk of developing advanced bladder cancer and potentially dying from disease. However, I have not seen persuasive evidence that a significant number of such patients exist, not in literature selected by the applicant, not in literature selected by Dr. Odujinrin, and not in data on individuals who participated in this study. How might one define such a population? In a reference provided by the applicant (1), 30-day surgical mortality in patients greater than 90 years of age was 5.6% for patient who were ASA* Class II, 5.6% for patients who were ASA class III, 18.4% for patients who were ASA Class IV, and 67% for patients who were ASA Class V. It appears the real increase in risk begins with ASA class IV. However, the description of ASA class IV patients is "Severe systemic disease that is a constant threat to life." It seems to me that identifying such a severely ill group of patients (ASA Class IV) as the patients for whom AD-32 is indicated raises a couple of important questions:

- What is the toxicity of bladder instrumentation and intravesical administration of AD-32 in such severely ill patients? For instance, would the bladder spasm associated with such treatment exacerbate existing cardiac arrythmias?

- What is the life expectancy of such patients? If it is short would such patients really benefit from repeated treatments with AD-32?

Finally, the applicant suggests that AD-32 should be approved for patients who refuse to undergo cystectomy. Unless AD-32 is proven to be safe and effective in patients who could undergo cystectomy, patients for whom cystectomy is indicated should be encouraged to have that life-saving operation. An obvious debate surfaces: would approving AD-32 for this indication be a negligent regulatory act encouraging patients to ignore standard therapy, or would it be a progressive move increasing options for patient choice? Taken to the extreme such a philosophy of drug approval could undermine drug

approval standards; drugs with an acceptable risk/benefit ratio for treatment of a refractory neoplasm could be approved for first-line therapy without regard to the efficacy of existing first-line regimens, on the basis that some patients might prefer it. Any drug with demonstrated efficacy in leukemia could be approved for first-line therapy without comparison to Idarubicin plus Ara C if a patient preferred it. On the other hand, when applied selectively, this philosophy could be viewed as providing the patient with the choice between imperfect options such as cystectomy, with the inconvenience of urinary diversion and an immediate mortality of x%, versus intravesical treatment with AD-32 with y % chance of death from bladder cancer due to delay of cystectomy. The Division looks forward to the discussion by the committee whether this philosophy of drug approval is worthy of consideration in the setting of refractory CIS.

Additional Analyses

The applicant presents two interesting analyses which were suggested by committee members during the last ODAC meeting. First, the time-to-cystectomy analysis in the full population of study patients clearly demonstrates that the group of 19 patients deemed by the applicant to have complete responses underwent cystectomy later than those not deemed to have a CR. This is expected: if investigators considered a patient to have a CR, an immediate operation would not be likely. If this analysis had not suggested a difference, then clearly one could not even consider approval for this indication. However, proving the association between CR and lack of cystectomy does not prove that AD-32 caused the CR or that AD-32 caused the delay in cystectomy. The applicant examines the baseline prognostic factors and finds them balanced. This is helpful. Taken together, these analyses lend some credence to the applicant's assertion that treatment with AD-32 was an independent factor in this analysis, and that treatment with AD-32 caused the delay in cystectomy. Finally, such analyses can seldom be definitive; in a non-randomized study, one can never be certain that unidentified and untested prognostic factors might not be responsible for the association between response and other outcomes such as time to cystectomy.

A second interesting analysis performed on the group of 19 patients deemed by the applicant to have CRs compares an individual's duration of response to previous therapies with the individual's duration of response to AD-32. Although one should be cautious about making statistical claims in retrospective exploratory analyses, it appears that the duration of response to AD-32 was longer than the duration of response to previous treatments. If anything, this analysis seems likely to have been biased against AD-32; this protocol called for frequent and careful follow-up which would have minimized the response duration of AD-32, whereas previous courses of therapy may not have had such frequent or rigorous follow-up. If one accepted the results of this analysis as definitive, then some of the underlying criticisms which led to a lower Agency response rate (7%) would have been addressed, and one might reclassify the additional 7% of "possible responses" as legitimate complete responses, yielding an Agency response rate of 14%.

I believe these two sets of analyses provide more support for the efficacy of AD-32 than was apparent during the last meeting of ODAC. However, there ~~is also~~ additional evidence of stage progression and of deaths from bladder cancer in patients who did not undergo cystectomy. This application presents a difficult risk-benefit judgment. I look forward to the re-examination of this matter by the Oncologic Drugs Advisory Committee.

/S/ MD 8/15/08

Grant Williams. M.D.
Medical Team Leader

*American Society of Anesthesiologists Physical Status Classification System in Predicting Risk

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STATEN

JUN 23 1998

Medical Team Leader Discussion and Recommendations

NDA: **#20,892** **Date of Review: 6/23/98**
Drug: **Valrubicin (AD-32)**
Indication: **BCG-Refractory CIS of the Urinary Bladder**

Refer to the Medical Officer Review by Dr. Odujinrin. We worked together closely on this application and I am in full agreement with his findings and recommendations. The purpose of this review is to respond to the applicant's meeting package submitted on June 11, 1998 and to summarize the Agency's final position on this NDA. Refer to the meeting package which is part of the approval package. The following points were discussed during the pre-meeting on June 17, 1998 and represent the consensus of the group attending including Dr. Scher (ODAC consultant attending by tele-conference), Dr. Justice (acting division director), Dr. Williams (medical team leader), Dr. Odujinrin (medical officer), Dr. White (primary reviewer for Bropirimine NDA application) and Ann Staten (project manager). The applicant responded to 11 issues raised by the advisory committee. Reviewer comments follow each point:

1. **"ODAC COMMENT/OBJECTION: The natural history of the disease does not appear to have been affected by valrubicin treatment."**

Refer to table 1 on page 1 of the June 11th submission. The applicant notes that 14 patients showed a "striking" difference in disease-free interval after Valrubicin than the last intravesical therapy received.

Reviewer comments:

- The last 5 cases in Table 1 are not considered CRs by even the most liberal FDA analysis. By FDA analysis, time to recurrence was 3 to 6 months instead of 9 months for the last 4 cases.

- 5 cases selected according to the following criteria seem to suggest a significant delay in the expected natural history of progression:

- A) Criteria: Last recurrence occurring < 6 months since start of prior Rx, and recurrence after Valrubicin occurring ≥ 12 months since start of Valrubicin.
  Results: **3 cases** (Case #12 not biopsy-proven CR at or after 6 months)

  B) Criteria: Last recurrence occurring 6 to 12 months since start of prior Rx, and recurrence after Valrubicin occurring ≥ 18 months since start of Valrubicin:
  Results: **2 cases**

- The scatter plot evaluates only claimed CRs:19 of 90 patients selected for good outcomes. A scatter plot of all 90 patients might not look as asymmetric.

- This analysis only looks at recurrence interval after last therapy. More impressive would be a pattern of recurrence at short intervals interrupted by therapy.

- It may be more difficult to ascertain the presence of residual disease in patients in the NDA that had:
  A) A lesser extent of disease (only one positive biopsy at baseline)
  B) Lack of positive baseline cytology

Reviewer conclusions from point 1:
The number of patients who might be classified as having experienced obvious clinical benefit according to this analysis is 5 according to this reviewer's criteria. Even applying more liberal standards, the number of patients so categorized would be less than 10% (9/90) of those treated with Valrubicin. These numbers are consistent with the Agency's finding of 7 patients who had definite complete response.

2. **"ODAC COMMENT/OBJECTION: Patient benefit has not been demonstrated in the trial."**

The sponsor presents an analysis of time to cystectomy of the 19 claimed CRs versus the non-responders. Time to cystectomy was significantly longer in nonresponders than in the responders ($p = 0.017$ by logrank test). Median time to cystectomy was 25.3 months for nonresponders and had not been reached in responders.

The sponsor also notes that 15 patients recurred initially with conditions for which cystectomy might not be indicated, i.e. patients with recurrent CIS documented only by cytology or patients with low-grade papillary disease but without biopsy-proven recurrent CIS.

Reviewer comments:

- The Sponsor's analysis of time to cystectomy for CRs versus Nonresponders ($p = 0.017$) does suggest an association between CR status and time to cystectomy. This does not prove that achieving CR is a surrogate for preventing cystectomy, it merely demonstrates an association.

- Citing Hudson et al (1992), all candidates failing Valrubicin are said to be candidates for cystectomy. However, Hudson et al (1995) also stated : "Responsiveness of low risk CIS patients to intravesical agents could proceed with a reasonable assumption of a low risk of metastases even if 1 or more intravesical therapies fail." One of the low risk factors cited was focal carcinoma in situ. The use of the phrase "one or more intravesical therapies" suggests that the phenomenon of low risk associated with unifocal disease is thought to continue to be operative even after a one or more recurrences. During meetings with the Agency, the sponsor has suggested that if there is any better prognosis associated with unifocal disease, it is limited to the initial presentation, and that all patients with recurrent TIS, even if biopsies reveal disease at only at a single site, have 'diffuse disease' hence the same prognosis as patients presenting with multifocal disease.

- It is not clear that continued lack of recurrence of CIS when a patient has recurred with papillary disease represents clinical benefit from treatment. The protocols for both the Bropirimine NDA and for Valrubicin studies prospectively deemed such events as failure of therapy.

3. **"ODAC COMMENT/OBJECTION: Heterogeneity of the disease - was this a drug effect of a patient selection effect?"**

Refer to table 3 on page 4 of the meeting package. The sponsor compares the claimed CRs with the nonresponders for the presence of potential prognostic factors including prior BCG therapy and multifocal disease.

