PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	L0.5	PD	VISCERAL PROGRESSION	
	L0.5	PD	VISCERAL PROGRESSION	
	L2.5	PD	BONY, VISCERAL PROGRESSION; PT DIED ON DAY REMOVED	
	MA	NE	DEATH; ADVERESE EVENT DUE TO STDY DRUG	PTE FATAL AFTER 4 DAYS; STUDY DRUG RELATED
	L2.5	PD	VISCERAL PROGRESSION (10/27/93) BY PER REVIEW; ON	
	MA	NE	OFF STUDY DUE TO AR; NO F/U; AES - HYPERCALCEMIA	UNCONTROLLED DIABETES
	L2.5	PD	BONY PROGRESSION	
	MA	NE	NO F/U AFTER 1ST VISIT; ADVERSE RX.-PTE	NONFATAL PTE ASSOCIATED WITH STUDY DRUG
	L0.5	SD	SOFT TISSUE PROGRESSION PER PI; NO MEASUR.S FOR RE	ASSIGNED PROGRESSION
	MA	PD	PROGRESSION ON PELVIC XRAY ON 5/17/95 -PEER REVIEW	
	L2.5	PD	SOFT TISSUE, VISCERAL PROGRESSION	
	L2.5	PD	MEASURABLE VISCERAL PROG. (7/7/94)	
	L0.5	PD	EVAL. VISCERAL PROG. 7/7/94	
	MA	NE	PT. REFUSED TREATMENT; NO F/U AFTER 5/11/94	
	L0.5	SD	PT. WITHDREW INFORMED CONSENT WITH SD DISEASE; LAS	
	MA	PD	OFF STUDY DUE TO AE (DYSPNEA, EFFUSIONS)	LYMPHANGITIC SPREAD ON 6/17/94
	L0.5	PD	MEASURABLE SOFT TISSUE PROG. 11/14/94	
	MA	PD	PROG. SOFT TISSUE (10/5/93)	
	L0.5	PD	PROG. SOFT TISSUE, BONE, VISCERA -10/6/94	
	MA	SD	BONY PROG. (ONLY SITE OF DISEASE) 4/4/95; CONTINUE	
	MA	PD	BONY PROG. (10/28/94); OFF-STUDY - 5/30/95	
	L0.5	PD	VISCERAL PROGRESSION	
	L2.5	SD	VISCERAL PROG. (11/23/94)	
	MA	NE	RADIOTHERAPY TO ONLY EVAL. SITE; NEW BONY LESION-1	
	L0.5	SD	PR IN SOFT TISSUE; VISCERAL PROG. (11/29/94)	
	MA	PR	SOFT TISSUE PROG. 1/19/95	
	L2.5	SD	BONE PROG. (2/7/95) ON BONE SCAN PER PI; NOT PEER	ASSIGNED PROGRESSION
	L0.5	PD	PROG. IN LUNG (6/22/94)	
	L2.5	PD	PROG. IN BONE (6/22/94);	
	L2.5	PD	PROG. HEPATIC METS.	
	MA	PR	BONY PROGRESSION ON 10/4/95	
	L0.5	NE	PT. WITHDREW CONSENT 7/15/94	
	MA	PD	NEW PLEURAL EFFUSION (11/26/94)	
	L0.5	NE	UNCLEAR IF PT. TOOK MEDS UNTIL 6/21/93; OFF-STUDY	
	L0.5	NE	DEATH ON STUDY DUE TO DISEASE	
	MA	PD	BONY PROG. (8/31/94); NO F/U AFTER 1/30/95	
	L2.5	PD	MEDIASTINAL PROG. (10/10/94); NO F/U AFTER 1/6/95	
	L2.5	PD	BONY PROG. (8/6/93)	
	L0.5	NE	OFF-STUDY DUE TO AE; DEATH-NOT CANCER RELATED	
	MA	CR	CR DATE: 12/27/93; VISCERAL & ST RESPONSE; CR ON S	
	MA	PD	PT. CONTINUED ON MEDICATION DESPITE 400% INCREASE	
	L2.5	SD	VISCERAL PROGRESSION BY PER PEER REVIEW	
	MA	PD	PROG. LIVER METS	
	MA	PD	PROG.SOFT TISSUE	

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	L0.5	SD	BONY PROGRESSION (11/18/94) NOT CONFIRMED BY PEER	
	L2.5	PD	CONTINUED ON RX UNTIL 9/21/94	
	MA	SD	NEW BONY LESIONS NOT CONFIRMED ON PEER REVIEW; NEW	ASSIGNED PROGRESSION
	L2.5	PD	PROG. BONY METS.	
	L0.5	NE	PT. NON-COMPLIANT; OFF-STUDY-2.1/94	
	MA	PR	BONY PROGRESSION	
	MA	PD	VISCERAL PROG.	
	L0.5	NE	OFF-STUDY DUE TO ADMINISTRATIVE PROBLEMS ? TYPE; D	
	L2.5	NE	NO ASSESSMENTS; OFF-STUDY-DID NOT MEET ELIGIBILITY	
	MA	PD	VISCERAL PROGRESSION	
	MA	PD	PROG. SOFT TISSUE, BONE	
	L0.5	PD	PROG. SOFT TISSUE, BONE	
	L2.5	CR	BONY PROGRESSION 8/22/95	
	MA	PD	BONY PROGRESSION;	
	L0.5	SD	SD ON STUDY	
	L2.5	PD	PROG. VISCERAL DISEASE	
	MA	PD	BONY PROG.	
	MA	PD	VISCERAL PROGRESSION	
	L0 5	NE	NON-COMPLIANT; OFF- STUDY 11/15/94	
	L0.5	PD	VISCERAL PROG.	
	L2.5	PD	INC. PLEURAL EFFUSION	
	L2.5	PD	VISCERAL PROGRESSION	
	MA	SD	INC. SOFT TISSUE DISEASE	
	MA	SD	INC. VISCERAL DISEASE	
	L0.5	PD	INC. VISCERAL DISEASE	
	L2.5	CR	ON STUDY IN CR; CR DATE -7/20/94	
	L0.5	CR	CR ON STUDY	
	L2.5	SD	SOFT TISSUE PROG.	
	L0.5	SD	ON STUDY W/ STABLE DISEASE	
	MA	SD	LL STABLE AS OF 4/14/95; CANDA PROG-10/9/95	
	MA	SD	SOFT TISSUE PROG.	
	L2.5	PD	BONY PROGRESSION	
	MA	SD	NEW VISCERAL METS.	
	L2.5	PD	PROG. VISCERAL DISEASE	
	L0.5	SD	METS IN PELVIC BONE ON 11/10/94; WORSE 1/26/95	
	MA	PD	VISCERAL PROGRESSION	
	L0.5	PD	PROG. LUNG NODULES	
	L2.5	PR	ON STUDY WITH PR	
	L0.5	PD	BONY , SOFT TISSUE PROG.	
	MA	PD	BONY PROGRESSION	
	L2.5	NE	ON RX; SOFT TISSUE CR;NO F/U BONY DZ.	NO BONE ASSESSMENTS SINCE ENROLLMENT
	L0.5	PD	SOFT TIS. & VISCERAL PROG.	
	MA	PD	VISCERAL PROGRESSION	
	L2.5	PD	VISCERAL PROG.	

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	MA	NE	SOFT TIS. STABLE ; NO F/U ON BONE; LAST FU 5/2/95	OFF STUDY DUE TO AE: SUPER.FICIAL DVT ; DRUG RELAT
	L0.5	PR	BONY PROGRESSION	
	L2.5	PD	SOFT TISSUE PROG.	
	L2.5	NE	VISCERAL PROG ; DIED 170 DAYS S/P DOS	
	L2.5	PD	SOFT TISSUE PROG.	
	MA	SD	PEER REV. BONY DZ STABLE	
	MA	PD	BONY PROGRESSION	
	L2.5	PD	BONY PROGRESSION	
	L0.5	PR	BONY PROGRESSION ON PEER REVIEW (8/18/95)	PR (5/4/95) NOT CONFIRMED;OFF-STUDY 10/18/95
	L0.5	PD	BONY, VISCERAL PROG.	
	L0.5	PD	VISCERAL PROG.	
	L2.5	PD	BONY PROG.	
	L0.5	PD	SOFT TISSUE PROG.	
	MA	PD	SOFT TISSUE PROGRESSION	
	MA	PD	RT. LUNG PROG, P. REV -8/31/94; OFF-RX 2/24/95	
	L2.5	PR	PR ON STUDY	
	L2.5	PR	OFF-STUDY 11/13/93 DUE TO AE (RECTAL CONCER)	DIED 11/19/95
	L0.5	PR	BONY PROG. BY P.REV. IN 1/95; OFF-;STUDY IN 5/95	
	L0.5	PD	BONY PROG.	
	L2.5	PR	PR ON STUDY	
	MA	PD	BONY, VISCERAL PROG.	
	MA	SD	VISCERAL PROG.	
	L2.5	NE	CONSIDERED PR BUT NO ASS. OF BONY DZ ON 7/11/95	
	L0.5	SD	NEW BONY LESIONS	
	L0.5	PD	BONY, VISCERAL PROG.	
	MA	CR	CR ON STUDY	
	MA	SD	SOFT TISSUE PROGRESSION	
	L2.5	PR	BONY PROGRESSION	
	MA	PD	SOFT TISSUE, BONY PROG.	
	L2.5	SD	SD ON STUDY	
	L0.5	PD	BONY, VISCERAL PROG IN 10/94; OFF-STUDY IN 4/95	
	L0.5	PR	PR ON STUDY	
	MA	NE	NO F/U OF BONY DZ.;OFF STUDY FOR AE-ABNORMAL LFTS	DRUG RELATED
	L0.5	PD	VISCERAL PROG.	
	L0.5	PD	SOFT TISSUE, VISCERAL PROG.	
	L2.5	PD	VISCERAL PROG.	
	MA	SD	PR NOT CONFIRMED ; NEW ST MASS NEXT VISIT	
	L2.5	SD	BONY. SOFT TISSUE PROG.	
	MA	SD	BONY. SOFT TISSUE PROG.	
	L0.5	SD	VISCERAL PROG.; PR (1/18/95) NOT CONFIRMED	
	L0.5	SD	SD (BONY DISEASE ONLY) ON STUDY	
	MA	PR	SOFT TISSUE PROG.	
	MA	PD	VISCERAL PROG.	
	L2.5	PR	CR ON STUDY	

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	L2.5	PR	PR ON STUDY	
	MA	SD	SOFT TISSUE PROG (12/21/93)	ON STUDY UNTIL 2/4/94
	L2.5	PR	PR ON STUDY	
	L0.5	PD	SOFT TISSUE PROG.	
	MA	PD	SOFT TISSUE, VISCERAL PROG.	
	L0.5	NE	NO SITE OF METASTATIC DISEASE	
	L2.5	CR	CR ON STUDY	
	L2.5	NE	PEER REVIEW DIDNOT CONFIRM LUNG PROG;	NO BONY ASSESSMENT
	MA	PR	DEATH ON STUDY NOT RELATED TO DISEASE	? ACUTE MI
	L0.5	PD	BONY. VISCERAL PROG.	
	L0.5	NE	PER REVIEW DID NOT CONFIRM METS	
	L2.5	CR	BONY PROGRESSION	
	MA	CR	SOFT TISSUE, VISCERAL METS	
	L0.5	PD	BONY PROG.; NO F/U ON STATUS AFTER 6/30/95	
	MA	SD	BONY PROG.; ON STUDY UNTIL 8/17/95	
	L0.5	CR	CR ON STUDY	
	L2.5	SD	SOFT TISSUE PROG.	
	MA	PR	OFF STUDY DUE TO AE (TROMBOPHLEBITIS,	POORLY CONTROLLED DM RELATED TO STUDY DRUG
	L2.5	NE	DEATH ON STUDY NOT DUE TO DISEASE	RESPIRATORY FAILURE
	L0.5	PD	BONY, VISCERAL METS	
	L2.5	SD	NEW BONY DISEASE	
	MA	PD	SOFT TISSUE PROG.	
	MA	PD	NEW SOFT TISSUE DISEASE	
	L0.5	PD	SOFT TISSUE PROG.	
	L2.5	PD	VISCERAL PROG.	
	L2.5	PD	VISCERAL PROG.	
	MA	PD	VISCERAL PROG.	
	MA	SD	SOFT TISSUE PROGRESSION	
	L0.5	PD	SOFT TISSUE PROG.	
	L2.5	CR	CR ON STUDY	
	L0.5	PR	PR ON STUDY	
	MA	SD	PROGRESSIVE BONY DZ (8/30/95); OFF STUDY 12/19/95	
	L2.5	CR	SOFT TISSUE CR- ON STUDY	
	MA	PD	BONY PROGRESSION	
	L2.5	PD	VISCERAL PROG.	
	L2.5	SD	NO EVIDENCE OF PROGRESSION	REMOVED FROM STUDY BY PI FOR "PD"
	MA	NE	PT. WITHDREW INFORMED CONSENT 4-5-94	NO REASON FOR STUDY REMOVAL
	MA	SD	BONY PROGRESSION	
	L0.5	PD	SOFT TISSUE PROGRESSION	
	L0.5	SD	SD ON STUDY	
	MA	SD	SOFT TISSUE, BONY PROGRESSION	
	L0.5	PD	VISCERAL PROGRESSION	
	L2.5	PR	PR ON STUDY	NO BONY ASSESSMENT IN 6/95
	MA	NE	DEATH ON STUDY; NOT DRUG RELATED	? INTESTINAL PERFORATION; ? DISEASE PROGRESSION

APPENDIX (FINAL) (173-4)

