Study Number: EN3329-A9301/A9302	
Title of Study: Intravesical AD 32 in Patients With Carcinoma In Situ of the Bladder Who Have Failed or Have Recurrence Following Treatment With BCG	
Investigators and Study Center(s): This study was conducted by 44 investigators at 41 study sites. The protocol chairmen were Dr. Robert Bahnson, University of Pittsburgh, Pittsburgh, PA and Dr. Stanley Brosman, Santa Monica Urologic Group, Santa Monica, CA.	
Publication (reference): None	
Study Period (years): 18-Nov-1993 to 30-Apr-1997	**Phase of Development**: II/III
Objectives: To assess the efficacy and safety of intravesical instillations of AD 32 in patients with carcinoma in situ (CIS) who had previously been treated with intravesical bacillus Calmette-Guérin (BCG) for CIS and in whom recurrence or failure had occurred after multiple courses of intravesical treatment; to determine the concentration of anthracyclines in the voided urine.	
Methodology: This was an open-label, noncomparative study. Each patient was to receive six weekly intravesical administrations of 800 mg of AD 32. At their discretion, patients could participate in a urine recovery study, in which anthracycline concentrations were determined in urine samples obtained during the 24-hour period following dose administration. The primary disease evaluation (PDE) occurred approximately 6 weeks after the last instillation of AD 32 (approximately 3 months after the start of treatment). Subsequent evaluations for disease response occurred at 3-month intervals until the patient had a recurrence. Information about disease status was obtained approximately every 6 months for patients who did not respond to treatment or who had recurrences.	
Number of Patients (planned and analyzed): 90 patients (planned and analyzed).	
Diagnosis and Main Criteria for Inclusion: Patients were required to have pathologically proven CIS with no evidence of muscle-invasive disease and must have received at least two prior courses of intravesical therapy for CIS. One of the prior therapies must have been BCG. Patients could have either failed BCG therapy or had a recurrence after responding to BCG.	
Test Product, Dose and Mode of Administration, Batch Number(s): AD 32 (Lot Numbers 515-44-0001, 515-44-0002, and 515-44-0003) was supplied in 5 mL vials containing 40 mg/mL AD 32 in NCI Diluent 12. For each 800 mg dose, four vials were further diluted with 55 mL sterile saline to a total instillate volume of 75 mL. The AD 32 solution was instilled by gravity flow via a catheter, and the patients were asked to retain the instillate for 2 hours.	
Duration of Treatment: Two patients (2%) did not complete treatment because of death (pneumonitis) and local bladder symptoms, respectively. One patient (1%) was considered to have completed treatment after receiving five doses; he had experienced severe bladder symptoms after the fifth dose and the investigator decided to omit the last dose and proceed with the PDE. Seventy-eight patients (87%) received the scheduled six weekly doses. Nine patients (10%) received seven or eight doses; in all cases, the patients had been unable to retain one or more of the scheduled doses for more than a few minutes, so extra doses were administered.	
Reference Therapy, Dose and Mode of Administration, Batch Number(s): None	
Criteria for Evaluation: Patients underwent cystoscopy with biopsy and/or cytology examinations at each post-treatment evaluation until disease recurrence was documented. Patients were considered to have a complete response to treatment if they had no evidence of disease, either CIS or papillary disease, at the PDE and at the next subsequent visit. (Patients whose only evidence of disease at any evaluation was a positive urine cytology were considered to have achieved a complete response if they were without evidence of disease at the next evaluation.) Safety was assessed by monitoring the occurrence of adverse	

events and by evaluating changes in bladder symptoms, clinical laboratory tests, ECGs, and physical examinations. The risk of salvage therapy with AD 32 was assessed by comparing the clinical stage at documented failure or recurrence with the clinical stage at baseline, and by determining the pathologic stage in patients who had cystectomies.

Statistical Methods: Because this was an open-label study of a single dose level, the statistics were mainly descriptive, ie, means, medians, and distributions. Life-table analyses of time to recurrence and time to cystectomy were performed. Efficacy and safety data were summarized for all patients and for subgroups of the patients based on baseline characteristics such as number of prior BCG courses, number of prior intravesical courses, time since last treatment, and presence of local bladder symptoms at study entry.