Reviewer comment:

Prognostic factors seem reasonably balanced between CRs and Non-responders.

4. **"ODAC COMMENT/OBJECTION: Complete response is not an appropriate endpoint for this study."**

The applicant defends complete response as a surrogate of patient benefit.

Reviewer comment:

The Agency agrees that complete response of adequate duration is an adequate endpoint for new drug approval in an appropriate population in whom cystectomy is otherwise required. Patients should have well-documented disease at baseline and should be followed in a rigorous manner. The efficacy outcome of a trial utilizing such an endpoint in a single-arm trial should be impressive and unequivocal considering the potential risk of delaying cystectomy.

5. **"ODAC COMMENT/OBJECTION: Complete response is not a surrogate of patient benefit"**

The sponsor notes that not patient with CR was documented to have metastatic disease or to have deeply invasive disease at cystectomy.

Reviewer comment
There seems to be an association between CR and good outcome. However, this does not demonstrate that the good outcome was causes by Valrubicin therapy.

6. **"ODAC COMMENT/OBJECTION: The most appropriate endpoint for the primary efficacy study would be time to a negative event ~~such as~~ cystectomy, invasive disease, metastatic disease, or death due to bladder cancer.**

The applicant defends CR as an appropriate endpoint.

Reviewer comment

Given the design of this trial, CR rate with duration of 1 year or more is the most appropriate endpoint.

7. **"ODAC COMMENT/OBJECTION: The fact that not all patients went to cystectomy after failure/recurrence suggests that the patients were not considered for immediate cystectomy at study entry.**

Refer to tables 4 and 5 on pages 8 and 9 of the meeting package. The sponsor outlines reasons why patients may not immediately proceed to cystectomy. 59% (37/63) of those with biopsy-proven recurrent CIS and whom the applicant considers to eligible for cystectomy did undergo the procedure. 16 of the remaining 26 "had characterisitcs that might make them poor surgical risks and may have affected the decision concerning cystectomy."

Reviewer comments

- 37/63 (59%) stated as eligible for cystectomy had the procedure. 19 patients were said to be ineligible: 12 patients recurred with Ta G1 or Ta G2 tumors only without CIS and 7 with positive cytologies for CIS but negative bladder biopsies.
  - -It is not clear how many of these 19 subsequently had a biopsy positive for TIS and yet still did not undergo cystectomy.
  - -The 4 patients lost to follow-up should be included in the denominator.

- Regardless of mitigating factors, if patient benefit is contingent upon avoiding cystectomy, and if a significant population did not undergo cystectomy, one must re-evaluate whether the entire population is deriving the claimed benefit of therapy.

8. **"ODAC COMMENT/OBJECTION: Administration of additional intravesical therapy to patients who had failure or recurrence implies that the population was "not so refractory" and did not represent a group of patients who were considered for immediate cystectomy."**

The sponsor notes that 33 patients (7 claimed CRs (37%) and 26 nonresponders(37%) received additional intravesical therapy.

Reviewer comment

See comment for item #7.

9. "ODAC COMMENT/OBJECTION: Randomized trials are necessary in this population.

The applicant states that a randomized trial cannot be performed in this setting

10. DATA FROM STUDY COMPLETED AFTER NDA CUTOFF DATE

The applicant describes data from recently completed trials in Europe demonstrating that Valrubicin can produce complete responses in 49% of patients with transitional cell carcinoma, even when a single marker papillary lesion is not resected at initial cystoscopy.

Reviewer comment
Summarized data on marker-lesion results in papillary disease sound interesting and suggest Valrubicin has anti-tumor activity. However, they have no direct bearing on the NDA submitted for BCG-refractory CIS.

11. UROLOGIC NOTES

The applicant makes several points from the literature. First the distinction between focal and diffuse CIS is questioned. Second, the applicant notes that TUR alone is inadequate therapy for CIS and that median time to recurrence from TUR alone is 3 months.

Reviewer comments:

- The reference to the 1991 article by Gils-Gielen, which is cited by the applicant as demonstrating that the prognosis is similar for focal and diffuse disease, refers to an evaluation of only 52 patients, 37 of whom received BCG which is highly effective in this setting. The conclusion of the article is disputed by Donald Lamm's editorial in which he notes that the study was under-powered and that trends in efficacy parameters were in favor of group with focal disease. 3 years later, in a 1995 review by Hudson and Herr (J Urol, 1995, Vol. 153 p564) diffuse disease is still cited an adverse prognostic factor to be used in stratification for trials evaluating intravesical therapy of CIS.

- The applicant states that patients with CIS treated with TUR alone recur at a median of 3 months as shown in the graph from the 1986 paper by Herr et al. However, all patients had diffuse (3 or more distinct areas of bladder mucosa) and often symptomatic CIS and obviously had CIS affecting more of the bladder mucosa than patients included in the Valrubicin studies.

Summary

The following summary was prepared as an introduction to the questions submitted to to the Oncologic Drugs Advisory Committee:

In 1996, during deliberations on an NDA for BCG-refractory carcinoma *in situ* of the urinary bladder, the Oncologic Drugs Advisory Committee agreed (by acclamation) with the following statements:

"Carcinoma *in situ* of the urinary bladder often responds to treatment with intravesical BCG. However, patients with diffuse multifocal bladder CIS that is refractory to intravesical BCG or patients who cannot tolerate this treatment are generally considered to be candidates for immediate cystectomy since they have a high risk of developing invasive and metastatic bladder cancer. In this setting, a medical treatment capable of producing durable complete remissions in a substantial proportion of patients could provide a meaningful clinical benefit allowing patients to delay or avoid the morbidity of bladder removal; provided, however, that the treatment toxicities were acceptable and patients were not placed at unreasonable risk of developing metastatic bladder cancer while cystectomy was delayed during this medical treatment. Non-randomized clinical trials could be adequate to support approval of such a treatment."

"On the other hand, in patients with CIS of the urinary bladder who are not candidates for immediate cystectomy, FDA believes randomized clinical trials are necessary to assess the benefit of a new drug. If there is no way to predict whether or when patients may need to undergo cystectomy, then a control group is needed to determine whether cystectomy was delayed and whether the delay significantly increased the patient's risk of developing metastatic cancer."

Treatment of CIS with AD 32 (Valrubicin)

The NDA for AD32 (Valrubicin) includes data from 90 patients in Studies 9301 and 9302 who had received at least 2 prior intravesical therapies for carcinoma *in situ* (CIS) of the bladder, including at least one course of BCG; 70% had received at least 2 courses of BCG and 30% had received one course of BCG. Of the 20 complete responses claimed by the Applicant, baseline CIS was documented at multiple biopsy sites (i.e., there was multifocal disease at baseline) in only 7 patients. In many of these patients, however, multiple sites of CIS had been documented in the past. Baseline cytology was positive in only 12 of the 20 patients.

After patients were treated by intravesical administration of AD32, the Applicant found that 20 of 90 (22%) patients had a complete response. The FDA, however, found that only 7 patients (8%; group A in the attached table) had well-documented complete responses according to protocol criteria and that an additional 7 patients had "potential complete responses." Such patients had either single lesions with inadequate or negative baseline cytologies (3 patients; group B) or had only one follow-up biopsy documenting complete response instead of the two sequential biopsies designated by protocol (4 patients; group C).

Duration of response, measured from the start of treatment, is outlined in the attached table for each of these 14 patients (16%) with complete response or "potential complete response." For the group of 14, median time to recurrence was 21 months, median time to last negative cystoscopy and negative cytology was 18 months, and median time to last negative biopsy was 13.5 months. After treatment with AD32, 7 of the 90 patients in

these trials maintained a complete response lasting until the time of data cutoff. Of the remaining 83 patients, 22 (26%) received additional intravesical therapy and 37 (45%) underwent cystectomy. Of the 37 patients who underwent cystectomy, 3 demonstrated stage progression to deeply-invasive disease (T3), with lymph node involvement in one patient. Four patients who did not undergo cystectomy have died with metastatic bladder cancer.

Toxicities were limited to the bladder and consisted of mild to moderate cystitis, bladder pain, and dysuria.

Advisory committee recommendation

On June 1, 1998, the Oncologics Drugs Advisory Committee was asked whether the Valrubicin studies were well-controlled studies demonstrating the safety and efficacy of for the proposed indication. The votes were as follow:

No	10
Yes	0
Abstain	1

Recommendations

I concur with the Oncology Drug Advisory Committee's assessment that the safety and efficacy of Valrubicin have not been demonstrated. As discussed in reviewer comments in the previous section of this review, arguments made subsequently in the June 17, 1998 meeting package have not changed this opinion. I recommend that a nonapproval letter be sent to Anthra. The following paragraph summarizes the information that should be included in such a letter. The nonapproval letter sent by the Agency for Bropirimine in 1996 was used for a template for organizing this information:

The Agency met with the applicant on June 19, 1998. The applicant intends to submit an amendment to this NDA limiting the indication to patients with BCG-refractory CIS for whom cystectomy is contraindicated. Pending receipt of a satisfactory application for such an indication, I recommend that the application not be approved.

/S/ 6/23/98

Grant Williams, M.D.

cc: Orig NDA 20-892
Div File
HFD-150 / Oddujinvir
/ GWilliams
/ Astatkar

MEDICAL OFFICER'S COMMENT ON ANTHRA LETTER DATED September 15,1998

Subject: Addition to Clinical Information in the package insert.