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	L2.5	SD	OFF-STUDY DUE TO AE (DYSPNEA , RESP. FAILURE	PERICARDITIS)
	L0.5	SD	SOFT TISSUE, VISCERAL PROGRESSION	
	L2.5	SD	SOFT TISSUE PROGRESSION	
	MA	SD	SD ON STUDY	
	L0.5	PD	VISCERAL PROGRESSION	
	L2.5	PR	SOFT TISSUE PROGRESSION	
	MA	PD	SOFT TISSUE PROGRESSION	
	MA	PR	SOFT TISSUE PROGRESSION	
	MA	PD	SOFT TISSUE, BONY PROGRESSION	
	L2.5	PD	SOFT TISSUE, BONY PROG.	
	L0.5	PD	SOFT TISSUE PROGRESSION	
	MA	PR	NEW SOFT TISSUE DISEASE	
	L0.5	NE	NO F/U ASSESSMENT	PT DID NOT MEET STUDY CRITERIA
	MA	PD	NEW VISCERAL LESIONS	
	L0.5	CR	CR ON STUDY	
	L2.5	PD	BONY PROGRESSION	
	L2.5	SD	VISCERAL PROGRESSION	
	L0.5	SD	PT WITHDREW CONSENT	
	L0.5	PD	SOFT TISSUE PROGRESSION	
	L2.5	PD	BONY, VISCERAL PROGRESSION	OFF-STUDY 8/31/94
	MA	NE	SOFT TISSUE ASSMT ONLY (NO BON, VIS); "pd"-PI	DEATH DUE TO SURGICAL COMPLICATION ; OFF-STUDY A
	L0.5	SD	REMOVED FROM STUDY FOR NON-COMPLIANCE	
	MA	PD	BONY PROGRESSION	LAST SEEN ALIVE 9/7/95; CURRENT STATUS UNKNOWN
	L0.5	NE	BONY DISEASE NEVER ASSESSED	ON STUDY W/O ADEQUATE ASSESSMENT
	L2.5	NE	OFF-STUDY DUE TO AE (HYPERTENSION, HYPERCALCEMIA)	
	L0.5	NE	NO PROGRESSION; NO VISCERAL ASSESSMENT(10/11/94)	NO F/U SINCE 10/11/94; NO OFF STUDY REASON
	MA	PD	BONY, VISCERAL PROGRESSION	
	L2.5	PD	BONY PROGRESSION	
	MA	PD	BONY PROGRESSION	
	L0.5	SD	SOFT TISSUE, VISCERAL PROGRESSION	
	L2.5	PD	BONY PROGRESSION	
	L0.5	PD	BONY PROGRESSION	
	L2.5	NE	DEATH ON STUDY DUE TO DISEASE PROGRESSION	
	L0.5	SD	VISCERAL PROG. (7/31/95); BONY PROG. (11/6/95)-PI	NO IMAGES FOR PEER REVIEW ; ASSIGN PD
	MA	SD	VISCERAL PROG.	
	MA	PD	VISCERAL PROGRESSION	
	L0.5	PR	PR ON STUDY	
	L0.5	SD	BONY PROGRESSION	
	L2.5	PD	VISCERAL PROG.	
	MA	NE	NO TUMOR MEASUREMENTS ON ENTRY OR F/U	
	MA	NE	OFF-STUDY DUE TO AE (HYPERTENSION, UNCONTROLLED)	STUDY DRUG RELATED
	L2.5	SD	BONY PROGRESSION (PELVIS)	
	L0.5	SD	BONY PROGRESSION;	
	L0.5	NE	OFF-STUDY DUE TO AE (NAUSEA, VOMITING)	DRUG RELATED

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	L2.5	PR	PR ON STUDY; NO BONE ASSESS. SINCE 4/13/95	
	MA	SD	VISCERAL PROGRESSION	STATUS UNKNOWN SINCE 4/24/95
	L2.5	PD	SOFT TISSUE PROGRESSION	STATUS UNKNOWN SINCE 4/24/95
	MA	SD	SOFT TISSUE, BONY, VISCERAL PROGRESSION	
	MA	CR	SOFT TISSUE, BONY PROGRESSION	
	L2.5	PD	SOFT TISSUE, VISCERAL PROGRESSION	
	L0.5	PD	SOFT TISSUE PROGRESSION	
	MA	PD	SOFT TISSUE , BONY PROGRESSION	
	L0.5	PD	RAPID VISCERAL DISEASE PROGRESSION; DEATH ON STUDY	AE (THRMBOCYTOPENIA) DISEASE RELATED
	L2.5	PD	SOFT TISSUE PROG. DOCUMENTED BY INVESTIGATOR	
	L0.5	SD	RAPID PROGRESSIOM; DEATH 4 DAYS OFF-STUDY	
	MA	PD	SOFT TISSUE , BONY, VISCERAL PROGRESSION	
	L0.5	PD	SOFT TISSUE PROGRESSION	
	L2.5	PD	SOFT TISSUE PROGRESSION	
	MA	PR	SOFT TISSUE PROGRESSION (12/9/94);	CR (10/20/94) NOT CONFIRMED
	L0.5	PD	SOFT TISSUE, VISCERAL PROG.; OFF-STUDY -9/13/95	
	L2.5	PD	SOFT TISSUE, BONY, AND VISCERAL PROGRESSION	
	L2.5	CR	CR ON STUDY	
	MA	PD	BONY PROG. ON 11/1/94	OFF-STUDY 1/10/95
	L0.5	SD	SOFT TISSUE PROG.	PR (11/25/94) NOT CONFIRMED
	MA	CR	CR ON STUDY	
	L2.5	PR	PR ON STUDY	
	L0.5	PD	SOFT TISSUE, VISCERAL PROGRESSION	
	MA	SD	BONY PROG.RESSION (1/17/95)	REMAINED ON STUDY UNTIL 6/2/95
	L2.5	PR	BONY PROGRESSION	
	MA	SD	DEATH ON STUDY REPORTEDLY DUE TO PROGRESSION	
	L2.5	PD	SOFT TISSUE PROGRESSION	
	MA	PD	BONY PROGRESSION	
	L0 5	PD	BONY PROGRESSION	
	L0.5	PR	PD REPORTED BY PI; NOT CONFIRMED ON PEER REVIEW	OFF-STUDY WITH PR
	MA	PD	VISCERAL PROGRESSION	
	L2.5	PD	SOFT TISSUE PROGRESSION	
	L0.5	SD	SOFT TISSUE, BONY, VISCERAL PROGRESSION	
	L2.5	SD	SD ON STUDY	
	MA	PR	PR ON STUDY	
	L0.5	PD	PROGRESSIVE SOFT TISSUE DISEASE	
	L2.5	CR	CR ON STUDY	
	MA	SD	PROGRESSIVE SOFT TISSUE DISEASE	
	L2.5	PD	PROGRESSIVE SOFT TISSUE DISEASE	
	L0.5	PD	SOFT TISSUE PROGRESSION (8/23/94);	OFF-STUDY (9/20/94)
	MA	PD	PROGRESSIVE SOFT TISSUE, VISCERAL DISEASE	
	L2.5	PR	PR ON STUDY	
	MA	PD	SOFT TISSUE PROGRESSION	
	L0.5	PD	PROGRESSIVE VISCERAL DISEASE	

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	L0.5	SD	NEW BONY DISEASE	OFF-STUDY 5/11/95
	L0.5	PD	BONY, SOFT TISSUE PROGRESSION	
	L0.5	PD	SOFT TISSUE PROGRESSON	
	L2.5	SD	SOFT TISSUE PROGRESSION	
	L2.5	SD	SOFT TISSUE PROGRESSION	
	MA	PD	SOFT TISSUE, VISCERAL PROGRESSION	
	MA	PD	VISCERAL PROGRESSION	
	L0.5	PR	BONY PROGRESSION	
	L0.5	NE	OFF STUDY DUE TO AE (CUTANEOUS DRUG ERUPTION)	PATIENT WITHDREW CONSENT
	L0.5	PD	SOFT TISSUE PROGRESSION	
	MA	SD	SOFT TISSUE PROGRESSION	
	L2.5	PD	BONY PROGRESSION	
	L2.5	PD	SOFT TISSUE, BONY, VISCERAL PROGRESSION	
	MA	PD	SOFT TISSUE PROGRESSION	
	MA	PD	BONY, VISCERAL PROGRESSION PER PI; "NONCOMPLIANT"	VISCERAL STUDIES NOT ASSESS ED (pr); ASSIGNED PD
	L0.5	SD	SOFT TISSUE PROGRESSION	
	L0.5	SD	DEATH ON STUDY	? ACUTE MI
	L0.5	PD	BONY PROGESSION 10/6/93; ON STUDY UNTIL 4/13/94	LAST F/U 4/29/94
	L0.5	PD	BONY, VISCERAL PROGRESSION	LAST F/U 5/5/94
	MA	PD	BONY, VISCERAL PROGRESSION	
	L2.5	PR	PR ON STUDY	
	MA	NE	PT. DID NOT MEET ELIGIBILITY REQUIREMENTS	
	L2.5	SD	SOFT TISSUE PROGRESSION	
	MA	PD	SOFT TISSUE PROGRESSION	
	L2.5	PD	VISCERAL PROGRESSON	
	L0.5	PD	BONY, VISCERAL PROGRESSION	
	MA	PD	OFF STUDY DUE TO AE (AXILLARY V. THROMBOSIS)	PROGRESSION - 6/14/94 (DISEASE RELATED AE)
	L0.5	SD	TF= SOF TTISSUE PROG. NOT CONFIRMED BY MEASUREMNT	
	L2.5	PR	PR ON STUDY	
	L0.5	SD	PT WITHDREW CONSENT	
	MA	PD	SOFT TISSUE PROGRESSION	
	L0.5	SD	NEW ADRENAL MASS (12/14/93); NO S.T. PROGRESSION	ON STUDY UNTIL 5/24/95
	L2.5	PD	BONY, VISCERAL PROGRESSON	
	L2.5	SD	VISCERAL PROGRESSION	ON STUDY UNTIL 6/13/95
	MA	PD	OFF STUDY DUE TO AE (CARDIAC FAILURE, AF)	SOFT TISSUE PROGRESSION NOTED
	L2.5	PD	BONY, VISCERAL PROGRESSION	
	MA	SD	BONY PROGRESSION (5/10/94) PER PI NOT CONFIRMED	TREATMENT FAILURE
	L0.5	SD	OFF STUDY DUE TO AE (NAUSEA,EDEMA,CHEST PAIN)	DIED FROM DZ W/IN 2 WKS STUDY REMOVAL
	MA	PD	SOFT TISSUE, VISCERAL PROGRESSION	
	L2.5	PD	SOFT TISSUE, BONY PROGRESSION	
	L2.5	PD	NEW VISCERAL DISEASE (12/15/93); OFF STUDY-1/4/94	
	L2.5	PR	BONY PROGRESSION ON 9/20/95;	BONE NOT ASSESSED AT TIME OF PR
	L0.5	PD	SOFT TISSUE PROGRESSION	
	L0.5	SD	NO F/U AFTER 5/16/95; OFF STUDY DRUG (7/4/95)	ASSIGNED TF DATE OF 7/4/95)

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	MA	PR	PR ON STUDY	
	MA	SD	SOFT TISSUE PROGRESSION (8/21/95)	
	L2.5	PD	SOFT TISSUE PROGRESSION	
	L0.5	SD	SOFT TISSUE, BONY PROGRESSION	
	MA	PD	PROGRESSIVE BONY DISEASE (4/20/94);	ONSTUDY UNTIL 11/9/94
	MA	PD	PROGRESSIVE BONY DISEASE	
	L0.5	PR	BONY, VISCERAL PROGRESSION	
	L2.5	NE	PT DID NOT MEET STUDY CRITERIA	
	MA	PD	PROGRESSIVE SOFT TISSUE DISEASE	
	L2.5	SD	VISCERAL PROGRESSION PER PI NOT CONFIRMED ON PEER	CHEST WALL MASS NOT ASSESSED
	L0.5	CR	VISCERAL PROGRESSION (11/9/94); OFF STUDY -1/12/95	
	MA	PD	BONY PROGRESSION	
	L0.5	PR	BONY, SOFT TISSUE PROGRESSION	
	L2.5	PR	BONY PROGRESSION PER INVESTIGATOR (7/6/94);	BONY PROGRESSION PER PEER REVIEW (8/24/94)
	L2.5	PR	PR ONSTUDY	
	L0.5	PD	BONY, VISCERAL PROGRESSION NOTED 4/13/94	ONSTUDY UNTIL 6/15/94
	MA	PR	SOFT TISSUE PROGRESSION	
	L2.5	PR	SOFT TISUE PROGRESSION	
	L0.5	SD	SOFT TISSUE PROGRESSION 2/15/95	PR (11/16/94) NOT CONFIRMED
	MA	PR	PR ON STUDY	
	MA	PD	SOFT TISSUE PROGRESSION	
	L2.5	PD	DEATH ON STUDY DUE TO DISEASE	
	L0.5	SD	VISCERAL PROGRESSION	
	L0.5	SD	BONY, SOFT TISSUE PROGRESSION	
	L2.5	CR	CR ON STUDY	
	L0.5	SD	25% INCREASE IN SOFT TISSUE MASS ON 4/19/94;	ON STUDY UNTIL 10/18/94
	L0.5	NE	PT DID NOT MEET PROTOCOL ENTRY CRITERIA	
	L2.5	PD	SOFT TISSUE, VISCERAL PROGRESSION	
	MA	SD	SOFT TISSUE, VISCERAL PROGRESSION	
	MA	SD	DEATH ON STUDY W/O EVIDENCE OF PROGRESSION	DEATH DUE TO MI
	L0.5	SD	SOFT TISSUE PROGRESSION	
	MA	SD	BONY PROGRESSION	
	L2.5	PD	BONY,VISCERAL PROGRESSION	
	L0.5	SD	PR (5/23/94) NOT CONFIRMED	SOFT TISSUE PROGRESSION ON 8/15/94
	MA	PD	VISCERAL PROGRESSION (6/6/94);	CONTINUED ON STUDY UNTIL 9/5/94
	L2.5	PD	VISCERAL PROGRESSION	
	MA	CR	CR ON STUDY	
	L2.5	CR	CR ON STUDY	
	L2.5	SD	SOFT TISSUE PROGRESSION	
	MA	SD	BONY PROGRESSION ON PEER REVEIW (3/13/95);	ONSTUDY UNTIL 6/12/95
	L0.5	SD	NO EVIDENCE OF PROGRESSION AT STUDY REMOVAL	
	L0.5	SD	OFF STUDY DUE TO AE (CONFUSION, LT.SIDED NUMBNESS,	?TIA, DIABETES) ;UNLIKELY RELATED TO DRUG
	L2.5	PR	PR ON STUDY	
	MA	PD	OFF STUDY DUE TO AE (DVT)	BONY PROGRESSION NOTED