SUMMARY:

The 90 patients who participated in this trial had a mean age at baseline of 68 years. A majority of the patients were males (88%), white (98%), and either current or past smokers (80%). The mean duration of bladder cancer at the time of study entry was 5 years (range, 1-27 years). Most of the patients (89%) had undergone two to four prior courses of intravesical therapy for transitional cell carcinoma; 10% of the patients had undergone five or more prior courses. BCG was administered during at least one of those prior courses in all patients; 70% of the patients had received more than one prior course of BCG. A majority of the patients (60%) had undergone one to four prior resections because of bladder cancer; and 6% had undergone more than ten prior resections.

Efficacy: Thirty-seven (37) patients had no pathologic evidence of bladder cancer, either CIS or papillary disease, at the PDE. Twenty (20) of these patients were considered to have a complete response to therapy, ie, they had no evidence of disease at both the PDE and the next subsequent visit. Thus, the rate of complete response was 22% based on all patients in the study and 23% based on the patients who completed the PDE and met important entry criteria. Using a life-table analysis, the likelihood of being disease-free was 25% at 6 months after the start of treatment, 20% at 9 months, and 17% at 12 months. One year after the PDE, the probability of being disease-free was 13%. As of the cutoff date for this report, 9 patients continued to have no evidence of disease, with a mean follow-up time of 22 months.

A second life-table analysis revealed that the likelihood of a patient having a cystectomy was approximately 15% at 6 months after AD 32 treatment, 34% at 12 months, and 42% at 2 years.

Safety: Prior to receiving AD 32, 45 patients (50%) had adverse events that qualified as local bladder symptoms. Local bladder symptoms were also the most commonly reported adverse events during the study, occurring in 81 patients (90%) between the administration of the first dose and the PDE and in 51 patients (57%) between the PDE and disease recurrence. Frequency, urgency, and dysuria were the most common specific symptoms. These occurred in 66%, 63%, and 60% of the patients, respectively, during treatment and in 37%, 23%, and 16% of the patients, respectively, during on-study follow-up. The number of prior BCG courses or prior intravesical courses of any kind had little effect on the occurrence of local bladder symptoms. In contrast, the presence of such symptoms at baseline increased the patient's risk of experiencing them during treatment and during on-study follow-up.

The most commonly reported adverse events that did not qualify as local bladder symptoms were urinary tract infection (18%), asthenia (7%), urinary retention (6%), and urine abnormality (6%) during treatment and urinary tract infection (8%), pain (3%), and nausea (3%) during on-study follow-up. Seven (7) patients had serious adverse events and seven patients died between 25 days and 1.5 years after receiving AD 32. None of the deaths or serious adverse events were related to AD 32. Intravesical administration of AD 32 had no effect on laboratory tests, EGGs, or physical examinations.

Thirty-four (34) patients who did not respond to AD 32 or who had recurrences underwent cystectomy between 4 months and 2 years after the initiation of therapy. There was little risk that attempting salvage treatment with AD 32 had increased the likelihood that the patients' disease would progress, as shown in the table below.

Clinical Stage at Baseline Versus Pathologic Stage at Cystectomy - 34 Patients With Cystectomies

		Pathologic Stage at Cystectomy								
		pT0	pT_a	pT_{is}	pT_1	pT_1/pT_{is}	pT_2	pT_{3b}	pT_{3b}/pT_{is}	NAV
Clinical Stage at Baseline	T_a/T_{is}	0	0	4	0	1	0	0	0	0
	T_{is}	4	1	13	2	1	2	0	1[a]	2
	T_1/T_{is}	0	0	0	0	1	1	1	0	0

NAV = not available.
[a] Patient had Stage pT_{3b} squamous cell disease and CIS.

Urine Recovery: Urine recovery of anthracyclines was determined in six patients (enrolled in this study or in Protocol A9303) after the administration of 14 doses of AD 32. The mean total amount of anthracyclines recovered within 24 hours was 792 mg, or 99% of the administered dose. Most of the dose (789 mg) was recovered as unmetabolized AD 32.