Reviewer's Comments: The 16 patients classified as Complete responders did not all have documented multiple biopsies both at 3 and 6 months, and definitely did not all have protocol defined cytology criteria for CR.
Figure A is not attached to the letter, but I assume it is the Kaplan- Meier plot showing response duration of CR patients on Valrubicin in comparison with their prior intravesical therapies. While the analysis as presented at ODAC appeared convincing, it will be inappropriate to place it in the label for the following reasons: The analysis had many statistical glitches which had already been pointed out in previous reports; e.g. claim of statistical significance, small number of patients, dependent structure of patients analyzed, and retrospective nature of the analyses. Additionally, approval of AD-32 is for a limited population. The figure is not necessarily representative of this population.
Table A was previously discussed at a June 19, meeting with the sponsor. The division's analysis of the 9 patients listed differs from the applicant's, in terms of patients with CR and duration of response. Hence it will be misleading to place the table in the label.

Reviewer's Comments: The deleted sections are unnecessary details, some of the claims are not totally in agreement with the division's claims. A valid section concerning development of advanced bladder cancer , cystectomy and treatment with AD-32 is worded rather clumsily that the meaning of this section is lost.

Reviewer's Comments: The official Agency position on the indication is as indicated above, and it is not a negotiable issue.

Warnings:, Information for patients:
I see no reason to change how we already have the wording in these two sections.

OLUWOLE O ODUJINRIN M.D.
MEDICAL OFFICER

MD 9-14-95

See Team Leader Comments

NDA MEDICAL OFFICER REVIEW #2

NDA#20,892

AD-32 (VALSTAR)

SPONSOR: Anthra Pharmaceuticals, Inc.

Date Submitted: December 31, 1997

Amendments:	**January**	**21, 1998**
	April	**29, 1998**
	May	**13, 19, 28, 29, 1998**
	June	**26, 1998**
	July	**27, 30, 1998**
	Aug	**10, 1998**

cc: Orig NDA 20-892
Div File
HFD-150/ ODuijnrin
1 GWilliams
1 AStaten

MEDICAL OFFICER REVIEW

NDA#20,892 TITLE: AD-32 (Valsar) for the Treatment of BCG Refractory Carcinoma in situ of the Urinary bladder in a selective patient subset.

SPONSOR : ANTHRA PHARMACEUTICALS INC.

1. SUMMARY OF SPONSOR'S PREVIOUS SUBMISSION OF AD-32 (Valrubicin)

AD-32 is a semisynthetic highly lipophylic analog of the anthracycline antibiotic doxorubicin proposed for intravesical use in the treatment of patients with biopsy-proven carcinoma in situ (CIS) of the bladder who are refractory to BCG immunotherapy. On December 31,1997, under the trade name Valrubicin, the sponsor submitted to the FDA , results of two studies (A9301 and A 9302) utilizing AD-32 in the treatment of 90 patients at 41 centers by 43 investigators for the stated indication. The results were presented at the Oncology Drug Advisory Committee (ODAC) meeting on June 1st , 1998. The sponsor provided evidence to support complete responses in 19 of the 90 patients treated with AD-32 for this indication. The Agency presented the results of its review of the data submitted. The FDA determined that there were 7 definite responses out of the 90 treated patients, with 7 questionable responders. ODAC members voted unanimously not to approve AD-32. With 11 negative votes , 1 abstention and no positive votes, the committee members indicated that the benefit of AD-32 in BCG-refractory CIS patients had not been demonstrated. Furthermore, considering that a large number of patients (at least 71 of 90 patients) were unresponsive to this therapy, the committee was concerned about the potential risk to patients from delaying cystectomy in order to give intravesical AD-32 treatment.

An eleven point proposal was submitted to the Agency for discussion at a meeting on June 19th, 1998. These points were discussed, but the Agency remained unconvinced that AD-32 had been demonstrated to be safe and effective. However, the Agency recognized the possibility that safety and efficacy might be demonstrable in a subset of patients for whom cystectomy was medically contraindicated. Anthra was to provide additional data that a defined population of CIS patients exists who are BCG refractory, but for whom cystectomy was medically contraindicated. Literature-based evidence defining contraindications to surgery was to be provided as well. If a sizable number of such patients could be convincingly demonstrated to exist, this might constitute an approvable basis for the drug. The Agency also expressed interest in the sponsor's suggestion concerning the need to re-evaluate patients who were protocol classified by Anthra as No

CR due to recurrence with only Ta G1/G2 disease. By reviewing this category of patients, it may be possible to increase the number of patients who are classified as CRs. The applicant excluded this group of patients from the CR category in its original protocol. Anthra subsequently submitted a major amendment to the NDA to address whether AD-32 might be approvable for patients who are not candidates for cystectomy.

This submission extended the regulatory clock by three months and provided the sponsor another opportunity for its amended application to be discussed at a subsequent ODAC meeting.

II. VALSTAR (VALRUBICIN): PROPOSED INDICATION:

The NDA is resubmitted under a new trade name, Valstar, with an amended proposed indication and usage:

III. DOCUMENTS REVIEWED:

Case Summaries of Responders, Vol. 1.40-1.44 received December 1997
Tables and Reports of Individual Treatment Studies Vol.1.33
Pre-meeting package dated June 11,1998
Major Amendment Vol. 2.1 received June 29,1998
Amendment No.27 received July 28,1998.
Amendment No28 received July 31,1998

IV. NEW ANALYSES

Anthra's five main points in support of use of valstar and for reconsideration of an approvable basis for AD-32.
FDA responses follow each argument

A) PATIENTS WHO ARE NOT CANDIDATES FOR SURGERY

If a significant subpopulation of BCG refractory CIS patients exists who are not candidates for cystectomy due to medical contraindications or patient refusal, they might represent a population for whom AD-32 treatment could be considered safe and effective. The sponsor provides the following criteria as indicators of surgical risk, hence medical contraindication to cystectomy:

- Age >75 years
- Age >75 years with or without a history of cardiovascular or pulmonary disease.
- History of cardiovascular or pulmonary disease plus other types of cancer.

The table below represents data on 16 patients who were enrolled in the study but according to the applicant, are not candidates for radical cystectomy based on the criteria indicated above. 4 of the 16 patients (25%) are in the applicant's classified group of complete responders on valrubicin therapy, while 2 of the 16 patients (12.5%) are in the FDA's group of responders.

TABLE 5

Characteristic(s)	Specific Condition(s)	N	Patient Numbers[a]
Age ≥75 yr	75-82 yr	4	
Age ≥75 yr + History or development of cardiovascular or pulmonary disease	TIA, COPD, CVA, MI	2	
History or development of cardiovascular disease	TIA, CAD, CABG, MI, angioplasty	5	
History or development of pulmonary disease	ARDS, emphysema, sclerosing procedure to lung	3	
History of cardiovascular or pulmonary disease + other type of cancer	COPD and lung cancer; CAD, MI, and renal cancer	2	

[a] Suffix "R" after a patient number identifies a CR.
[b] Patient died of myocardial infarction 2 months after clinical failure.

Literature Review:

The sponsor provides literature documentation to support the position and criteria outlined in the table above. The arguments can be summarized as follows:

Bladder cancer is largely a disease of older people, median age at presentation is between 65 and 70 years, and the incidence increases with age. A large percentage of patients undergoing treatment for bladder cancer therefore have multiple comorbid conditions. Since smoking is a major etiologic factor for development of bladder cancer, pulmonary and cardiovascular diseases further complicate the clinical competence of these elderly patients to withstand such an arduous procedure as radical cystectomy

Radical cystectomy involves extensive removal of organs and tissue in both male and female patients. The procedure usually takes 6 to10 hours to complete, resulting in. large fluid shifts and other hemodynamic complications. Radical cystectomy therefore meets the criteria of high risk noncardiac surgery as defined by the American College of Cardiology/American Heart Association Task Force Guidelines.

The overall mortality from cystectomy is 2.5%. In elderly patients, the mortality is higher (3% to6%) than in younger patients(1%to3%).(Skinner et.al.)

Coexistence of multiple risk factors greatly increase the risk of surgical complications and operative mortality. These factors include: Age, cardiovascular function, pulmonary function, hepatic function and nutritional status. Pre-operative nutritional status is not uncommonly poor in elderly patients.

Patient refusal of Cystectomy

In the latest amendment submitted July 30th 1998, the sponsor provides clinical notes of investigators indicating patient refusal of cystectomy when offered this treatment option after failure of intravesical therapy of CIS. The sponsor considers patient refusal of cystectomy an acceptable indication for valrubicin (valstar).

FDA RESPONSE

The sponsor lists a group of sixteen patients who are not considered to be candidates for medical reasons. The response rates to valrubicin therapy as judged by both the sponsor, 4 of 16 (25%) and the FDA, 2 of 16 (12.5%) are similar to the rates in the total population of patients studied, 21% and 8% respectively. Hence this is not a unique group of patients, but appears to be a representative sample of the population of patients in the study.
Two patients in this group have successfully undergone radical cystectomy since this list of patients was compiled. Both patients had deep muscle invasive disease at cystectomy (pT3b/pTis). Both patients are over age 75 years.

Literature Review :

The literature is replete with information on radical cystectomy in elderly patients.(Ref 1-14) A preponderance of the information advocates the need for cystectomy in this population of patients. Surgery can be performed with acceptable morbidity and mortality if meticulous attention is paid to the pre and postoperative needs of the patient.
The following represents samples of conclusions of many of the articles. Some of the articles were included in the sponsor's submission. These articles directly respond to all of the concerns raised by the sponsor regarding radical cystectomy in this patient population.