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	MA	SD	PROGRESSIVE SOFT TISSUE DISEASE (11/29/94);	PR (9/6/94) NOT CONFIRMED
	L0.5	PR	PR ON STUDY	
	L2.5	PD	PROGRESSIVE VISCERAL DISEASE	
	L0.5	PD	PROGRESSIVE SOFT TISSUE DISEASE	
	MA	SD	PROGRESSIVE SOFT TISSUE, VISCERAL DISEASE	
	MA	PD	SOFT TISSUE PROGRESSION	
	L0.5	PD	SOFT TISSUE PROGRESSION	
	L2.5	PR	PR ON STUDY	
	MA	SD	BONY PROGRESSION	
	L2.5	PD	BONY PROGRESSION	
	L2.5	PD	BONY PROGRESSION	
	L0.5	PD	BONY PROGRESSION	
	MA	PR	SOFT TISSUE PROGRESSION	
	MA	SD	SOFT TISSUE PROGRESSION	ON STUDY UNTIL 9/19/95
	L0.5	PD	VISCERAL PROGRESSON (11/1/94)	ON STUDY UNTIL 1/3/95)
	L2.5	SD	SOFT TISSUE PROGRESSION	
	MA	SD	PR (11/18/94) NOT CONFIRMED	BONY , SOFT TISSUE PROGRESSION (2/2/3/95)
	L2.5	SD	NO ASSESSMENTS ON11/9/94	SOFT TISSUE PROGRESSION ON 9/16/94
	L0.5	PR	OFF STUDY DUE TO AE ON DAY 456 9/23/95) IN PR	HAS F/U VIST ON 11/6/95 ?
	L2.5	SD	SD ON STUDY	
	MA	PD	SOFT TISSUE PROGRESSION	
	L0.5	PR	PR ON STUDY	
	MA	PD	OFF STUDY DUE TO AE (STROKE)	CAUSE OF DEATH NOT DISEASE RELATED
	L2.5	PD	BONY PROGRESSION	
	L0.5	PR	CR (5/9/95) ON STUDY	
	MA	PD	PROGRESSIVE BONY DISEASE	
	L0.5	SD	SD ONSTUDY	
	L2.5	SD	PROGRESSIVE BONY DISEASE	ON STUDY MED UNTIL DEATH
	L0.5	NE	PT DID NOT MEET ELIGIBILITY CRITERIA	
	MA	SD	SOFT TISSUE PROGRESSION (5/5/95);	PR (1/4/95)NOT CONFIRMED
	L0.5	PR	PR ON STUDY	
	L2.5	PR	PR ON STUDY	
	MA	PD	SOFT TISSUE PROGRESSION	
	MA	PD	SOFT TISSUE, VISCERAL PROGRESSON	
	L0.5	PD	VISCERAL PROGRESSION	
	L2.5	NE	NO BONE ASSESSMENTS UNTIL 3/30/95	BONY PROGRESSION AT ASSESSMENT
	L2.5	PD	SOFT TISSUE PROGRESSION	
	L0.5	PD	BONY, VISCERAL PROGRESSION	
	MA	PD	BONY PROGRESSION	
	L2.5	SD	SOFT TISSUE, BONY PROGRESSION (3/2/94)	OFF-STUDY 6/8/94
	MA	PR	SOFT TISSUE PROGRESSION (8/25/94)	
	L2.5	PD	SOFT TISSUE,VISCERAL PROGRESSION	
	L0.5	SD	SOFT TISSUE PROGRESSION	
	L0.5	PD	SOFT TISSUE PROGRESSION	

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	MA	SD	NO EIVDENCE OF PROGRESSION (11/10/94)	PD PER PI NOT CONFIRMED ON PEER REVIEW
	L2.5	SD	CR (2/3/94) NOT CONFIRMED	SOFT TISSUE PROGRESSION (55/94)
	L0.5	SD	PR (8/15/94) NOT CONFIRMED; ST PROGRES (12/19/94)	OFF STUDY - 2/22/95
	MA	PR	SOFT TISSUE PROGRESSION	
	L2.5	PR	SOFT TISSUE PROGRESSION	
	MA	SD	SOFT TISSUE PROGRESSION	
	L0.5	PD	SOFT TISSUE PROGRESSION 6/24/94	OFF-STUDY 8/23/94
	L2.5	PR	SOFT TISSUE PROGRESSION	
	L2.5	PD	SOFT TISSUE PROGRESSION	
	MA	NE	PT DID NOT MEET ELIGIBILITY CRITERIA	
	L0.5	SD	SD; NO ASSESSMENTS ON 4/12/94	OFF STUDY DUE TO AE; ? RELATIONSHIP TO DEATH
	MA	PR	PR ON STUDY (3/28/95)	
	L2.5	PR	VISCERAL PROGRESSION	
	L0.5	NE	NO ASSESSMENTS ON STUDY	OFF-STUDY -9/8/94
	L2.5	PR	PR ON STUDY	
	L0.5	PD	SOFT TISSUE PROGRESSION	
	MA	PD	BONY PROGRESSION	
	L2.5	SD	SD ON STUDY	
	L0.5	PR	VISCERAL PROGRESSION	
	MA	PR	SOFT TISUE, VISCERAL PROGRESSION	
	L0.5	PD	PROGRESSIVE BONY,VISCERAL DISEASE	
	MA	PD	BONY DISEASE	
	MA	SD	SD ON STUDY	
	L2.5	SD	SD ON STUDY	
	L0.5	PD	VISCERAL PROGRESSION	
	MA	PD	SOFT TISSUE PROGRESSION	
	L0.5	NE	NO ASSESSMENTS AFTER ENROLLMENT	
	L2.5	PD	BONY PROGRESSION REPORTED 9/29/93	ON STUDY UNTIL 12/14/93
	L0.5	SD	SOFT TISSUE , VISCERAL PROGRESSION	
	L0.5	PD	BONY, VISCERAL PROGRESSION 12/21/93	OFF STUDY 1/12/94
	L2.5	PD	BONY PROGRESSION	
	MA	PD	VISCERAL PROGRESSION	
	MA	PD	SOFT TISSUE, BONY PROGRESSION	
	L0.5	PD	BONY PROGRESSION (1/10/95)	OFF-STUDY 2/15/95; NO FURTHER F/U
	L0.5	PD	SOFT TISSUE, BONY PROGRESSION	
	L2.5	CR	CR ON STUDY	
	MA	PD	BONY, VISCERAL PROGRESSION	
	L0.5	SD	SOFT TISSUE (CHEST WALL) PROGRESSION	
	L2.5	SD	VISCERAL PROGRESSION	
	L2.5	PD	BONY PROGRESSION	
	L0.5	PD	SOF TTISSUE, VISCERAL PROGRESSION	
	L2.5	SD	NO T-SPINE, SKULL XRAY ON ENTRY -HOT SPOTS ON SCAN	ASSIGNED NE
	L2.5	NE	VISCERAL PROGRESSION (9/24/93); OFF-STUDY 12/10/93	
	MA	PR	SOFT TISSUE PROGRESSION	

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	L0.5	SD	BONY PROGRESSION	
	MA	SD	SD ON STUDY	
	L0.5	SD	PR (11/9/94) NOT CONFIRMED	
	L2.5	NE	BONY DISEASE NEVER ASSESSED; LAST VISIT 8/25/94	CONSIDER TREATMENT FAILURE AT LAST VISIT
	L0.5	NE	LACK OF XRAYS FOR INVOLVED SITES	
	L2.5	PD	PROGRESSIVE DISEASE	
	MA	PD	PROGRESSIVE SOFT TISSUE DISEASE	
	L0.5	NE	OFF STUDY DUE TO AE	
	L0.5	PD	VISCERAL PROGRESSION ON STUDY	
	L0.5	SD	SD ON STUDY AS OF 11/27/95	
	L2.5	PD	SOFT TISSUE PROGRESSION	
	MA	SD	SOFT TISSUE PROG. (.50% INCREASE) ON 6/13/94	ASSIGNED PROGRESSION
	L0.5	SD	PROGRESSIVE SOFT TISSUE DISEASE	
	L2.5	NE	DID NOT MEET ELIGIBILITY CRITERIA; NO F/U	ASSIGNED TF
	MA	NE	CNS METS DXED 11/1/93; NO PRE-STUDY CNS EVALUATION	
	MA	PD	PATHOLOGIC FX. OF LT ILIUM-PI; PAGET'S DISEAE (PR)	ASIGNED PROGRESSION
	L2.5	NE	NO EVIDENCE BONY DISEASE (PR); NO OTHER SITES DZ	
	L0.5	SD	PR (1/16/95) NOT CONFIRMED;	SOFT TISSUE PROGRESSION (3/31/95)
	L0.5	PR	BONY PROGRESSION (PI) -11/9/94; NOT CONFIRMED (PR)	ASSIGN TF
	L2.5	SD	DEATH ON STUDY DUE TO AE (CARDIAC FAILURE,	THROMBOCYTOPENIA) NOT DRUG RELATED
	MA	CR	VISCERAL PROGRESSION (12/16/94);	OFF-STUDY -3/22/95
	L0 5	PD	BONY PROGRESSION	
	L2.5	NE	HEPATIC ULTRASOUNDS NOT EVALUABLE;	OFF STUDY DUE TO ADMINISTRATIVE PROBLEM
	MA	PD	BONY PROGRESSION 4/11/94	ON STUDY UNTIL 8/1/94
	MA	PR	PR ON STUDY	
	L2.5	PR	SOFT TISSUE PROGRESSION 6/21/95	
	L0.5	PR	PR ON STUDY 4/5/95	
	MA	SD	SOFT TISS PROG. PER PI (9/15/94); NOT CONFIRMED	ASSIGNED TF
	L2.5	PD	PROGRESSIVE SOFT TISSUE DISEASE (10/10/94)	NO F/U AFTER 10/10/94
	L0.5	NE	DEATH ON STUDY	NO VISIT BET. STUDY INITIATION AND DEATH
	L2.5	PD	SOFT TISSUE, BONY , VISCERAL DISEASE	
	L0.5	NE	BRAIN MET DXED ON 9/30/94	NE DUE TO CNS DZ AT ENTRY
	MA	NE	DEATH ON STUDY NOT DUE TO CANCER	SUDDEN DEATH ? CAUSE
	MA	PD	BONY PROGRESSION	
	MA	PD	BONY PROGRESSION	
	L0.5	SD	PR (6/30/94) NOT CONFIRMED	SOFT TISSUE PROGRESSION 9/29/94
	L0.5	SD	PR (11/26/93) NOT CONFIRMED; BONY PROGRESS 2/18/94	
	MA	SD	INCREASE IN LUNG LESION < 25% = SD	REMOVED BY INVESTIGATOR FOR PD = TREATMENT FAIL
	MA	PD	BONY, VISCERAL PROGRESSION	
	L2.5	PD	BONY, VISCERAL PROGRESSION	
	L0.5	PD	BONY, VISCERAL PROGRESSION	
	MA	SD	BONY PROGRESSION (PI) NOT CONFIRMED PEER REVI EW	
	L2.5	PD	SOFT TISSUE PROGRESSION	
	L0.5	PD	SOFT TISSUE, BONY DISEASE	

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	MA	SD	VISCERAL PROGRESSION 3/21/94; OFF-STUDY 5/9/94	
	L2.5	SD	VISCERAL PROGRESSION	
	L0.5	PD	BONY PROGRESSION	
	MA	PR	VISCERAL PROGRESSION	
	L0.5	SD	BONY PROGRES.(7/14/94) NOT CONFIRMED PEER REVIEW	
	L2.5	PD	SOFT TISSUE, VISCERAL PROGRESSION	
	MA	PD	SOFT TISSUE, VISCERAL PROGRESSION	
	L0.5	SD	SOFT TISSUE, BONY PROGRESSION	
	L0.5	SD	PR (8/30/94) NOT CONFIRMED; OFF-STUDY-3/2/95	BONY PROGRESSION BY PEER REVIEW (11/29/94)
	MA	PD	SOFT TISSUE, VISCERAL PROGRESSION	
	L2.5	PD	BONY PROGRESSION (1/23/95) OFF-STUDY-3/2/95	
	L0.5	PD	VISCERAL PROGRESION	ON STUDY UNTIL 3/2/95
	L0.5	SD	SOFT TISSUE PROGRESSION	
	MA	PD	SOFT TISSUE PROGRESSION	
	MA	SD	SOFT TISSUE PROGRESSION	
	L0.5	SD	SD ON STUDY	
	L2.5	NE	NO TUMOR ASSESSMENTS DURING STUDY	
	L0.5	PD	BONY PROGRESSION (6/30/94); OFF-STUDY 3/8/95	
	MA	SD	VISCERAL DZ STABLE; ON PEER REV. NO BONY DZ=SD	OFF STUDY DUE TO AE - NEW LYMPHOMA
	L2.5	PD	SOFT TISSUE, BONY PROGRESSION	
	L0.5	PD	BONY, VISCERAL PROGRESSION	
	L2.5	PR	SOFT TISSUE PROGRESSION	
	MA	PD	SOFT TISSUE, BONY, VISCERAL PROGRESSION	
	MA	PD	VISCERAL PROGRESSION	
	L2.5	SD	SD ON STUDY	
	L2.5	NE	OFF STUDY FOR AE (PATH. FX . LT. HIP),	NO BASELINE BONE SCAN; DZ PROGRESSION PER P.I.
	L2.5	SD	VISCERAL PROGRESSION	
	L0.5	NE	NO BASELINE BONE SCAN; OFF-STUDY - 11/17/94	
	L2 5	PD	SOFT TISSUE PROGRESSION	
	L0 5	NE	NE ONSTUDY; NO BASELINE BONE SCAN	
	L0.5	PD	SOFT TISSUE, BONY, VISCERAL PROGRESSION	
	MA	SD	SOFT TISSUE, BONY, VISCERAL PROGRESSION	
	L2.5	PD	VISCERAL PROGRESSION -9/29/94; OFF-STUDY 11/2/94	
	MA	CR	CR ON STUDY	
	L2.5	PD	VISCERAL PROGRESSION	
	L0.5	PD	SOFT TISSUE PROGRESSION	
	MA	SD	BONY INVOLVEMENT CONFIRMED BY SECOND PEER REVIEW	
	L2.5	PD	SOFT TISSUE, BONY, VISCERAL PORGRESSION	
	L0.5	PD	SOFT TISSUE, VISCERAL PROGRESSION	
	MA	SD	BONY PROGRESSION 12/21/94; NO FURTHER BONE ASSESS.	ON STUDY UNTIL 8/22/95
	L0.5	SD	VISCERAL PROGRESSION	
	L2.5	PD	VISCERAL PROGRESSION	DEATH ON STUDY DAY 122
	L0.5	PD	BONY PROGRESSION	
	L2.5	SD	VISCERAL PROGRESSION PER PI; NOT CONFIRMED - PEER	REVIEW