"Patients in their eighth decade are becoming an increasingly important group numerically in the practice of uro-oncology, and it will be necessary to develop more sophisticated and flexible approaches for their management. Provided that care is taken to plan for their altered physiologic requirements. it is clear that comparable (or better) outcomes can be anticipated from well-designed treatment programs that involve surgery, radiation or chemotherapy, applied as single modalities or in combination.....Advanced age alone should not preclude the provision of active and effective strategies of treatment." (Skinner E, Raghavan D, et.al Ref 1 page312)

"Elderly patients have increased risk from urologic surgery, mostly owing to associated comorbid factors. They are also a population that can benefit greatly from surgery...Most of this increased risk can be anticipated and managed so that surgery is safe....With effective pre and postoperative care the risks are minimized, the probability of a successful outcome is maximized, and the quality of life is improved for most."(Smith,R, Osterweil D, et.al. Ref 2 page 40)

"The treatment goal in any cancer surgery is to cure the primary neoplasm and preserve quality of life. We believe these can best be achieved by cystectomy for invasive bladder cancer even in the 80 year old patient. Conservative or alternative strategies often result in

progressive, uncontrolled pelvic cancer which is associated with bleeding, pain, disability obstipation and repeated bladder manipulations. Frequent hospitalizations for months or years until death are often required unless the local bladder tumor is definitively treated..... Radical cystectomy in this population offers the best opportunity for sustained disease free quality survival."(Strumbakis N, Herr HW, Ref 3)

"...radical cystectomy is a relatively safe procedure for elderly patients with invasive transitional cell carcinoma of the urinary bladder. ...The insignificant increase in the operative risk in older patients is by far less than the major effects of alternative treatment and the associated morbidity and mortality. Death related to under treated cancer is much more common than death related to intercurrent medical diseases, and the quality of life during survival is strongly affected. Thus , the elderly patient who is found unsuitable for surgery is deprived not only of his right to definitive curative therapy but also is exposed to significantly higher morbidity and mortality and worse quality of life than are patients who undergo operations." (Ref 7)

Patient Refusal of Cystectomy

The choice of therapy for a disease should be determined by science-based evidence of safety and efficacy of that particular therapy. These are the issues under consideration for determininig approvability of valrubicin for use in patients with CIS bladder cancer who have failed BCG treatment. Patient refusal to accept the recommedation for indicated therapy of any disease usually calls for better patient education about the disease. Urologic oncology is no exception to this medical dictum. As emphasized by Skinner, "Given the potential for successful outcomes of treatment, we must place greater emphasis on educating the elderly about the symptoms of bladder cancer, encouraging them to present as early as possible, thus facilitating the best possible results of treatment."(1).

B) RESPONSE TO INTRAVESICAL TREATMENT IN COMPLETE RESPONDERS:

The applicant suggests that use of intravesical AD-32 changed the course of the disease in the 19 patients claimed by Anthra to be complete responders (CR). This is demonstrated by comparing an individual's duration of response on AD32 treatment duration of response to prior therapy received by the same patient. Figure 1 purports to demonstrate that "a statistically significant difference" exists between the response to valrubicin therapy and the response to each of the previous three treatment regimens received by the patient. The same information is also presented as scatter plots in which response to valrubicin therapy is compared to the last intravesical therapy of any kind or to BCG.

FIGURE 1

Response to Prior Intravesical Therapies Versus Response to Valrubicin in CRs (N=19)

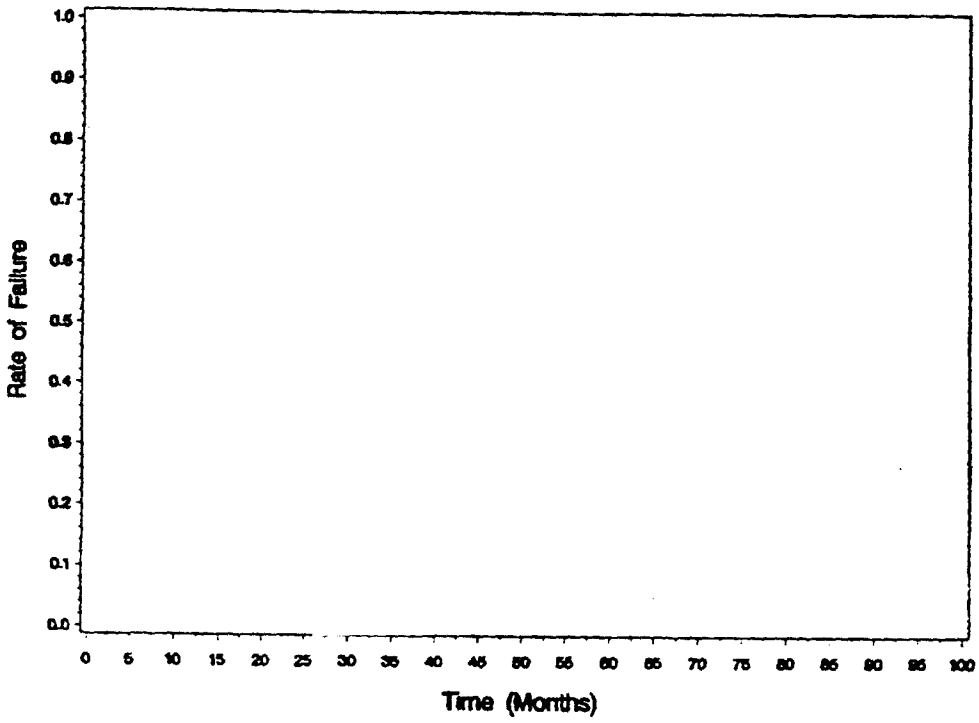


FIGURE 2

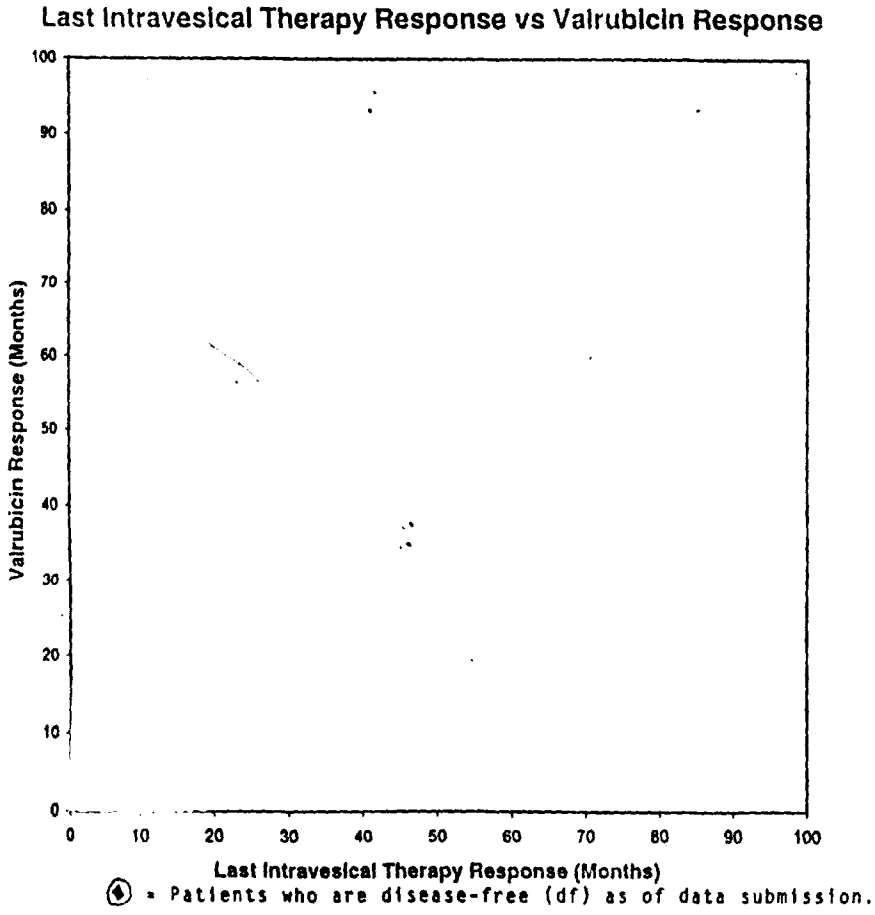
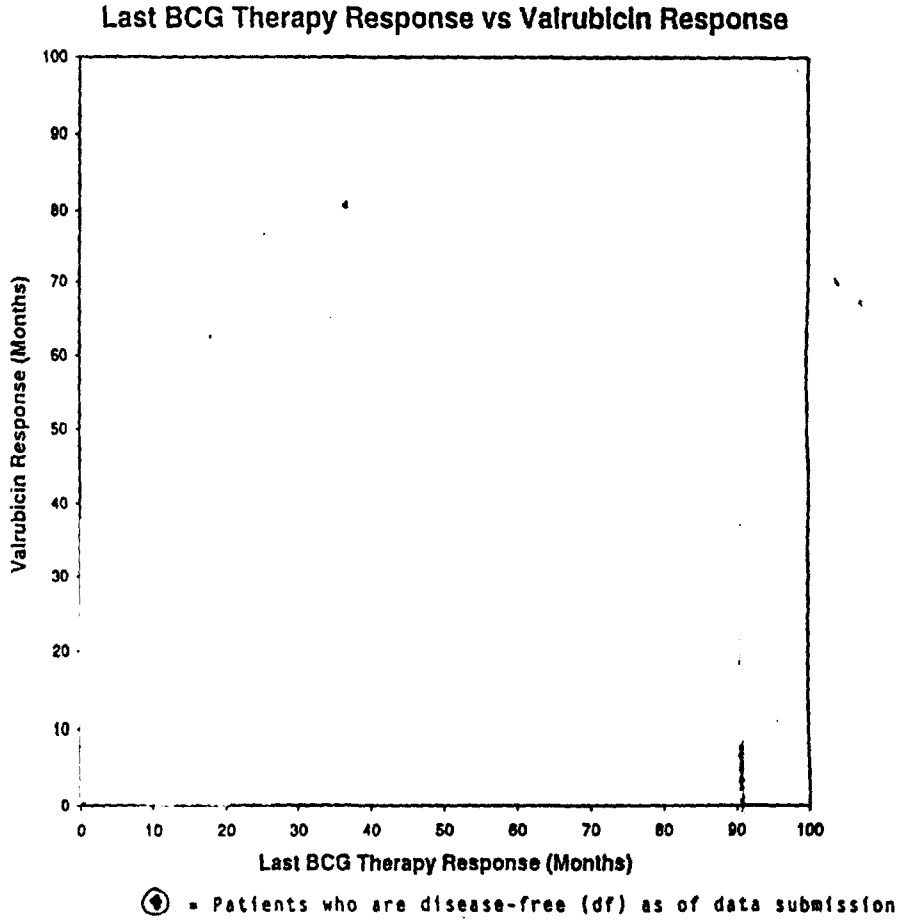


FIGURE 3



FDA RESPONSE

See the statistical review by Gang Chen Ph.D for more details.

The Agency did show in its review of the original submission that 7 of the 90 patients who received intravesical AD-32 treatment had obvious complete responses. The time to recurrence in this group of patients ranged from 12 months to 27+ months. This small group of patients therefore did derive benefit from the treatment received by delaying cystectomy. There were 7 others in whom responses were possible, but such responses were not strictly documented. These differences in the Agency's number of CR patients and the duration of the CRs naturally affect the analysis of the data presented by the applicant.

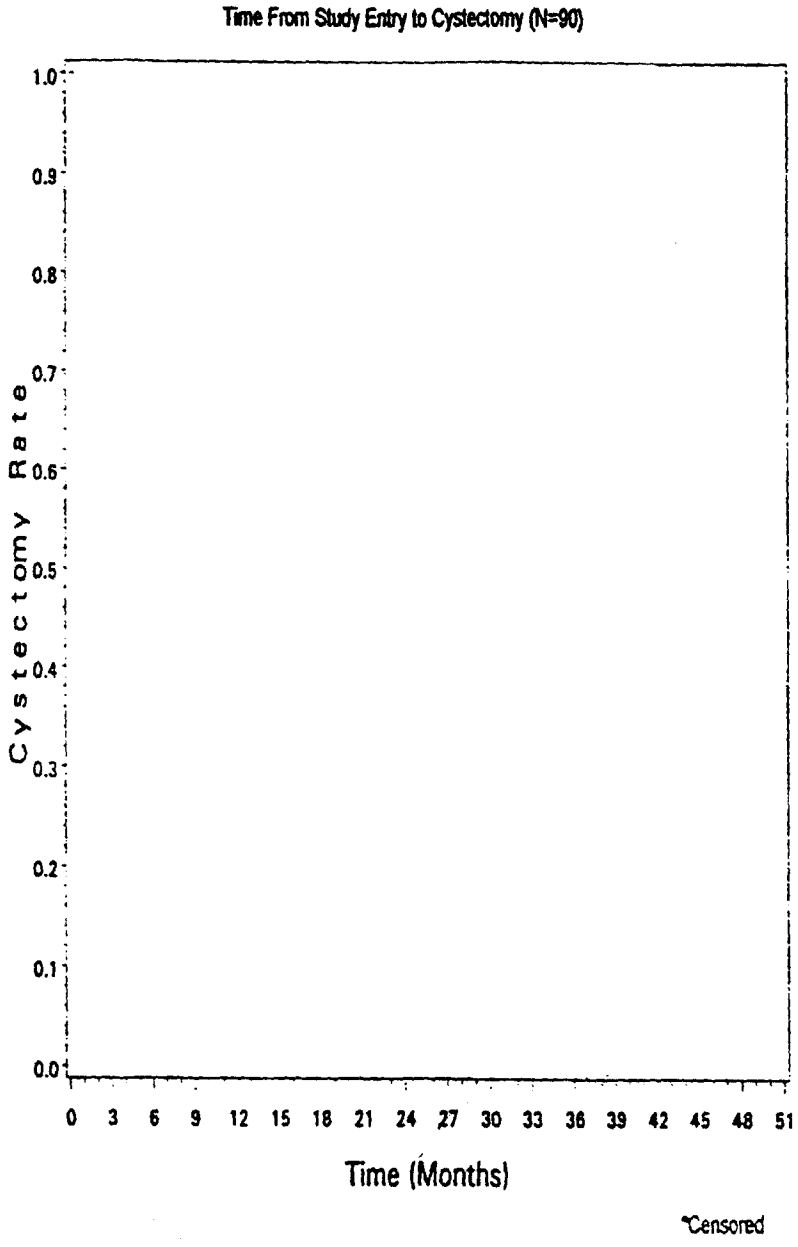
Given this caveat, data presented by the applicant giving an analysis of duration of response to prior intravesical therapies versus response to valrubicin would suggest that CR patients were disease free longer on AD-32 therapy than with prior intravesical treatments. The Kaplan Meier plots provided are exploratory, but do show a trend in favor of AD 32 treatment. The scatter plots can be interpreted as yielding the same conclusion. Statistical significance cannot, however. be determined from the data presented and the *p-value* is uninterpretable, since this is a retrospective, non-randomized analysis.

The log-rank test is invalid because of the dependent structure of the groups of data being compared. A test statistic based on paired or matched data analysis would have been more appropriate. The scatter plot evaluates only claimed CRs: 19 of 90 patients selected for good outcomes. A scatter plot of all 90 patients might not appear so asymmetric.

C) TIME TO CYSTECTOMY IN RESPONDERS VERSUS NON- RESPONDERS:

The applicant provides Kaplan-Meier analysis of time to cystectomy in the 19 CRs and 71 non CRs in which a claim of "statistically significant difference" is shown between the two groups. A median time to cystectomy of 25.3 months is claimed for non-responders, while the median time for responders "has not yet been reached." The applicant thus implies that improvement in time to a negative event, in this case cystectomy, is a benefit that should be viewed as a positive effect of AD-32 treatment.

FIGURE 2



FDA RESPONSE

The Kaplan-Meier analysis of time to cystectomy provided by the sponsor on the entire population of 90 patients in the study does suggest an association between CR status and time to cystectomy. However, an association between response and time to cystectomy does not prove that AD-32 was responsible for the response or delay in cystectomy. One must also be confident that the observed "responses" were legitimate and would not have been observed even without intravesical therapy. It is quite possible that patients with less aggressive disease are both more likely to respond to therapy-related manipulations (TUR) and also are less likely to undergo cystectomy even without AD-32 treatment.

D) HOMOGENEITY OF THE POPULATION:

The sponsor attempts to show that patients in the CR group do not represent a favorable class, but are similar in baseline and demographic characteristics to the non-CR patients. The accompanying table represents demographic and baseline characteristics of the patients in each group.

Table 1. Comparison of Demographic and Baseline Characteristics

	All (N=90)	CRs (N=19)	Nonresponders (N=71)
Male	88%	89%	87%
White	98%	100%	97%
60-79 yr	79%	95%	75%
Median duration of transitional cell carcinoma[a]	3.3 yr	3.3 yr	3.4 yr
Median duration of Tis[a]	25 mo	28 mo	24 mo
Baseline local bladder symptoms	50%	68%	45%
≥2 Prior BCG	70%	68%	70%
Last BCG ≤3 mo before study entry	2%	5%	1%
Last BCG >3–24 mo before study entry	73%	68%	75%
Cytology (+) at baseline	63%	58%	65%
≥2 (+) biopsy sites at baseline	53%	47%	55%
History of ≥2 (+) biopsy sites	Not done	89%	Not done
Two sites (+) for Tis at baseline and (+) cytology	38%	32%	39%
Received intravesical tx after failure/recurrence	37%	37%	37%

[a] Time from initial diagnosis to study entry.

The sponsor implies that the natural history of the disease as well as prior intravesical therapy was not different in either category of patients.

FDA RESPONSE

Demographic and baseline data appear reasonably balanced between Responders and Non-Responders. The BCG information however suggests that more patients in the CR group could potentially still be BCG responsive, since 5% of CR patients versus 1% of Non responders had their last BCG treatment ≤ 3months before study entry.

E) CLINICAL BENEFIT (CB)

The sponsor proposes the use of change in clinical profile of disease as an indicator of clinical benefit (CB) rather than the CR (complete response) criteria utilized in the protocol. Through this mechanism, the sponsor proposes to add 10 more patients to the group of patients who derived benefit from AD-32 treatment. These 10 patients failed valrubicin therapy with low grade papillary tumors only (stage Ta, grade 1 or 2) and might have had their response category upstaged to this more favorable category to indicate lack of recurrence of CIS.

As a result of this reclassification, the sponsor claims 29 CB and 61 non CB patients, as opposed to 19 CR and 71 non CR patients. The table below includes the sponsor's list of 10 additional patients who failed with TaG1 or TaG2 disease, and the claimed duration of benefit on therapy.