PATNO	TDRSDOS	RESPONSE	COMMENTS	ADDITIONAL COMMENTS
	MA	PR	BONY PROGRESSION NOT CONFIRMED ON PEER REVIEW	
	L0.5	PD	VISCERAL PROGRESSION	
	L2.5	PD	VISCERAL PROGRESSION (7/5/94)	OFF STUDY-9/19/94
	MA	NE	DEATH ON STUDY (FELL OUT OF WHEEL CHAIR);	NO ASSESSMENTS
	L0.5	SD	VISCERAL, SOFT TISSUE PROGRESSION	
	MA	NE	OFF STUDY DUE TO AE (FLUID RETENSION)	STUDY DRUG RELATED
	L2.5	PD	PI REPORTS BONY, VISCERAL PROGRESSION;	NO STUDIES AVAILABLE TO REVIEW; ASSIGN PROGRESSI
	MA	PD	BONY PROGRESSION	
	L2.5	SD	PR (8/29/94) NOT CONFIIRMED;	BONY PROGRESSION-12/12/94
	MA	SD	PR (1/2/95) NOT CONFIRMED;	BONY PROGRESSION-4/3/95
	L0.5	PD	BONY PROGRESSION (6/8/94)	OFF-STUDY ON 9/14/94
	L2.5	PR	PR ON STUDY	
	L0.5	PD	VISCERAL PROGRESSION PER PI	IMAGES NOT REVIEWED BY PEER REVIEW
	MA	PD	BONY PROGRESSION -8/5/94	OFF-STUDY 11/30/94
	L2.5	PD	SOFT TISSUE.BONY PROGRESSION	ON STUDY UNTIL 9/19/94
	MA	NE	OF STUDY DUE TO AE (DIZZINESS)-POSS. DRUG RELATED	NO SITES OF INVOLVEMENT AT STUDY ENTRY
	L2.5	NE	NO SITES OF INVOLVEMENT ON STUDY ENTRY	REMAINS ON STUDY
	L0.5	NE	OFF-STUDY DUE TO AE W/O ASSESSMENT	(SEPSIS, PNEUMONIA, GALL STONES)
	L0.5	NE	OFF STUDY DUE TO NON-COMPLIANCE	
	MA	PR	OFF STUDY IN PR DUE TO AE NOT DRUG RELATED	ISCHEMIC CEREBRAL INFARCTION WITH AF
	MA	PD	SOFT TISSUE, VISCERAL, PROGRESSION -11/29 /94	OFF-STUDY-1/27/95
	L0.5	SD	BONY PROGRESSION	ON STUDY UNTIL 12/5/95
	L2.5	PD	VISCERAL PROGRESSION	
	L0.5	PD	SOFT TISSSUE PROGRESSION	

PTNO	TDR	RES	TF DATE	DEATH	TYPE OF AE	COMMENTS	RELATIONS
	MA	NE	7/28/94		OFF STUDY DUE TO AE	EDEMA DUE TO FLUID RETENTION	YES
	MA	NE	12/24/93		OFF STUDY DUE TO AE	ELEVATED LFTS	YES
	MA	SD			OFF-STUDY DUE TO AE (DYSPNEA) WITH ? PTE	ALSO HAD DISEASE PROGRESSION	YES
	MA	NE	6/29/93		OFF-STUDY DUE TO AE	ARTERIAL HYPERTENSION	YES
	MA	NE	7/1/94		OFF-STUDY DUE TO AE (PTE)	DEATH DUE TC PTE	YES
	MA	NE	2/9/94		OFF-STUDY DUE TO AE (SUPERFICIAL DVT)	DVT W/IN 9 DAYS OF INITIATION OF TREATMENT	YES
	MA	PD			OFFSTUDY DUE TO AE (DYSPNEA, PLUERAL EFFUSIONS)	DISEASE PROGRESSION -LYMPHANGITIIC LUNG	UNLIKELY
	MA	PD			OFF STUDY WITH AE DUE TO PROGRESSION	HYPERCALCEMIA	UNLIKELY
	MA	PD	6/14/94		OFF STUDY DUE TO AXILLARY VEIN THROMBOSIS	DISEASE PROGRESSION NOTED	UNLIKELY
	MA	PR	8/28/94		OFF-STUDY DUE TO AE (THROMBOPHLEBITIS)	DIABETES MELLITUS, POORLY CONTROLLED	UNLIKELY
	MA	PR			OFF-STUDY DUE TO AE (PHLEBOTHROMBOSIS OF RT LEG)	PROGESSION OF DISEASE ALSO FOUND	POSSIBLE
	MA	NE	7/26/94		OF STUDY DUE TO AE; DIZZINESS	NO MEASURABLE DISEASE AT STUDY ENTRY	POSSIBLE
	MA	NE	5/15/93		OFF-STUDY DUE TO AE (HYPERCALCEMIA)	DIABETES POORLY CONTROLLED	POSSIBLE
	MA	SD			OFF-STUDY DUE TO AE (UTERINE CARCINOMA)	HAD PROGRESSION ALSO	POSSIBLE
	MA	PD			OFF-STUDY DUE TO AE (DVT)	HAD BONY PROGRESSION AT OFF-STUDY	POSSIBLE
	MA	SD	8/19/95		OFF-STUDY DUETO AE (LYMPHOMA)	STUDY DRUG DISCONTINUED & CHEMO GIVE FOR LYMPHOM	NO
	MA	NE	2/26/95	YES	OFF-STUDY DUE TO AE ASSOCIATED WITH DISEASE	PATHOLOIGC FX LT. HIP (2/26/950	NO
	MA	PR	7/5/95		OFF STUDY IN PR DUE TO AE (ATRIAL FIB AND	SEIZUERE DUE TO ISCHEMIC INFARCTION)	NO
	MA	PD			OFF-STUDY DUE TO AE ASSOCIATED WITH PROGRESSION	MENTAL CONFUSION	NO
	MA	NE	11/21/94	YES	DEATH ON STUDY OF UNCLEAR ETIOLOGY	NO EVIDENC E OF PROGRESSION	NO
	MA	SD	4/4/94	YES	DEATH ON STUDY DUE TO MI	NO EVIDENCE OF PROGRESSION	NO
	MA	PD			OFF STUDY DUE TO CHF; ATRIAL FIB	HAD DISEASE PROGRESSION AT TIME OF AE	NO
	MA	PD		YES	DEATH ON STUDY DUE TO STROKE	HAD DISEASE PROGRESSION AT TIME OF AE	NO
	MA	SD	3/1/95	YES	DEATH ON STUDY DUE TO ? PROGRESSION	? PROGRESSION	NO
	MA	NE	5/24/94	YES	DEATH ON STUDY ? INTESTINAL PERFORATION	? PROGRESSIVE DISEASE	NO
	MA	PR	4/28/94	YES	SUDDEN DEATH ON STUDY	? ACUTE MI	NO
	L2.5	PD			OFF-STUDY WITH AE AND PROGRESSION	NAUSEA, VOMTING, SUPERFICIAL DVT (5/94)	YES
	L2.5	PD			OFF-STUDY WITH AE AND SOFT TISSUE PROGRESSION	NAUSEA & VOMITING, GRADE 4	YES
	L2.5	PD			OFF-STUDY DUE TO PROGRESSION	THROMBOCYTOPENIA, CHF	UNLIKELY
	L2.5	NE	10/25/94		OFF-STUDY DUE TO AE (HYPERTENSION, HYPERCALCEMIA)	PROGRESSION OF DISEASE ?	POSSIBLE
	L2.5	NE			PT WITHDREW CONSENT DUE TO INCREASED PAIN	INCREASED BONY PAIN, ELEVATED LFTS	POSSIBLE
	L2.5	NE	10/3/94		OFF-STUDY DUE TO AE (NO BASELINE BONE SCAN)	AE: PATHOLOGIAL FX OF LEFT HIP	NO
	L2.5	PD			OFF-STUDY WITH AE DUE TO TUMOR PROGRESSION	DYSPHAGIA DUE TO TUMOR PROGRESSION	NO
	L2.5	PR	11/13/93		OFF STUDY DUE TO AE (RECTAL CANCER)	DIED FIVE DAYS LATER	NO
	L2.5	SD	8/20/94		OFF-STUDY DUE TO AE -PERICARDITIS, RESP. FAILURE	DYSPNEA	NO
	L2.5	SD	5/8/95	YES	DEATH ON STUDY DUE TO CARDIAC FAILURE	HAD THROMBOCYTOPENIA	NO
	L2.5	NE	2/3/94	YES	DEATH ON STUDY DUE TO AE (RESPIRATORY FAILURE)	BRONCHOPLEURAL CUTANEOUS FISTULA	NO
	L0 5	NA	4/30/94		OFF-STUDY DUE TO AE	NAUSEA & VOMITING, SEVERE	YES
	L0.5	NA	5/9/94		OFF STUDY DUE TO AE	NAUSEA & VOMITING, GRADE 3	YES
	L0.5	SD			OFF-STUDY DUE TO AE;	FIXED CUTANEOUS DRUG ERUPTION	YES
	L0.5	SD	7/28/94		OFF STUDY DUE TO ADVERSE REACTION	UNCONTROLLED DIABETES, ? TIA	UNLIKELY
	L0 5	PR	9/22/95		OFF STUDY DUE TO AE ON DAY 456 (9/23/95);	NAUSEA, VOMITING, AM HEADACHES ,	UNLIKELY
	L0.5	PD			OFF STUDY DUE TO AE WITH BONY PROGRESSION	CONFUSION DUE TO HYPERCALCEMIA	UNLIKELY
	L0 5	SD	5/3/94		OFFSTUDY DUE TO ADVERSE REACTION; DEATH W/IN 2 WK	NAUSEA,, EDEMA, CHEST PAIN	POSSIBLE

PTNO	TDR	RES	TF DATE	DEATH	TYPE OF AE	COMMENTS	RELATIONS
	L0.5	PR	9/22/95		OFF STUDY DUE TO AE-HEADACHES,NAUSEA, VOMTING,	NO EVIDENCE OF PROGRESSION	POSSIBLE
	L0.5	NE	8/26/94		OFF-STUDY DUE TO AE W/O ASSESSMENT	PNUEMONIA, GALL STONES, SEPSIS	NO
	L0.5	NE	7/25/93		OFFSTUDY DUE TO AE; DEATH NOT CONCER RELATED	GI BLEED WITH PAIN; SOMNOLENCE	NO
	_0.5	SD	1/21/94		OFF STUDY WITH AE (INCREASED ASCITES - PD)	HYPONATREMIA ON ALDACTONE	NO

STUDY REPORT: AR/BC 3

Title: Open, randomized, multicenter, phase II Trial comparing once daily doses of 0.5 mg and 2.5 mg CGS 20 267 with twice daily 250 mg aminoglutethimide plus daily 30 mg hydrocortisone or 37.5 mg cortisone acetate as second-line endocrine therapy in postmenopausal patients with advanced breast cancer

DESCRIPTION OF THE STUDY:

Introduction:

AR/BC3 is an open, randomized multicenter phase II trial which compared the efficacy of letrozole 0.5 mg, letrozole 2.5 mg, and aminoglutethimide (with adrenocorticoid replacement) in postmenopausal women with advanced breast cancer which is of unknown receptor or of positive (ER and/or PR) receptor status and which had previously been treated with antiestrogen therapy. The study which enrolled five hundred fifty seven women commenced on September 16, 1993 and was completed on May 31, 1996. Appendix I summarizes the protocol and the four amendments to the original protocol. No major changes in the conduct of the study resulted from the protocol amendments.

Trial Objectives:

Primary objective of this trial was to assess the antitumor efficacy as evaluated by objective response rate and duration of response, time to treatment failure (TTF), and time to progression (TTP) in three treatment arms and, if more than one hundred deaths were reported, to evaluate survival in the three treatment arms. Secondary objectives included: (1) determination of the effects of daily doses of 0.5 mg letrozole, 2.5 mg CGS letrozole, and twice daily 250 mg aminoglutethimide plus HC or CA on plasma estrogen levels (E1, E1S, and E2) and (2) assessment of the trough plasma drug concentration level during treatment with daily doses of 0.5 mg letrozole and 2.5 mg letrozole.