Table 2. Patients With Clinical Benefit

COMPLETE RESPONDERS		PATIENTS WHO FAILED WITH TaG1 OR TaG2	
Anthra Patient ID (FDA Patient Number)	*Time to Failure or Last Follow-up (months)[a]*	*Anthra Patient ID*	*Time to >TaG2 or Last Follow-up (months)[b]*
	15		9
	24		19
	15+		27[c]
	24+		8
	21		6+
	12		10[c]
	27+		17+
	18		20
	36		3+
	24+		34+
	21+		
	21+		
	18		
	12		
	21+		
	9		
	9		
	9		
	9		

[a] A "+" indicates that the patient was still disease-free at the month shown, which was the time of the last follow-up.
[b] A "+" indicates that, at the time indicated, the patient still had TaG1 or TaG2 disease and no further biopsy data are available.
[c] Based on date of cystectomy. Patient had no evidence of disease >TaG2 before cystectomy.

Time to cystectomy as a measure of clinical benefit.

Time to cystectomy (TTC) is also used to further characterize CB and CR patients. In CB patients, TTC is "significantly different" in CB from that in the non-CB patients, as it is in CR versus non-CR patients. A larger difference is claimed in CB and non CB patients, in comparison with CR and non CR patients. The sponsor therefore believes that CB should be a better measure of efficacy of AD-32 than CR.

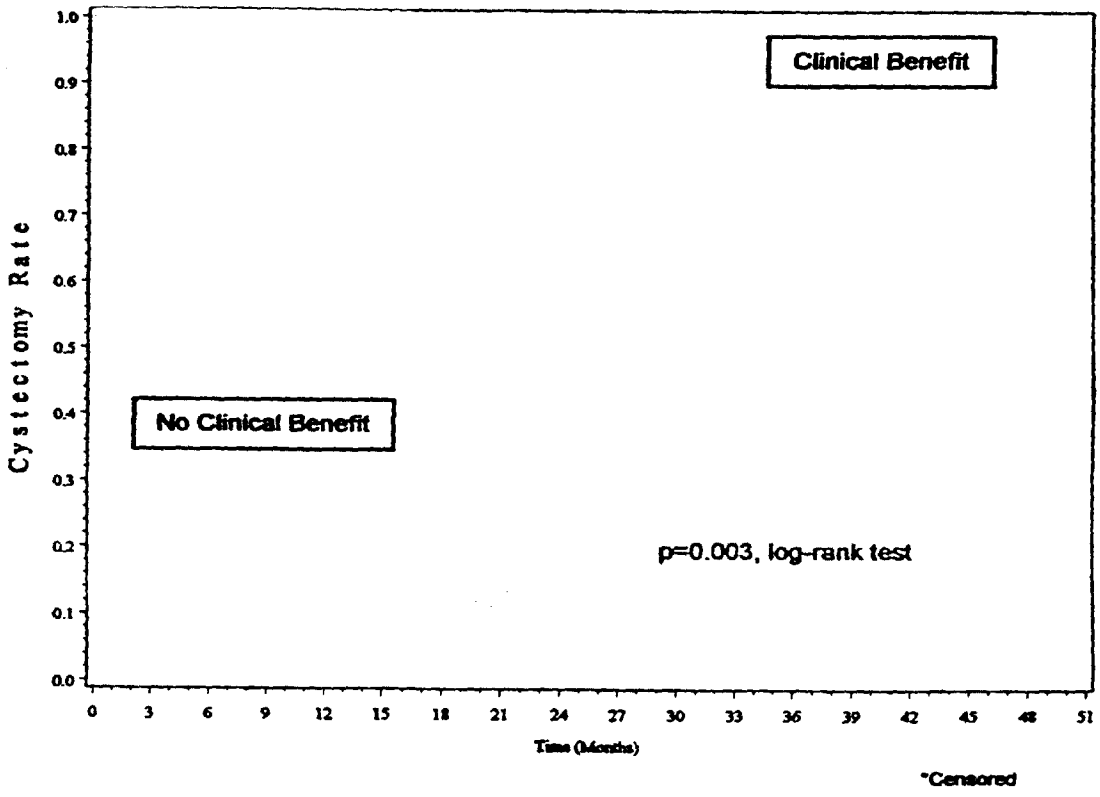
In June,1998, 37 of 90 patients had undergone cystectomy, for a cystectomy rate of 41%. 7 additional patients had undergone cystectomy since June 1st. 1998 (6 radical cystectomy and 1 partial cystectomy). The total cystectomy rate is most recently 44 of 90 patients

(49%) Three of the seven patients were found to have advanced pathologic disease (T3) at cystectomy. One additional patient has died due to advanced bladder cancer.
The figure below represents the sponsor's graphic representation of cystectomy rate over time in CB versus non CB patients. The updated figure for the 44 patients is similar to that for the 37 patients cystectomized by December 31,1997.

On the basis of increased cystectomy rate and increased time to cystectomy for patients with CR, the applicant believes that CB should be a better measure of efficacy of AD-32 than CR.

The data that were used to generate this analysis were included in the Access database submitted to the FDA as part of Minor Amendment 16 (April 29, 1998).

FIGURE 6
Time to Cystectomy for Patients With Clinical Benefit (N=29) and Patients Without Clinical Benefit (N=61)



FDA RESPONSE

The Agency's response is divided into three sections:

1. The sponsor's 10 additional patients who failed with TaGI or TaG2 lesions.

2. The FDA re-analysis of the 19 CR patients claimed by the sponsor, to determine if the Agency's count of responders or duration of response could be readjusted based on this re-classifying Ta G1/G2 relapses.

3. Use of Clinical Benefit (CB) rather than Complete Response (CR) as a clinical evaluation end point.

1) Data on the 10 patients as presented in the Clinical Data Section Vol. 33. Patient Efficacy Profile are shown in the accompanying tables:

The 10 patients are presented in two categories: Definite CR and No-CR

Definite CR 2 Patients: #s

This category of patients are considered complete responders. Both patients show:

- Pathologic documentation of Tis and Ta.
- Positive cytology at baseline with change to negative at 3 mos. post treatment.
- Bladder mapping documenting change from Tis to Ta at same sites is provided.
- Duration of benefit of 8 months and 6 months respectively.

No-CR 8 Patients: #s , and

-2 patients: #s are unevaluable. Review of available pathology reports show no convincing history of CIS. Pt had cystectomy at 2 years post AD-32 due to presumed recurrent CIS. Cystectomy specimen revealed no CIS but Ta G3 disease.

-4 patients: #s had positive cytologies consistently both at baseline and at PDE

-2 patients: #s ; had no follow up biopsies post study and had negative urine cytologies consistently.

2) Agency's re-analysis of its CR status:

A review of the records reveal 3 patients classified by the applicant but not by the FDA as CR (FDA#s 4, 10 and 18) that could be considered for re-analysis of findings based on failure due to TaG1/G2 lesions. The results of these patients are given as presented in the sponsor's summary table of Patient Efficacy Profile. The results of FDA re-analysis of the data are presented in the table below.

FDA PATIENT # (ANTHRA #)	FDA FINDINGS
4	At 18 mos. has positive Urine cytology along with Ta lesion. Subsequent Urine cytology results are not available
10	Failed at 6 months due to positive Urine cytology prior to **Ta G2and Tis** lesions at 7 months
18	Failed at 9 months due to positive Urine cytology prior to **Ta G1-2** lesion at 12 months Urine cytology was not repeated at 12 months.

In none of these patients does a designation of CR seem appropriate.

3) Clinical Benefit as a better determinant of surrogate end point than Complete Response: The sponsor provides data to support the view that CB is a more valid measure of patient benefit in this disease than time to clinical failure (CR). Kaplan Meier analysis of the data for cystectomized versus non cystectomized patients are presented for pre and post ODAC cut off dates, and the results are similar. The curves are similar to that for complete response (CR) and again are considered by the Agency as exploratory.

The conclusion that Kaplan Meier analyses show CB to be a more appropriate measure of end point is questionable. Complete Response of adequate duration remains a useful end point for new drug approval in an appropriate population of patients with CIS in whom cystectomy is required. The efficacy outcome of a trial utilizing such an end point in a single arm-trial should be impressive and unequivocal considering the risk of delaying cystectomy.

The time to cystectomy figure provided along with the updated information on cystctomized versus non-cystectomized patients suggests that there are 6 patients with advanced bladder cancer (T3) and no deaths among the 44 cystectomized patients while there are 4 deaths due to bladder cancer among the 46 non-cystectomized patients.

V SUMMARY

Anthra Pharmaceuticals Inc. has resubmitted a major amendment to its original NDA application for the intravesical use of AD-32 (Valrubicin/Valstar) for the treatment of patients with carcinoma-in-situ of the bladder who are refractory to BCG. The members of the Oncology Drug Advisory Committee (ODAC), at a recent meeting on the application and by a unanimous vote, were unconvinced about the safety and efficacy of AD-32 for the claimed indication. This amendment represents the sponsor's effort to show that there exists a population of patients who are not candidates for cystectomy due to medical contraindication or patient refusal, and that this population represents a suitable group for whom AD-32 is a safe and effective treatment.

The data presented by the applicant however, have failed to show that a special population of patients exists for whom surgery is contraindicated. On the contrary, literature-based evidence, including that supplied by the applicant, encourages early cystectomy in patients who fail intravesical therapy in this disease, regardless of age. With appropriate pre and post operative care the comorbid medical problems that prevail in this elderly population of patients can be ameliorated. Patient refusal to accept cystectomy calls for education of the patient concerning the risks of progressive and metastatic bladder cancer or even death if cystectomy is delayed in patients who have failed multiple intravesical therapy.

The sponsor has demonstrated that patients who responded to valrubicin were disease-free longer on AD-32 than on their previous intravesical therapies. However, given the small number of patients involved (nineteen), and the exploratory , retrospective nature of the analysis, the importance of this finding is less clear.

The applicant has also demonstrated an association between CR status and time to cystectomy. Again, the sample size is small and the conclusions one could draw vis-a -vis the contribution of AD-32 treatment to this finding is questionable.

The population of patients in the study appears homogenous, with similar demographic and baseline data among responding and non-responding patients.

2 more patients can be added to the Complete Response category through a broadening of the criteria to include Ta G1/2 patients.

The data submitted do not support the view that any endpoint other than durable Complete Response is an appropriate measure of clinical benefit in this disease.

FDA analysis can document that valrubicin benefits only a small minority of patients (8%-16 %). More convincing however, are data showing that early cystectomy saves lives and prevents disseminated disease in non-responsive patients or patients who recur following response to drug therapy. Mortality rate due to bladder cancer is zero in 44 cystectomized patients and 10% (four of 46) in uncystectomized patients. These data can be interpreted as

indicating a need for early intervention with radical cystectomy since a large majority of patients (79%-92%) treated with valrubicin are unresponsive to this treatment.

CONCLUSION:

The applicant has not provided specific evidence that a special population of patients exists that would necessitate a change from the original decision to "not approve" the use of Valrubicin in patients with BCG refractory CIS of the bladder. An expansion of clinical criteria to include patients who recur with Ta G1/G2 disease has increased the response rate to 16% with this therapy. The studies conducted and the recent additional analyses failed to establish evidence of sufficient clinical benefit to justify the potential risk of delaying cystectomy and potentially increasing the number of future deaths from bladder cancer in the general population. The number of deaths from metastatic bladder cancer in 46 non cystectomized patients in this study has risen from 1 at the time of NDA submission in December 1997 to 4 at the time of ODAC presentation on June 1st 1998 submission. On the contrary, there have been no bladder cancer related deaths in 44 cystectomized patients.

RESULTS OF THE ODAC MEETING OF SEPTEMBER 1ST, 1998 AND FINAL RECOMMENDATIONS.

The Sponsor and this Reviewer provided information on the following issues which constituted the reason for a second appearance before ODAC on the same application:

- Re-evaluation of Response Rate
- Re-evaluation of Risk involved in delaying cystectomy
- Identification of a population of patients who might be candidates for AD-32 treatment.

The Committee believed that response to Valstar is small (less than 20%), but that it provides a therapeutic alternative for patients who are unable to tolerate cystectomy due to medical contra-indication to the procedure. The efficacy is considered acceptable in this setting. The committee voted for approval in this selected population by a vote of :

9-Yes 2-No 1- Abstention.

The committee however expressed concern about the risk of delaying cystectomy in patients who are able to tolerate the procedure. Approval for use in the general population was therefore not recommended by a vote of :

5-Yes 6-No 1- Abstention.

The committee declined to consider approval of Valstar solely due to patient choice of refusal of cystectomy.

REVIEWER'S COMMENTS AND FINAL RECOMMENDATION.

The applicant provided convincing evidence that patients who responded to the drug demonstrated a longer response on Valstar than on their previous intravesical therapies, suggesting that the drug alters the natural history of the disease in these patients. Time to cystectomy is longer in these patients than in non-responding patients, even though questions remain whether the drug is responsible for this difference.

The division believes that Valstar should be approved for use in patients who cannot tolerate cystectomy due to medical risks of the procedure. The risk : benefit ratio does not support use of this drug in patients who can tolerate the procedure.

/S/

OLUWOLE O. ODUJINRIN M.D. 9/17/98

MEDICAL OFFICER

/S/

MD 9/16/98

GRANT WILLIAMS M.D.

MEDICAL TEAM LEADER

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STATE
JUN 24 1998

NDA MEDICAL OFFICER REVIEW

NDA 20-892

AD-32 (VALRUBICIN)

SPONSOR: Anthra Pharmaceuticals, Inc.

Date Submitted: December 31, 1997

Amendments:	**January**	**21, 1998**
	April	**29, 1998**
	May	**13, 1998**
	May	**19, 1998**
	May	**28, 1998**
	May	**29, 1998**

FDA MEDICAL OFFICER REVIEW
AD-32 (VALRUBICIN)
NDA #20,892

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7.0 APPENDICES

Applicant's Claimed Individual Summary Tables for all 20 Complete Responses.

APPEARS THIS WAY
ON ORIGINAL

1.0 INTRODUCTION

1.1 General Information

1.1.1 NDA#: 20892

1.1.2 Drug Name :

Generic Name AD-32 (N-Trifluoroacetyl adriamycin-14-valerate)
Trade Name Valrubicin

1.1.3 Applicant: Anthra Pharmaceuticals, Inc
103 Carnegie Center Suite 102
Princeton, NJ 08540

1.1.4 Pharmacologic Category: Cytotoxic Antineoplastic

1.1.5 Proposed Indication: "intravesical use in the treatment of patients with biopsy-proven carcinoma in situ of the urinary bladder who are refractory to BCG immunotherapy."

1.1.6 Dosage Form and route of administration : Sterile 40mg/ml solution to be given intravesically

1.1.7 Important Related Drugs: AD-32 is an anthracycline analogue

1.2 BACKGROUND:

Pharmacology

AD-32 is a semisynthetic highly lipophylic analogue of the anthracycline antibiotic doxorubicin, with a chemical formula $C_{34}H_{36}F_3NO_{13}$, and a molecular weight of 724 It is to be supplied as a sterile nonaqueous nonpyrogenic solution only for intravesical instillation in the urinary bladder. It interferes with DNA and RNA synthesis. Its principal de-esterified metabolite inhibits topoisomerase II. It is not cell-cycle specific.

In vivo studies revealed prolongation of survival of mice bearing tumors from P388 lymphocytic leukemia and L1210 leukemia cell lines. In vitro cytotoxicity studies of AD32 against a series of human bladder tumor cell lines obtained from patients with papillary transitional cell carcinoma revealed significant activity. Toxicological studies reveal that AD 32 produced no dermal irritation and only mild ocular irritation in rabbits. It differs from the parent compound both structurally and in its pharmacological and pharmacokinetic properties. Unlike doxorubicin, AD-32 traverses cell membranes rapidly, does not bind to or intercalate with DNA, is metabolized extensively, and is eliminated rapidly.

Pharmacokinetic studies have been conducted in patients with refractory superficial bladder cancer who received 200 to 900 mg doses of AD32 1 to 2 weeks after undergoing transurethral resection. Serum anthracycline levels were measured 6 hours after intravesical instillation. Serum levels of unmetabolized drug and the two major metabolites (N-trifluoroacetyladriamycin and N-trifluoro-acetyladriamycinol) were very low, ranging from undetectable to 19 ng/ml. When a 600 mg dose of AD32 was administered intravesically to 3 patients, the total systemic anthracycline exposure (sum of the approximate median AUCs of parent drug and the two metabolites) was 8.2×10^{-8} moles/L. This amount represents $1/1,000^{th}$ of that seen following intravenous or intraperitoneal administration of myelosuppressive doses. However, as demonstrated in at least one clinical instance of intravesical administration AD32, the potential exists for systemic exposure from AD32 instillation into a bladder which has been unknowingly compromised by perforation.

Information available to date on such studies reveal that elimination of the drug following intravenous administration is primarily through the hepatobiliary system, with 50-60% of both parent drug and metabolite excreted in bile. The metabolites readily form glucuronide conjugates, and enterohepatic recirculation is observed. Only 4%to 10% of parent drug and metabolites are found in urine. The effects of renal or hepatic dysfunction on the disposition of AD32 have not been assessed. AD-32 induces less gastrointestinal toxicity and less alopecia than doxorubicin in these studies. It did not produce local tissue irritation following inadvertent extravasation during administration.

In prior clinical trials, the maximum tolerated dose level (MTD) of AD-32 has been determined to be 800mg/75ml instillate in phase I/II clinical studies involving a total of 250 patients with in situ transitional cell carcinoma of the bladder who received weekly doses ranging from 200 mg to 900mg. This MTD dose was used in subsequent studies in 130 patients who had received prior treatment course(s) with intravesical BCG immunotherapy. Six weekly injections of 800mg AD-32 were instilled. Fifty two of 130 patients (40%) were disease-free 6 weeks after treatment, as determined by negative cystoscopy, cytology, and random bladder biopsies. This dose regimen is the one proposed for use in the NDA.

The indication for AD32 which the Applicant is seeking is for "intravesical use in the treatment of patients with biopsy-proven carcinoma in situ of the urinary bladder who are refractory to BCG immunotherapy."