Trial Design / Conduct:

This trial was an open, randomized, comparative trial conducted in eighty-six centers in eleven countries in postmenopausal women with receptor positive or receptor unknown breast cancer which had progressed on antiestrogen therapy. The cancer had to have progressed after the patient had received at least six months of adjuvant antiestrogen therapy and was currently on therapy, within twelve months of the patient's discontinuation from adjuvant antiestrogen therapy, or while the patient was being treated with antiestrogen therapy for advanced disease. Patients were randomized using a fixed block design (number per block not stated in the protocol) per country from a central randomization center at Ciba-Geigy, Basle to one of the following treatments: letrozole 0.5 mg PO, letrozole 2.5 mg PO, or aminoglutethimide 250 mg BID PO with daily adrenocortical supplementation using either hydrocortisone 20 mg q AM and

10 mg q PM or cortisone acetate 25 mg q AM and 12.5 mg q PM. Patients were continued on treatment until evidence of progression, death, occurrence of an adverse event or some other event lead to withdrawal for study. Patients were assessed prior to trial entry, at two weeks, four weeks, and eight weeks for tolerability, and then every three months for efficacy and tolerability until study removal. Study completion occurred when the last patient enrolled was followed for nine months. Patients removed from study were followed every three months for survival. Table AR/BC3- R1 lists the countries involved in this study, the number of patients enrolled by country, and the response rate per arm by country.

Table AR/BC3- R1: Enrollment by Country with Response Rate

			Response Rate (CR and PR) No. Response / No. Pts. per Arm (%)		
Country	No. of Sites	No. Enrolled	Letrozole 0.5 mg (N = 34)	Letrozole 2.5 mg (N = 34)	AG (N = 22)
Argentina	18	178	5/55 (9.0)	6/51 (11.8)	5/52 (9.6)
Australia	16	77	2/27 (7.4)	5/25 (20.0)	5/25 (20.0)
Austria	3	12	1/3 (33.0)	0/5 (00.0)	0/4 (00.0)
France	12	102	8/37 (21.6)	7/34 (20.6)	4/31 (12.9)
Germany	5	11	0/5 (00.0)	0/5 (00.0)	1/5 (00.0)
Hungary	2	11	1/4 (00.0)	0/2 (00.0)	0/5 (00.0)
Ireland	1	3	0/1 (00.0)	0/1 (00.0)	0/1 (00.0)
Israel	8	46	6/15 (40.0)	4/15 (26.7)	3/16 (18.8)
Italy	13	58	4/19 (21.0)	6/20 (30.0)	2/19 (10.5)
New Zealand	4	26	3/9 (33.3)	1/9 (11.1)	0/8 (00.0)
Russia	4	53	4/18 (22.2)	5/17 (29.4)	3/18 (16.7)

The majority of patients who participated in this trial were from Argentina, France, Australia, Italy and Russia. Randomization to treatment arms is evenly distributed except in France where fewer patients were enrolled on the AG arm as compared to the two letrozole arms and in Hungary where fewer patients were enrolled on the letrozole 2.5 mg arm.

STUDY RESULTS:

Study Population Demographics

The study population appeared to be well balanced with regard to baseline characteristics as illustrated in the Table ARBC3-R2 which is based on information in the study report. No statistical tests of homogeneity were applied to these parameters by Ciba-Geigy since "randomization would result in equal distribution of these characteristics between treatment

group". The Chi Square Test for Homogeneity was applied to the baseline characteristics by the agency and no statistically significant differences were observed.

Table AR/BC3-R2: Demographic Characteristics at Baseline

Parameter	Letrozole 0.5 (N = 192)	Letrozole 2.5 (N = 185)	Aminoglutethimide (N = 178)	Chi Square Test for Homogeneity, P-value, two-sided
Median Age (Range) in Years	64.0	66.0	65.0	
Age ≤ 55 yrs.	38 (19.8%)	23 (12.4%)	30 (16.9%)	p = 0.21
Age 56 - 69 yrs.	92 (47.9%)	109 (58.9%)	92 (51.7%)	
Age ≥ 70 yrs.	62 (32.3%)	53 (28.6%)	56 (31.5%)	
Body Mass Index (kg/m2)	26.4 (17.3 - 40.6)	25.8 (13.7 - 57.6)	25.8 (16.5 - 46.4)	Not done
WHO Performance Status				
0	69 (35.9%)	79 (42.7%)	68 (38.2%)	
1	104 (54.2%)	84 (45.4%)	92 (51.7%)	p = 0.54
2	19 (9.9%)	22 (11.9%)	18 (10.1%)	
Receptor Status				
ER+ & PR+	71 (37.0%)	71 (38.4%)	59 (33.0%)	
ER+ or PR+	36 (18.8%)	41 (22.2%)	31 (17.4%)	p = 0.42
ER, PR Unknown	85 (44.3%)	73 (39.5%)	88 (49.4%)	
Disease Free Interval				
Stage IV	22 (11.5%)	29 (15.7%)	27 (15.2%)	
< 24 months	46 (24.0%)	42 (22.7%)	45 (25.3%)	p = 0.71
≥ 24 months	124 (64.6%)	114 (61.6%)	105 (59.0%)	
Sites of Disease				
Visceral, Bone, & Soft Tissue	15 (7.8%)	13 (7.0%)	8 (4.5%)	
Visceral & Bone	22 (11.5%)	28 (15.1%)	21 (11.8%)	
Visceral & Soft Tissue	17 (8.9%)	19 (10.3%)	17 (9.6%)	
Visceral Only	31 (16.1%)	30 (16.2%)	25 (14.0%)	p = 0.85
Bone & Soft Tissue	21 (10.9%)	16 (8.6%)	23 (12.9%)	
Bone Only	36 (18.8%)	38 (20.5%)	34 (19.1%)	
Soft Tissue Only	43 (22.4%)	39 (21.2%)	46 (25.8%)	
Unknown	7 (3.6%)	2 (1.1%)	4 (2.2%)	
Dominant Site of Disease				p = 0.49
Soft Tissue	43 (22.4%)	39 (21.2%)	46 (25.8%)	
Bone	57 (29.7%)	54 (29.2%)	57 (32.0%)	
Visceral	85 (44.3%)	90 (48.6%)	71 (39.9%)	
Unknown	7 (3.6%)	2 (1.1%)	4 (2.2%)	

Parameter	Letrozole 0.5 (N = 192)	Letrozole 2.5 (N = 185)	Aminoglutethimide (N = 178)	Chi Square Test for Homogeneity, P-value, two-sided
Types of Prior Therapy				
Hormonal				
Adjuvant	68 (35.4%)	69 (37.3%)	71 (39.9%)	p = 0.29
Therapeutic	113 (58.9%)	95 (51.4%)	89 (50.0%)	
Both	11 (5.7%)	20 (10.8%)	18 (10.1%)	
None	0 (0.0%)	1 (0.5%)	0 (0.0%)	
Chemotherapy				
None	90 (46.2%)	97 (52.4 %)	100 (56.2 %)	
Neoadjuvant	12 (6.3%)	13 (7.0%)	5 (02.5%)	p = 0.31
Adjuvant	65 (33.9%)	46 (24.9%)	46 (25.8%)	
Therapeutic	40 (20.8%)	46 (24.9%)	38 (21.3%)	
Both Adj./ Therapeutic	8 (4.2%)	10 (5.4%)	10 (5.6%)	
Response to Prior AntiE2 Therapy	30 (15.6%)	37 (20.0%)	41 (23.0%)	
CR + PR	45 (23.4%)	43 (23.2%)	31 (17.4%)	p = 0.23
NC + U > 6 months*	45 (23.4%)	29 (15.7%)	33 (18.5%)	
U < 6 months** and PD	72 (37.5%)	76 (41.1%)	73 (41.0%)	
NA				

* Unknown response but on antiestrogen therapy for > 6 months so considered as stable disease or NC

** Unknown but on antiestrogen therapy for less than six months so considered as progressive disease

An increased number of patients in the letrozole 0.5 arm had adjuvant chemotherapy as compared to the other two arms. No other imbalances are noted. The majority of patients have had only one exposure to antiestrogen therapy usually in therapeutic setting. Ten per cent or less of the patients had both adjuvant and therapeutic chemotherapy in addition to antiestrogen therapy.

Patient Disposition

Patient disposition at the end of the trial is reported in Table AR/BC3-R3. The majority of the study population has progressed at the time of study closure. At the time of study closure more than twice as many patients remained on study on the letrozole 2.5 mg arm as on aminoglutethimide arm. On each arm a few patients were removed from study without evidence of progression on peer review (long after patient was removed from study). Misinterpretation of disease status refers to these patients whose assessment was considered to be consistent with progressive disease by the primary investigator but were not confirmed on peer review. Other patients were removed for events consistent with treatment failure: adverse event, withdrawal of consent, non-compliance, ineligibility. Appendix II is a listing of those patients by the patient number with the reason for study removal if removal was for reasons other than progression. The number of adverse events is not significantly different in any treatment arm but the number of patients removed from study for *drug related* adverse events is increased on the aminoglutethimide arm.

Table AR/BC3 - R3: Patient Disposition by Treatment Arm

Disposition	Letrozole 0.5 (N = 193)*	Letrozole 2.5 (N = 185)	Aminoglutethimide (N = 179)*
On Treatment without Evidence of Progression	34 (17.6%)	47 (25.4%)	22 (12.3%)
Removed from Study due to Progression	138 (71.5%)	116 (62.7%)	137 (76.5%)
Removed from Study for Reasons other than Progression	21 (10.9%)	21 (11.4%)	20 (11.2%)
Ineligible	0	4	3
Withdrew Consent	4	1	1
Non-compliant	2	0	4
Adverse Event	6	7	6
Unknown /Not Assessed	2	3	1
Lost to Follow-up	0	0	1
Misinterpretation of Disease Status	7	6	3

*Included the two patients enrolled on study and removed on the same day when found to be ineligible

Efficacy Endpoints

Response Rates for Each Treatment Arm

At each visit after visit three the investigator assigned the patient a response category based on the IUCC definition of response. All complete and partial responses had to be confirmed at the next visit (usually three month after the visit at which tumor response was identified). If stable disease (no change) was the designated response at one visit but was not confirmed at the next visit (in three months time) progressive disease was the final designation. A peer review committee in each country reviewed all measurements, photographs and other images for each patient and scored a response designation. The peer review committee response was compared with the investigator response. In those cases where a differences in response category designated by the investigator and by the peer review committee was noted, the peer review response and the committee comments regarding the change in response category were recorded and included in Listing 22 of the study report. The ***confirmed*** **peer review response was the response reported** by the applicant and used for all statistical analyses.

All response information was reviewed by the medical officer using the line listings derived from the CRFs and from the peer review assessments / comments. All patients reported to have **stable disease (no change) as the best response even if not confirmed at the next visit** were considered to have **stable disease** by the medical reviewer. Patients, who had documented progression at any site **even if all sites were not assessed at the visit where progression was noted,** were considered to have **progressive disease**. If the patient did not remain on study for three months, but the data listing provided evidence of tumor progression, the patient was considered to have **progressive disease**. Patients were considered nonevaluable if no response category had been assigned to the patient previously and no documentation of progression (no

assessment of sites of disease) was found in the line listings at the time that patient was removed from study

Table AR/BC3 - R4: Response Rates by Treatment Arm

Response Category	Letrozole 0.5 N = 192		N =193	Letrozole 2.5 N = 185		Aminoglutethimide N = 180	N = 179
	Ciba N (%)		FDA N (%)	Ciba N (%)	FDA N (%)	Ciba N (%)	FDA N (%)
Complete Response	7 (3.6)		6 (3.1)	6 (3.2)	6 (3.2)	3 (1.9)	3 (1.7)
Partial Response	25 (13.0)		28 (14.5)	27 (14.6)	28 (15.1)	17 (9.6)	19 (10.6)
Stable Disease (No Change)	31 (16.1)		31 (16.1)	33 (17.8)	34 (18.4)	32 (18.0)	33 (18.4)
Progressive Disease	112 (58.3)		110 (57.0)	106 (57.3)	97 (52.5)	109 (61.2)	103 (57.6)
Not Evaluable /Assessable	17 (8.9)		18 (9.3)	13 (7.0)	20 (10.8)	17 (9.6)	21 (11.7)

Patient (not included in the Ciba analysis since the patient was enrolled on study for one day and did not receive any study drug, L0.5) was considered NE for response in the FDA intent to treat analysis. After FDA review of the data, tumor response assignments were changed for ten patients on the letrozole 0.5 mg arm. In four instances tumor response was downgraded, in six instances tumor response was upgraded. Tumor response categories was changed twenty times on the letrozole 2.5 mg arm. Twelve patients, including eleven patients categorized as progressive disease and one PR were changed to NE after review of the tumor assessment data. Response categories were changed for thirteen patients on the AG arm. In six instances the response was upgraded, in six changed to NE, and in one was downgraded. Patient (enrolled on the AG arm of the study for one day and never treated) was considered as NE in the FDA intent to treat analysis. Appendix III is a listing of any changes in response assessments, dates of events, and other differences in study information thought important by the reviewer. In Appendix IV, changes in response on each study arm are listed in tabular form. No statistical difference in response rates in any comparison between three treatment arms is observed. Odd ratios favor response on the letrozole arms as compared to aminoglutethimide with trends toward statistical significance.