Superficial Transitional Cell Carcinoma of the Bladder

Superficial transitional cell carcinoma of the bladder (stage T_S,T_1 or T_{IS}) accounts for approximately 80% of the 52,000 new cases of bladder cancer recorded each year in the US (1). Localized treatment with surgical resection of tumor with or without intravesical therapy is the treatment of choice. Agents instilled either as prophylaxis or therapy after

transurethral resection (TUR) include thiotepa, mitomycin C and BCG (2). BCG has emerged as the intravesical agent of choice in patients with superficial transitional cell carcinoma (TCC) who are at high risk for tumor recurrence or stage progression. Several studies have described the benefit of intravesical therapy with BCG in the treatment of CIS ,Ta and T1 tumors (3-6). Complete remission has been reported in approximately 50% of patients with a follow up of 3-5 years, and approximately 30 % with 10 year follow up. Many of these studies have been randomized trials of BCG versus TUR only. From these studies a two-fold reduction (28% vs 14%) in disease progression has beep demonstrated from Lamm's meta analysis of these trials (7). Similar results have been reported by Herr in 86 high risk patients after a 10-year follow up (62% vs.37%) (8). However, the risk of localized recurrences remain high for the majority of patients. The combination of low mortality rate and high recurrence rate leads to a relatively high prevalence of superficial bladder cancer

CIS, however, is the most aggressive form of superficial bladder cancer with a high risk of progression to muscle invasive disease. 54% to 83% of patients develop invasive disease within 4 years in the absence of intravesical therapy (9-10). The use of BCG immunotherapy has effectively delayed cystectomy in many of these patients. In contrast to BCG, intravesical chemotherapy has not achieved the same degree of success either as therapy or prophylaxis of TCC including CIS. The benefit of intravesical therapy in CIS has been modest. The two drugs used most frequently in CIS, doxorubicin and mitomycin C, have yielded complete response (CR) rates that range from 34% to 42% (11). Treatment of CIS patients following relapse on BCG or in patients who are BCG intolerant is even less promising. Other drugs which have been evaluated have included oral immunotherapy or chemoprophylaxis agents such as the interferon inducer, bropirimine (12), oral lactobacillus and high dose vitamins (13).

The evaluation of the results of treatment for CIS is complicated by several factors. There is a high degree of variation in the natural history of patients with superficial bladder cancer. Factors associated with poor prognosis include increasing grade, large lesion (especially >3.0cm), CIS, multifocality, location (especially the dome), p53 status and short time interval between recurrences (14,15). The time to progression to muscle invasion has ranged from 2 to 48 months (median of 39 months), varying with such prognostic factors (16). There are wide variations in reported progression rates even within studies describing patients with similar clinical stage at baseline (17). Cookson suggests that "these discrepancies in progression rates include differences in staging among pathologists, tumor grade, definition of progression, completeness of the transurethral resection, amount and type of adjuvant therapy and length of follow up." Finally, superficial bladder cancer is a pan-urothelial disease often involving the prostatic urethra and other extravesical urinary tract regions. Unrecognized disease in these areas can confound reported results. The most important objective of any local therapy is the prevention or delay of disease progression. Before one could be convinced that a new treatment in this disease had such an effect, one would need to carefully consider these enumerated factors

1.3 Summary of Regulatory History

Superficial bladder cancer has twice been discussed before the Oncology Drugs Advisory Committee, in 1988 a general discussion of the disease and endpoints and in 1996 in relation to the Bropirimine NDA for BCG-refractory CIS.

1988 discussion of CIS approval issues before ODAC

In 1988, George R. Prout, Jr., M.D., an academic urologist, discussed the topic of superficial bladder before the FDA Oncology Drugs Advisory Committee and this was summarized in a document by John Johnson, M.D. of the FDA in 1989. The following are a couple of points from this document which related to the design of trials for treatment of CIS. These points have been uniformly communicated to applicants designing studies in CIS:

- Delay in cystectomy for a meaningful time was suggested as worthwhile benefit. A good complete response rate with complete responses greater than 1 year was considered an adequate basis for approval.

- Persistence of CIS after TUR should be confirmed by positive urine cytology.

Correspondence and meetings with the Applicant

The following are main points made by FDA in an August 24, 1993 letter to Anthra Pharmaceuticals, Inc. regarding protocols submitted for CIS:

1. The population for uncontrolled trials should consist of patients failing 2 courses of BCG. A comparative trial would be required for those failing only a 6-week course.
2. A sufficient rate of CRs lasting more than one year could be the basis for approval.
3. It should be clarified that a positive cytology will be required after TUR of papillary lesions.
4. Follow-up should be every 3 months.
5. The definition of CR should include negative bladder studies at 12 or 15 weeks and again 1-3 months later.

Minutes of meeting with Applicant on January 18, 1996

As documented in the FDA minutes of this meeting, the sponsor asked whether a time to recurrence of 6 months in greater than 20% of patients was clinically meaningful and asked whether this was an acceptable endpoint for pivotal studies. The FDA answer was no, the FDA needed data on CRs lasting 1 year beyond the first response at 3 months. The proportion of responders needed for approval would have to be determined at the time of review by FDA and ODAC. FDA asked for a database of at least 90 patients. The FDA also stated that the company needed to document that each patient with a complete response had DIFFUSE CIS. Attachments to the minutes asked the sponsor to document time since last BCG (since up to 10% of BCG responders are late responders) and to

document the presence of DIFFUSE CIS with either 2 biopsies at baseline or evidence of diffuse disease in the past.

1996 Bropirimine NDA discussion before ODAC

It is important to consider the application which the Agency reviewed for this indication. On September 11, 1996 the Oncology Drugs Advisory Committee reviewed the NDA for Bropirimine for BCG-refractory or BCG-intolerant bladder CIS. As documented in the FDA medical officer review of Bropirimine, in uncontrolled trials involving 104 such patients, the sponsor claimed a complete response rate of 24% with a median duration of 210 days and the FDA found a 9% complete response rate with a median duration of 167 days. FDA discussions prior to NDA submission had suggested that a 50% CR rate with a median duration of 1 year in patients who would require immediate cystectomy if untreated (i.e. patients with refractory diffuse or multifocal disease) would be sufficient for approval. The committee voted unanimously that the findings were not sufficient evidence for efficacy to support an NDA in this indication.

In determining the complete response rate of 9%, the FDA disallowed responses in patients who did not have both a positive biopsy and a positive cytology at baseline (7 patients) or whose positive cytology was done only on the same day as the biopsy (2 patients). In patients with documentation of a positive cytology only on the day of biopsy, it was felt that the perceived response could have been from fulguration alone rather than from intravesical therapy The FDA also disallowed responses in 3 patients with inadequate follow-up only and disallowed 5 responses in patients who had a combination of the above deficiencies. Although the following deficiencies would have violated the letter of the protocol, the FDA did not disallow responses for the following reasons: unifocal CIS (17 patients)*, <6 biopsies (10 patients), voided cytology (10 patients), or last BCG 3-4 months prior to Bropirimine (7 patients).

***Reviewer comment:** For the FDA analysis of Bropirimine, although the finding of only unifocal disease did not disallow response, all patients were required to have positive cytology after biopsy. The AD32 protocols were amended to allow patients to be entered with negative urine cytologies at baseline.

The committee was also asked the following questions (paraphrased):

Patients with diffuse (multifocal) bladder CIS that is refractory to BCG or patients intolerant of BCG are generally considered to be candidates for immediate cystectomy, since they have a high risk of developing invasive and metastatic bladder cancer. In this setting a treatment producing durable complete remissions in a substantial proportion of patients could provide meaningful clinical benefit by delaying the morbidity of cystectomy; provided that the toxicities of treatment were acceptable and they were not placed at an unreasonable risk of metastatic bladder cancer while cystectomy was delayed. Non-

randomized clinical trials could be adequate to support approval under such circumstances. Does the committee agree?

The committee agreed by acclamation.

The committee then proceeded to answer a series of questions that made it clear that an uncontrolled trial would be an acceptable design for this disease only in patients who were candidates for immediate cystectomy. Further, it was noted that most of the patients in the Bropirimine trials had unifocal disease, and that the prognosis for unifocal disease was better than that for multifocal disease. The committee did not specify the CR rate and duration needed, but in discussion, Dr Ragahvan the Urologic Oncologist on the committee, suggested that a 25% CR rate would be acceptable if with longer follow-up, there is no increase in number of patients with metastatic disease.

Summary and conclusions from background review

Multifocality of disease is an important finding supporting the claim that patients entering a study have no reasonable option other than cystectomy; hence in such patients, a durable CR is tantamount to delaying cystectomy and is evidence of clinical benefit even in an uncontrolled trial. On 3/1/95, the Applicant amended the protocol to include patients without positive baseline cytology; there was no formal discussion with the Agency on the advisability of this amendment. One might consider looking separately at the group with negative baseline cytologies for several reasons: first, since mapping the bladder with biopsies is an inexact process, the exact site of initial disease might be missed on rebiopsy but might still be detected on follow-up cytology if baseline cytology had been positive; second, the absence of a positive cytology at baseline might indicate a lesser extent of disease; and third, it should be noted that lack of baseline positive cytology was a reason for disallowing complete responses in the FDA medical officer analysis of the Bropirimine NDA.

2.0 PIVOTAL CLINICAL STUDIES (A 9301 and A 9302)

PROTOCOL TITLE: Intravesical AD-32 in Patients with Carcinoma in situ (CIS) of the Bladder Who Have Failed or Have Recurrence Following Treatment With BCG

2.1 STUDY OBJECTIVES

1) To assess the efficacy of intravesical instillations of AD-32 in patients with carcinoma-in-situ (CIS) who had previously been treated with intravesical BCG for CIS and in whom recurrence or failure had occurred after multiple courses of intravesical treatment.
2) To evaluate the qualitative and quantitative toxicities associated with intravesical therapy.
3) To determine the concentration of anthracyclines in the voided urine of patients who chose to participate in a urine recovery study.