Table AR/BC3 - R5: Comparison of Response Rates by Study Arm

Comparison	Odds Ratio, 95% Confidence Intervals, and P Value, two-sided
L0.5 vs L2.5	OR: 0.95 (95% CI: 0.56, 1.60), p = 0.85
L0.5 vs AG	OR: 1.53 (95% CI: 0.85, 2.77), p = 0.15
L2.5 vs AG	OR: 1.61 (95% CI: 0.90, 2.87), p = 0.11

Response Rates in the Population Not at Risk for Withdrawal Response

Since patients being treated with antiestrogen therapy, could, at the time that progression was

assessment of sites of disease) was found in the line listings at the time that patient was removed from study

Table AR/BC3 - R4: Response Rates by Treatment Arm

Response Category	Letrozole 0.5 N = 192	N =193	Letrozole 2.5 N = 185		Aminoglutethimide N = 180	N = 179
	Ciba N (%)	FDA N (%)	Ciba N (%)	FDA N (%)	Ciba N (%)	FDA N (%)
Complete Response	7 (3.6)	6 (3.1)	6 (3.2)	6 (3.2)	3 (1.9)	3 (1.7)
Partial Response	25 (13.0)	28 (14.5)	27 (14.6)	28 (15.1)	17 (9.6)	19 (10.6)
Stable Disease (No Change)	31 (16.1)	31 (16.1)	33 (17.8)	34 (18.4)	32 (18.0)	33 (18.4)
Progressive Disease	112 (58.3)	110 (57.0)	106 (57.3)	97 (52.5)	109 (61.2)	103 (57.6)
Not Evaluable /Assessable	17 (8.9)	18 (9.3)	13 (7.0)	20 (10.8)	17 (9.6)	21 (11.7)

Patient (not included in the Ciba analysis since the patient was enrolled on study for one day and did not receive any study drug, L0.5) was considered NE for response in the FDA intent to treat analysis. After FDA review of the data, tumor response assignments were changed for ten patients on the letrozole 0.5 mg arm. In four instances tumor response was downgraded, in six instances tumor response was upgraded. Tumor response categories was changed twenty times on the letrozole 2.5 mg arm. Twelve patients, including eleven patients categorized as progressive disease and one PR were changed to NE after review of the tumor assessment data. Response categories were changed for thirteen patients on the AG arm. In six instances the response was upgraded, in six changed to NE, and in one was downgraded. Patient (enrolled on the AG arm of the study for one day and never treated) was considered as NE in the FDA intent to treat analysis. Appendix III is a listing of any changes in response assessments, dates of events, and other differences in study information thought important by the reviewer. In Appendix IV, changes in response on each study arm are listed in tabular form. No statistical difference in response rates in any comparison between three treatment arms is observed. Odd ratios favor response on the letrozole arms as compared to aminoglutethimide with trends toward statistical significance.

Table AR/BC3 - R5: Comparison of Response Rates by Study Arm

Comparison	Odds Ratio, 95% Confidence Intervals, and P Value. two-sided
L0.5 vs L2.5	OR: 0.95 (95% CI: 0.56, 1.60), p = 0.85
L0.5 vs AG	OR: 1.53 (95% CI: 0.85, 2.73), p = 0.15
L2.5 vs AG	OR: 1.61 (95% CI: 0.90, 2.87), p = 0.11

Response Rates in the Population Not at Risk for Withdrawal Response

Since patients being treated with antiestrogen therapy, could, at the time that progression was

detected, immediately be enrolled on AR/BC3, the response rates and other time to event information may be confounded by antiestrogen withdrawal response. About eight per cent of patients who respond to antiestrogen therapy (i.e. complete response, partial response, or stable disease for greater than six months at the time of progression) will respond to withdrawal of the antiestrogen therapy. This response may even be a complete response and may be of several months duration. To eliminate this confounding factor the subset of patients who would not be eligible for antiestrogen withdrawal response were analyzed separately for tumor response, for time to progression, and for treatment failure. This subset included: (1) patients with advanced disease who did not respond to antiestrogen therapy, (2) patients who had completed at least six months of adjuvant antiestrogen therapy and were still on therapy and were found to have progressive disease, and (3) patients who, within twelve months of discontinuation of adjuvant antiestrogen therapy, were found to have progression. One hundred twenty (62.7%) patients on the letrozole 0.5 mg arm, one hundred nine (58.9%) patients on the letrozole 2.5 mg arm, and one hundred fifteen (64.2%) on the aminoglutethimide arm are included in this subset. The tumor response rates for this subset are presented in the following table (AR/BC3 - R6).

Table AR/BC3 - R6: Response Rates in the Subset Not at Risk for Estrogen Withdrawal

Response Category	Letrozole 0.5 (N =120)	Letrozole 2.5 (N = 109)	Aminoglutethimide (N = 115)
Complete Response	3 (2.5%)	4 (3.7%)	2 (1.7%)
Partial Response	18 (15.0%)	15 (13.8%)	7 (6.1%)
Stable Disease	18 (15.0%)	17 (15.6%)	15 (13.05%)
Progressive Disease	66 (55.0%)	62 (56.9%)	76 (66.1%)
Not Evaluable / Assessable	15 (12.5%)	11 (10.0%)	15 (13.05%)
Comparison	Odds Ratio, (95% Confidence Intervals), P - value, Two sided		
Letrozole 0.5 vs Letrozole 2.5	OR = 1.01, (95% CI: 0.51, 1.99), p = 0.99		
Letrozole 0.5 vs Aminoglutethimide	OR = 2.50, (95% CI: 1.09, 5.72), p = 0.03		
Letrozole 2.5 vs Aminoglutethimide	OR = 2.49, (95% CI: 1.07, 5.77), p = 0.03		

Note that the odds of response are statistically significantly better for letrozole 0.5 mg and letrozole 2.5 mg than for the comparator, aminoglutethimide, suggesting that letrozole treatment may be more effective in the population for which the drug is targeted than aminoglutethimide. No difference in the odds of response is detected in the comparison of the two dose of letrozole in this subgroup.

In summary, the data on response shows that letrozole has similar response rates to aminoglutethimide in post-menopausal breast cancer patients with receptor positive or receptor unknown disease who have had previous antiestrogen therapy. No difference in the odds of response could be detected in a comparison between the two doses of letrozole. Comparisons of each dose of letrozole with aminoglutethimide tend to favor letrozole over the comparator. In an

exploratory subset analysis, in patients who are not at risk for an antiestrogen withdrawal response, both letrozole concentrations were statistically significantly better than aminoglutethimide in terms of response.

Duration of Response and Time to Response

The duration of response and the time to response are shown in Table AR/BC3 - R7. Duration of response is defined by the FDA as that period of time between the date that objective response (CR or PR) is observed and the date that progression is observed. The duration of response included in the Study Report for AR/BC3 submitted by Ciba is not presented since response duration is calculated as the time period from the first day of treatment to the date of progression. Little difference in the duration of response is noted between the treatment arms. In this study the median duration of response is longest in the glutethimide arm. The time to response is also shortest in the aminoglutethimide arm, however the lower limit of the 95% confidence interval is very close in all arm. The longer time to response noted in the letrozole arm suggests that with the continued letrozole treatment patients with stable disease will continue to improve to partial responders, while with aminoglutethimide treatment, if response is not observed within the first three -four months of treatment, response later is unlikely.

Table AR/BC3-R7: Duration of Response and Time to Response by Treatment Arm

Parameter	Letrozole 0.5 mg	Letrozole 2.5 mg	Aminoglutethimide
No. Responders	34	34	22
No. Censored	21	25	12
Median Duration of Response in Days (95% Confidence Interval)	619 (532, -)	706 (522, -)	450 (350, -)
Median Time to Response in Days (95% Confidence Interval)	164 (91, 185)	171.5 (96, 183)	91 (88, 96)

Time to Progression

Time to progression was measured from the date that the patient was enrolled on study to the date that the patient had objective evidence of progression by physical examination and/or laboratory testing. Hypercalcemia by itself is not considered acceptable as evidence of progression since hormone-like drugs may cause a "calcium" flare when treatment is initiated but which is not associated with tumor progression. In several instances the date of progression reported in the line listings (Vol. 11- 15) was one day prior to the date that patient was removed from study. The progression date did not correspond to the date on which progression was determined from objective data in the investigator line listings. (See Appendix III). A difference between the applicant and the FDA in the number of patients who were considered to have progressed is noted. (See Appendix III). As a result differences are seen in the median time to progression as reported by the applicant and the reviewer. At time of study closure, one hundred sixty-six patients remained on study without evidence of progression. Sixteen patients were

removed from trial without evidence of progression and forty-two patients were removed for other reasons. In Table AR/BC3 - R8 information about the time to progression as determined by Ciba and by the agency for each treatment arm is presented and in Table AR/BC3 - R9 the unadjusted relative risks are presented.

Table AR/BC3-R8: Time to Progression by Study Arm with Comparison of the Relative Risk

Parameter	Letrozole 0.5		Letrozole 2.5		Aminoglutethimide	
	Ciba (N = 192)	FDA (N = 193)	Ciba (N = 185)	FDA (N = 185)	Ciba (N = 178)	FDA (N =179)
No. Progressed (%)	141 (73.4)	138 (71.5)	124 (67.0)	116 (62.7)	139 (78.1)	137 (76.5)
No. Censored (%)	51 (26.6)	55 (28.5)	61 (33.0)	69 (37.3)	39 (21.9)	42 (23.5)
Median TTP, Days (95% Confidence Interval)	104 (97, 176)	103 (96, 179)	104 (94, 182)	121 (93, 258)	102 (92, 172)	112 (92, 171)

Table AR/BC3-R9: Relative Risk of Progression by Treatment Arm

Comparison	Ciba - Geigy	FDA
	Risk Ratio, (95% Confidence Interval) P Value, Two-sided, Unadjusted	Risk Ratio, (95% Confidence Interval) P Value, Two-sided, Unadjusted
Letrozole 0.5 vs Letrozole 2.5	1.12 (0.88, 1.46) 0.34	RR = 1.16 (95% CI: 0.91, 1.49) p = 0.24
Letrozole 0.5 vs Aminoglutethimide	0.86 (0.68, 1.09) 0.20	RR = 0.85 (95% CI: 0.67, 1.08) p = 0.18
Letrozole 2.5 vs Aminoglutethimide	0.77 (0.60, 0.98) 0.04	RR = 0.73 (95% CI: 0.57, 0.94) p = 0.01

The median time to progression is longest in the letrozole 2.5 mg arm at 121 days The risk of progression is significantly less on the letrozole 2.5 mg arm as compared to aminoglutethimide with "tight" 95% confidence intervals around the relative risk. Median time to progression is shortest in letrozole 0.5 mg treatment arm with the relative risk of progression of 0.85 or 85% of the risk of progression on aminoglutethimide with a trend toward significance. The relative risk of progression is less with letrozole 2.5 mg as compared to letrozole 0.5 mg, but the difference between arms is not significant. The findings of statistically significant decrease in the risk of progression on the letrozole 2.5 mg arm compared to aminoglutethimide and a reduced risk of progression (though not statistically significant) on the letrozole 0.5 mg arm compared to the aminoglutethimide arm are consistent with a therapeutic benefit for letrozole therapy in postmenopausal women with receptor positive or receptor unknown breast cancer previously treated with antiestrogens.

removed from trial without evidence of progression and forty-two patients were removed for other reasons. In Table AR/BC3 - R8 information about the time to progression as determined by Ciba and by the agency for each treatment arm is presented and in Table AR/BC3 - R9 the unadjusted relative risks are presented.

Table AR/BC3-R8: Time to Progression by Study Arm with Comparison of the Relative Risk

Parameter	Letrozole 0.5		Letrozole 2.5		Aminoglutethimide	
	Ciba (N = 192)	FDA (N = 193)	Ciba (N = 185)	FDA (N = 185)	Ciba (N = 178)	FDA (N =179)
No. Progressed (%)	141 (73.4)	138 (71.5)	124 (67.0)	116 (62.7)	139 (78.1)	137 (76.5)
No. Censored (%)	51 (26.6)	55 (28.5)	61 (33.0)	69 (37.3)	39 (21.9)	42 (23.5)
Median TTP, Days (95% Confidence Interval)	104 (97, 176)	103 (96, 179)	104 (94, 182)	121 ~~123~~ (93, 258)	102 (92, 172)	112 (92, 171)

Table AR/BC3-R9: Relative Risk of Progression by Treatment Arm

Comparison	Ciba - Geigy	FDA
	Risk Ratio, (95% Confidence Interval) P Value, Two-sided, Unadjusted	Risk Ratio, (95% Confidence Interval) P Value, Two-sided, Unadjusted
Letrozole 0.5 vs Letrozole 2.5	1.12 (0.88, 1.46) 0.34	RR = 1.16 (95% CI: 0.91, 1.49) p = ~~0.24~~ 0.25
Letrozole 0.5 vs Aminoglutethimide	0.86 (0.68, 1.09) 0.20	RR = 0.85 (95% CI: 0.67, 1.08) p = 0.18
Letrozole 2.5 vs Aminoglutethimide	0.77 (0.60, 0.98) 0.04	RR = ~~0.73~~ 0.74 (95% CI: 0.57, 0.94) p = ~~0.01~~ 0.02

Corrected 7/11/97 BJK

The median time to progression is longest in the letrozole 2.5 mg arm at 121 days The risk of progression is significantly less on the letrozole 2.5 mg arm as compared to aminoglutethimide with "tight" 95% confidence intervals around the relative risk. Median time to progression is shortest in letrozole 0.5 mg treatment arm with the relative risk of progression of 0.85 or 85% of the risk of progression on aminoglutethimide with a trend toward significance. The relative risk of progression is less with letrozole 2.5 mg as compared to letrozole 0.5 mg, but the difference between arms is not significant. The findings of statistically significant decrease in the risk of progression on the letrozole 2.5 mg arm compared to aminoglutethimide and a reduced risk of progression (though not statistically significant) on the letrozole 0.5 mg arm compared to the aminoglutethimide arm are consistent with a therapeutic benefit for letrozole therapy in postmenopausal women with receptor positive or receptor unknown breast cancer previously treated with antiestrogens.

Time to Progression in the Population Not at Risk for Withdrawal Response

Time to progression was analyzed by the FDA in the subpopulation of patients who was not at risk for an antiestrogen withdrawal response. A difference in time to progression in this group is strongly suggestive of therapeutic benefit for letrozole in postmenopausal patients refractory to antiestrogens. Table AR/BC3 - R10 displays the median time to progression and the relative risk of progression for this subset.

Table AR/BC3-R10: Time to Progression and Relative Risks in the Subset Not at Risk for Withdrawal Response

Parameter	Letrozole 0.5 (N = 120)	Letrozole 2.5 (N = 108)	Aminoglutethimide (N = 115)
No. Progressed (%)	85	72	88
No. Censored (%)	35	36	27
Median Time to Progression in Days (95% Confidence Intervals)	101 (90, 181)	108 (90, 180)	92 (86, 130)
Comparison	Relative Risk; 95% Confidence Intervals; P-Value, Two-sided, Unadjusted		
Letrozole 0.5 vs Letrozole 2.5	RR = 1.06, (95% CI: 0.77, 1.45), p = 0.72		
Letrozole 0.5 vs Aminoglutethimide	RR = 0.76, (95% CI: 0.56, 1.02), p = 0.07		
Letrozole 2.5 vs Aminoglutethimide	RR = 0.73, (95% CI: 0.53, 0.97), p = 0.05		

A statistically significantly difference in the relative risk of progression in favor of letrozole 2.5 mg as compared to aminoglutethimide is observed with a trend in favor of letrozole 0.5 mg over aminoglutethimide with regard to the risk of progression.

Time to Treatment Failure

Time to treatment failure is defined as the interval from the first day of treatment to diagnosis of progression, withdrawal from trial for any reason except disease misinterpretation, or death from any cause, whichever is the earliest event. The majority of patients who came off study did so because of progression. Slightly more than ten per cent of the patients on each arm were removed for study for reasons other than progression as noted in Table AR/BC3-R3. Those patients who were removed from study by the investigators for progression and whose progression was not confirmed on peer review were censored for both progression and treatment failure by the applicant and by the agency since treatment "failure" had not occurred. Table AR/BC3-R10 provides the information for treatment failure events by study arm as well as the relative risk of treatment failure.

Table AR/BC3-R10: Time to Treatment Failure and Comparison of Risks Between Study Arms

Parameter	Letrozole 0.5		Letrozole 2.5		Aminoglutethimide	
	Ciba (N = 192)	FDA (N = 193)	Ciba (N = 185)	FDA (N = 185)	Ciba (N = 178)	FDA (N = 179)
No. of Treatment Failures (%)	149 (77.6)	152 (78.8)	127 (68.6)	130 (70.3)	150 (84.3)	153 (85.5)
No. Censored	43 (22.4)	41 (21.2)	58 (31.4)	55 (29.7)	28 (15.7)	26 (14.5)
Median TT F, Days (95% Confidence Intervals)	100 (94, 168)	98 (91, 159)	103 (94, 180)	102 (92, 180)	96 (91, 162)	96 (90, 163)
	Ciba		FDA			
Comparison	Relative Risk (95% Confidence Interval) P-Value, Two-sided, Unadjusted		Relative Risk (95% Confidence Interval) P-Value, Two-sided, Unadjusted			
Letrozole 0.5 vs Letrozole 2.5	RR = 1.15 (0.91, 1.49) p = 0.24		RR = 1.17 (0.92, 1.48) p = 0.19			
Letrozole 0.5 vs AG	RR = 0.84 (0.67, 1.06) p = 0.14		RR = 0.84 (0.67, 1.06) p = 0.14			
Letrozole 2.5 vs AG	RR = 0.73 (0.58, 0.93) p = 0.01		RR = 0.72 (0.57, 0.82) p = 0.007			

Median time to treatment failure was longest in the letrozole 2.5 mg arm and shortest in the letrozole 0.5 mg arm. Relative risk of treatment failure was slightly better numerically for the higher letrozole dose, however, no statistical difference between the letrozole arms is observed. In comparison with aminoglutethimide less risk of treatment failure is observed for both letrozole arms. The relative risk of treatment failure is statistically significantly less for letrozole 2.5 mg compared to aminoglutethimide and a trend toward statistical significance is demonstrated for the letrozole 0.5 mg arm in comparison to aminoglutethimide. The risk of treatment failure is at least similar, if not less, for treatment with letrozole as compare to treatment with aminoglutethimide.

Treatment Failure in the Subset Not at Risk for Estrogen Withdrawal

In the subset analysis of the one hundred twenty patients treated with letrozole 0.5 mg (ninty-six treatment failures and twenty-four censored patients) the median time to treatment failure was 93 days (95% CI: 88, 125). Of the one hundred eight patients treated with letrozole 2.5 mg seventy-eight had failed and thirty were censored. Median time to treatment failure in this subset was 92 days (95% CI: 89, 171). On the aminoglutethimide arm one hundred of the one hundred fifteen patients had failed and fifteen were censored. Median time to treatment failure in this subset was 88 days (95% CI: 84, 93). The risk of treatment failure when letrozole 0.5 is compared to

letrozole 2.5 is not significantly different (RR = 1.11; 95% CI 0.82, 1.50; p = 0.51, two-sided). The risk of treatment failure when letrozole 0.5 is compared to aminoglutethimide is almost significantly less for letrozole (RR = 0.76; 95% CI 0.57, 1.01; p = 0.06). When letrozole 2.5 mg as compared to aminoglutethimide, the risk of treatment failure is significantly less for letrozole (RR = 0.70; 95% CI: 0.52, 0.95, p = 0.02).

Survival

No significant difference in survival is noted for patients on any of three study arms. However, less than half of patients on any arm have expired. The best chance of survival is observed in the letrozole 2.5 mg arm and tends toward significance (p = 0.14). Comparison of the survival duration between the two doses of letrozole favors the letrozole 2.5 mg arm and tends toward significance. Survival risk for aminoglutethimide as compared to letrozole 0.5 mg is about equal. Survival information is presented in the following table (AR/BC3 - R11).

Table AR/BC3-R11: Survival by Treatment Arm with Comparison of Survival between Treatment Arms

Parameter	Letrozole 0.5		Letrozole 2.5		Aminoglutethimide	
	Ciba (N = 192)	FDA (N = 193)	Ciba (N= 185)	FDA (n = 185)	Ciba (N = 178)	FDA (N = 179)
No. Dead (%)	79 (41.1)	79 (40.9)	63 (34.1)	63 (34.1)	76 (42.7)	76 (42.4)
Median Time to Death, Days (95% Confidence Interval)	637 (495, 762)	636 (494, 761)	793 (611, +)	792 (610, +)	593 (505, 846)	592 (504, 845)
Comparison	Ciba-Geigy		FDA			
	Relative Risk (95% Confidence Interval) P-Value, Two-sided, Unadjusted		Relative Risk (95% Confidence Interval) P-Value, Two-sided, Unadjusted			
Letrozole 0.5 vs Letrozole 2.5	RR = 1.28 (0.92, 1.83) p = 0.14		RR = 1.28 (0.92, 1.79) p = 0.14			
Letrozole 0.5 vs AG	RR = 1.07 (0.78, 1.47) p = 0.67		RR = 1.06 (0.78, 1.46) p = 0.70			
Letrozole 2.5 vs AG	RR = 0.80 (0.57, 1.12) p = 0.19		RR = 0.80 (0.57; 1.12) p = 0.18			

Secondary Variables

Performance Status

Eligibility criteria included a baseline performance status between 0 and 2. A performance status of zero (100% performance) was reported by 35.9% of the patients on the letrozole 0.5 mg arm,

letrozole 2.5 is not significantly different (RR = 1.11; 95% CI 0.82, 1.50; p = 0.51, two-sided). The risk of treatment failure when letrozole 0.5 is compared to aminoglutethimide is almost significantly less for letrozole (RR = 0.76; 95% CI 0.57, 1.01; p = 0.06). When letrozole 2.5 mg as compared to aminoglutethimide, the risk of treatment failure is significantly less for letrozole (RR = 0.70; 95% CI: 0.52, 0.95, p = 0.02).

Survival

No significant difference in survival is noted for patients on any of three study arms. However, less than half of patients on any arm have expired. The best chance of survival is observed in the letrozole 2.5 mg arm and tends toward significance (p = 0.14). Comparison of the survival duration between the two doses of letrozole favors the letrozole 2.5 mg arm and tends toward significance. Survival risk for aminoglutethimide as compared to letrozole 0.5 mg is about equal. Survival information is presented in the following table (AR/BC3 - R11).

Table AR/BC3-R11: Survival by Treatment Arm with Comparison of Survival between Treatment Arms

Parameter	Letrozole 0.5		Letrozole 2.5		Aminoglutethimide	
	Ciba (N = 192)	FDA (N = 193)	Ciba (N= 185)	FDA (n = 185)	Ciba (N = 178)	FDA (N = 179)
No. Dead (%)	79 (41.1)	79 (40.9)	63 (34.1)	63 (34.1)	76 (42.7)	76 (42.4)
Median Time to Death, Days (95% Confidence Interval)	637 (495, 762)	636 (494, 761)	793 (611, +)	792 (610, +)	593 (505, 846)	592 (504, 845)
Comparison	Ciba-Geigy		FDA			
	Relative Risk (95% Confidence Interval) P-Value, Two-sided, Unadjusted		Relative Risk (95% Confidence Interval) P-Value, Two-sided, Unadjusted			
Letrozole 0.5 vs Letrozole 2.5	RR = 1.28 (0.92, 1.83) p = 0.14		RR = 1.28 (0.92, 1.79) p = ~~0.14~~ p = 0.15			
Letrozole 0.5 vs AG	RR = 1.07 (0.78, 1.47) p = 0.67		RR = 1.06 (0.78, 1.46) p = 0.70			
Letrozole 2.5 vs AG	RR = 0.80 (0.57, 1.12) p = 0.19		RR = 0.80 (0.57, 1.12) p = ~~0.18~~ p = 0.19			

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Secondary Variables

Performance Status

Eligibility criteria included a baseline performance status between 0 and 2. A performance status of zero (100% performance) was reported by 35.9% of the patients on the letrozole 0.5 mg arm,

42.7% of the patients on the letrozole 2.5 mg arm, and 38.2% of the patients on the aminoglutethimide arm. A baseline performance status of one was reported by 54.2% of the patients on the letrozole 0.5 mg arm, 45.4% of the patients on letrozole 2.5 mg arm, and 51.7% of the patients on the aminoglutethimide arm. A baseline performance status of 2 was reported in 9.9% of the patients on the letrozole 0.5 mg arm, 11.9% of the patients on the letrozole 2.5 mg arm, and by 10.1% of the patients on the aminoglutethimide arm. Between study visits three and ten 9.6% of the patients on the letrozole 2.5 mg arm reported a decline to a performance status grade 3 or 4, 11.9% of the patients on the aminoglutethimide arm reported a decline to a performance status grade 3 or 4, and 13.0% of the patients on the letrozole 0.5 mg arm reported a decline to a performance status grade 3 or 4. Overall 39.6% of the patients on the letrozole 0.5 mg arm, 41.1% of the patients on the letrozole 2.5 mg arm, and 37.1% of the patients on the aminoglutethimide arm had a deterioration in their performance status. The decline in performance is most likely linked to progression of disease. The applicant has not analyzed performance status in responders vs nonresponders, nor has the applicant attempted to correlate decline in performance status with removal from study for progression. Over the duration of the study most patients reported stabilization or improvement in performance status. Since the patients who remain on study are likely to have objective tumor response, performance status would be expected to stabilize or improve.

Pain Severity

At baseline 50% of the patients on the aminoglutethimide arm had no pain, while 5.1% severe or intractable pain. On the letrozole 0.5 mg arm 40.6% of the patients had no pain, while 4.1% had severe or intractable pain. On the letrozole 2.5 mg arm 42.7% of patients had no pain, while 3.2% had severe or intractable pain. Over the first twelve months of the study the percentage of patients on each treatment arm in each pain category (none, mild, moderate, severe) remained constant. Between 30 - 41% of the patients had increase in severity of pain over the study period as would be expected in patients who begin to experience tumor progression before removal from study. By month 18 only patients whose pain category was "none, mild, or moderate" remained on study. One study treatment did not significantly improve pain as compared to another.

Quality of Life Data

No clinically significant differences were detected between the treatment arms in any of the functional scales and symptom scales/items at baseline or in the average level over the first twelve months of study. Insufficient data prevents any meaningful analysis after month twelve on study. Since statistically significant differences were not observed between the study arms, QOL data will not be discussed further.

Pharmacokinetic Data

Letrozole Plasma Concentrations

On the letrozole 0.5 mg arm the mean trough plasma levels of letrozole were between 40 - 50 nmol/l with a coefficient of variation of 54.5 to 75.8% (based on greater than 10 samples). Steady state trough plasma concentrations were reached within two weeks of treatment. With letrozole 2.5 mg the mean trough plasma level after two months of daily dosing was 290 - 377 nmol/L with a coefficient of variation of 51.4 -56.5% (with greater than ten samples). Steady state plasma concentrations were reached within one to two months of treatment. The ratio of the letrozole 2.5 mg dose to the letrozole 0.5 mg dose was 8.62 (95% CI: 7.51, 9.89) for a 170% dose over-proportionality at the 2.5 mg dose. (Dose ratio of letrozole 2.5 to 0.5 mg is 5, the observed ratio 8.62 for the comparisons of the letrozole concentrations is 1.72 times or 172% greater than the expected ratio of 5.) Within patient coefficient of variation in plasma drug concentrations was 45%. Similar dose over proportionality in plasma concentrations was noted in other studies when daily administration of letrozole 0.5 and letrozole 2.5 mg were studied.

Serum Concentrations of E1, E2, and E1S

Baseline values for E1 (estradiol) were suppressed more than 80% in both letrozole arms and by 65 - 70% in the aminoglutethimide arm. Baseline values for E1S were also suppressed to greater than 80% of the pretreatment value in both letrozole arms and to about 75% of pretreatment values in the AG arm. For E2 (estrone) suppression to 62 -70% of the baseline levels was observed in both letrozole arms, while in the aminoglutethimide arm suppression was to about 55% of baseline. The level of suppression of the various estrogen compounds is similar to that reported in other studies when estrogen suppression is studied utilizing the same doses of letrozole. Odds ratios comparing the three treatments for estrogen suppression are presented in the study report, but are not included here due to the insensitivity of the assays measuring E1, E1S, and E2 concentrations. In the letrozole 0.5 mg arm 54.6% of the E1 values, 44.7% of the E1S values and 15.1% of the E2 values were below the limit of quantification. In the letrozole 2.5 mg arm 63.2% of the E1 values, 52.5% of the E1S values, and 19.2% of the E2 values were below the limit of quantification. In the aminoglutethimide arm 15.9% of the E1 values, 15.6% of the E1S values, and 8.6% of the E2 values were below the limits of quantification. If a meaningful difference in the degree of suppression related to letrozole dose is to be detected, more sensitive assays which accurately measure very concentrations of various estrogen moieties must be utilized.

Pharmacokinetic / Pharmacodynamic Data

The effect of drug concentration on the time to progression for letrozole was analyzed by comparing the time to progression in four subpopulations based on the trough letrozole plasma concentration. The study population was divided into four groups on the basis of the mean plasma letrozole concentration ($\leq$ 30 nmol/L, 30 to $\leq$ 100 nmol/L, 100 to $\leq$ 300 nmol/L, and >

300 nmol/L). Table AR/BC3-R provides the risk ratios for the comparison of the time to progression for the four groups. For those patients with the lowest plasma letrozole concentrations (0 - 30 nmol/L) the risk of progression is statistically significantly greater compared to risk of progression in any other group (30 to ≤ 100 nmol/L, 100 to ≤ 300 nmol/L, and > 300 nmol). Comparison of the risk of progression between the other groups (letrozole concentration > 30 nmol/L) did not show any significant difference.

Table AR/BC3 - R11: Risk Ratios for Comparison of the Time to Progression by Plasma Letrozole Concentrations

Comparison of Concentration Categories	Risk Ratio	95% Confidence Interval	P - Value
(nmol/L)	0.64	(0.43, 0.95)	0.03
(nmol/L)	0.54	(0.36, 0.83)	0.004
(nmol/L)	0.67	(0.44, 1.00)	0.06
(nmol/L)	0.85	(0.57, 1.28)	0.44
(nmol/L)	1.05	(0.69, 1.59)	0.82
(nmol/L)	1.23	(0.80, 1.90)	0.35

No difference in risk of progression could be detected based on suppression of estrone, estrone-1-sulfate, or estradiol, but the problem of assay sensitivity may hamper the detection of a difference in progression related to differences in the degree of estrogen suppression.

Efficacy Summary

In AR/BC3 the response rate in the three treatment arms is similar. The odds ratios for the comparison of the response rates for the two doses of letrozole shows no statistical difference between the two treatments. Comparison of either dose of letrozole with aminoglutethimide in terms of response favors the letrozole arm and tends toward significance in both cases. Median time to progression is longest on the letrozole 2.5 mg arm. The relative risk of progression on the letrozole 2.5 mg arm is 0.73 (95% CI: 0.57, 0.94) and statistically significantly less ($p = 0.015$, two-sided) than the risk of progression with aminoglutethimide. The relative risk of progression with the letrozole 0.5 mg treatment is 0.85 (95% CI: 0.67, 1.08) and tends toward significance ($p = 0.18$, two-sided) when compared to aminoglutethimide. Letrozole 2.5 mg is associated with statistically significant less risk of treatment failure (RR = 0.72, 95% CI: 0.57, 0.82; $p = 0.007$, two sided) than is aminoglutethimide. Median survival is slightly longer on the letrozole 2.5 mg arm (792 days). No statistically significant difference in the risk of death is found in comparisons between the three treatment arms, however less than 50% of the study participants on any arm have died. Overall the data tend to confirm that the efficacy profile of letrozole is similar to, if not better than, the efficacy profile for aminoglutethimide.

SAFETY REVIEW - AR/BC3

Adverse Events: Frequency

Adverse reactions, whether drug related or not, were reported for 138 patients (71.5%) on the letrozole 0.5 arm, for 133 patients (71.9%) on the letrozole 2.5 mg arm, and for 125 patients (69.8%) on the aminoglutethimide arm. With regard to classification of adverse reactions, whether related to drug or not, the incidence in each arm was similar with the exception of hemic and lymphatic system where twice as many events occurred on the letrozole 0.5 arm as compared to the AG arm and four times as many events on the letrozole 2.5 mg arm as on the aminoglutethimide arm. With regard to nervous system events only one third as many events occurred on the letrozole 2.5 mg arm as on the other two arms. More than twice as many events involving skin and appendages occurred on the AG arm as compared to the letrozole 0.5 mg and one third more events involving the skin and appendages occurred on the AG arm as compared to the letrozole 2.5 mg arm.

Adverse Events: Severity

With regard to the severity of adverse events irrespective of relationship to study treatment, the distribution of mild, moderate, severe, or life threatening adverse events is reported in the Table AR/BC3-S1. Fewer mild and severe adverse events were reported on the aminoglutethimide arm with more adverse events of moderate severity. In both letrozole arms the number of mild, moderate, and severe adverse events are similar. Two more life threatening adverse reactions occurred on the letrozole 2.5 mg arm than on the letrozole 0.5 mg arm.

Table AR/BC3-S1: Highest Degree of Severity of AEs during Trial Irrespective of Relationship to Treatment

Severity of Adverse Reactions	Letrozole 0.5		Letrozole 2.5		Aminoglutethimide	
	N	%	N	%	N	%
Mild	42	21.9	39	21.1	31	17.4
Moderate	49	25.5	49	26.5	59	33.1
Severe	41	21.4	38	20.5	28	15.7
Life Threatening	3	1.6	5	2.7	5	2.8

Life threatening adverse reactions on the letrozole 0.5 mg arm include: hepatic encephalopathy due to disease, hypertension with TIA and cardiac failure due to cardiomyopathy not related to drug therapy On the letrozole 2.5 mg arm the following life threatening adverse reactions were reported: dyspnea and hypotension due to disease , hemiplegia , pulmonary edema , quadriplegia and CVA Five life threatening adverse reactions were reported on the aminoglutethimide arm and include: intestinal obstruction gastric carcinoma , acute renal failure somnolence , and hemiplegia .

Adverse Reactions: Special Populations

No difference was noted in the occurrence of adverse reactions, whether related to drug or not, between any treatment arm when patients were stratified by age: ≤ 55 years, 56 - 69 years, and ≥ 70 years. No increase in adverse reactions was noted in any strata on any of the study arms when study participants were stratified by age. No increase in the severity of adverse reactions could be related to letrozole dose. With regard to renal function impairment no increase in adverse events was noted in patients with impaired renal function on either letrozole arm. On the aminoglutethimide arm, however, more adverse reactions were reported. With regard to treatment related adverse reactions no difference in the severity of the adverse reactions was noted on any treatment arm in patients with normal or impaired renal function.

When the frequency of adverse events is compared in patients with impaired hepatic function (≥ grade 3 SGOT, SGPT, bilirubin, or gamma-GT *or* ≥ grade 3 alkaline phosphatase elevation with grade 2 SGOT, SGPT, bilirubin, or gamma-GT) and in patients with normal liver function no difference is noted. With regard to treatment related adverse events, a slight increase (not significant) in the number of adverse events is noted in patients treated with aminoglutethimide arm who have impaired hepatic function No difference in the degree of severity of adverse events was observed on any treatment arm when patients with normal or with impaired hepatic function are compared.

Types of Adverse Reactions

Adverse experiences reported by more than 5% of the study population irrespective of ***relationship to study drug*** are reported in the following table (AR/BC3-S2).

These adverse events, can be contrasted to adverse experiences ***related to trial treatment*** which occurred in more that 3% of the study population as presented in Table AR/BC3-S3 (copied from Exhibits 9.1.2.-2).

The profile of adverse events for the study drug is very favorable for adverse events which are related to study drug. As expected, rash is more common in the aminoglutethimide arm and in this trial was responsible for study discontinuation in two patients. Nausea was as common on the letrozole arms as on the aminoglutethimide arm. About twice as many patients reported somnolence on the aminoglutethimide arm. Hot flushes and hypercholesterolemia consistent with estrogen deprivation occurred equally on all arms. The relative increase in hypertension on the AG arm may be related to the concurrent use of steroids. Since the incidence of asthenia was not equally prevalent on both letrozole arms, question is raised as to whether this adverse event is related to the drug or to the disease process. More dyspepsia is seen with aminoglutethimide and may be attributable to the twice daily dose of steroids required with aminoglutethimide therapy. Fatigue as an adverse events was reported equally in all arms. The incidence of headache and dizziness were increased on the letrozole 0.5 arm as compared to the letrozole 2.5 mg arm suggesting that this adverse event is not dose related.

Table AR/BC3 -S2: Adverse Experiences Reported in > 5% of Patients Irrespective of Trial Drug Relationship

Adverse Experience	Letrozole 0.5 (N = 192)		Letrozole 2.5 (N = 185)		Aminoglutethimide (N = 178)	
	N	%	N	%	N	%
Musculoskeletal Pain	34	17.7	30	16.2	24	13.5
Nausea	21	10.9	29	15.7	24	13.5
Rash	6	3.1	7	3.8	23	12.9
Headache	20	10.4	111	5.9	12	6.7
Hypertension	19	9.9	12	6.5	11	6.2
Vomiting	13	6.8	13	7.0	16	9.0
Somnolence	6	3.1	8	4.3	16	9.0
Abdominal Pain	9	4.7	12	6.5	14	7.9
Asthenia	14	7.3	7	3.8	9	5.1
Arthralgia	14	7.3	7	3.8	5	2.8
Dyspnea	13	6.8	10	5.4	8	4.5
Constipation	10	5.2	10	5.4	12	6.7
Hypercholesterolemia	10	5.2	9	4.9	11	6.2
Diarrhea	8	4.2	11	5.9	7	3.9
Hot flushes	6	3.1	11	5.9	7	3.9
Viral Infection	7	3.6	11	5.9	5	2.8
Coughing	11	5.7	7	3.8	9	5.1
Chest Pain	3	1.6	10	5.4	5	2.8
Fatigue	10	5.2	8	4.3	6	3.4
Insomnia	10	5.2	1	0.5	7	3.9
Anorexia	8	4.2	7	3.8	9	5.1

Table AR/BC3-S3: Adverse Experiences Reported in > 3% of Study Population

Adverse Experience	Letrozole 0.5 (N = 192)		Letrozole 2.5 (N = 185)		Aminoglutethimide (N = 178)	
	N	%	N	%	N	%
Rash	2	1.0	5	2.7	20	11.2
Nausea	14	7.3	19	10.3	17	9.6
Somnolence	5	2.6	6	3.2	13	7.3
Vomiting	7	3.6	7	3.8	10	5.6
Hypercholesterolemia	7	3.6	5	2.7	9	5.1
Hot Flushes	5	2.6	9	4.9	6	3.4
Abdominal Pain	3	1.6	1	0.5	8	4.5
Hypertension	2	1.0	0	0.0	7	3.9
Asthenia	7	3.6	3	1.6	4	2.2
Dyspepsia	3	1.6	2	1.1	6	3.4
Fatigue	5	2.6	6	3.2	5	2.8
Headache	6	3.1	2	1.1	5	2.8
Dizziness	6	3.1	2	1.1	4	2.2

Some of the adverse events observed in the trial in 1 - 3% of patients and considered to be related to study drug are reported in the following table (which comes from Exhibit 9.1.2.-3 in the Submission).

The following adverse events related to study drug occurred more frequently on the letrozole arms: constipation, alopecia, conjunctivitis, vertigo, and arthralgia. The following adverse events were reported more than three times as frequently on the aminoglutethimide arm as on either letrozole arm: rash, hypertension, increased gamma-GT, abdominal pain, dyspepsia, pruritus, and abnormal vision. The type of adverse events reported in this study are similar to those reported in the literature for aminoglutethimide.

Differences in the frequency of adverse events related to study treatment on each arm were analyzed by age (≤ age 55, 56 - 69, and ≥ age 70. On the letrozole 0.5 mg arm dizziness, somnolence and fatigue were reported only in patients > age 55. Thirteen of fourteen patients who reported nausea were > age 55. No difference in vomiting, hypercholesterolemia, asthenia, headache, and hot flushes were noted. On the letrozole 2.5 mg no increase in the commonly reported AEs was noted in patients ≥ age 70. No vomiting was reported in patients greater than age 70. Hot flushes, somnolence, and fatigue occurred equally in all age groups. Nineteen

patients reported nausea with four of the nineteen ≥ age 70. On the aminoglutethimide arm

Table AR/BC3 - S3: Adverse Experiences Related to the Study Drugs in 1-3% of the Patients

Adverse Event	Letrozole 0.5		Letrozole 2.5		Aminoglutethimide	
	N	%	N	%	N	%
Increased Weight	2	1.0	2	1.1	5	2.8
Constipation	1	0.5	5	2.7	0	0.0
Diarrhea	4	2.1	3	1.6	4	2.2
Anorexia	2	1.0	4	2.2	3	1.7
Peripheral edema	3	1.6	2	1.1	4	2.2
Pruritus	2	1.0	1	0.5	3	1.7
Abnormal vision	1	0.5	1	0.5	3	1.7
Increased gamma-GT	1	0.5	0	0.0	3	1.7
Increased Appetite	2	1.0	2	1.1	2	1.1
Musculoskeletal Pain	1	0.5	2	1.1	2	1.1
Increased Sweating	1	0.5	2	1.1	1	0.6
Alopecia	0	0.0	2	1.1	1	0.6
Dyspnea	1	0.5	0	0.0	2	1.1
Conjunctivitis	0	0.0	2	1.1	0	0.0
Insomnia	0	0.0	0	0.0	2	1.1
Vertigo	0	0.0	2	1.1	0	0.0
Flatulence	0	0.0	0	0.0	2	1.1
Arthralgia	2	1.0	0	0.0	0	0.0

adverse events were more common in patients ≥ 56 years of age. Nausea, vomiting, somnolence, and hypertension were reported only in patients ≥ age 56. Only one of the twenty reports of rash associated with AG occurred in a patient ≤ age 55.

Duration of Exposure to Treatment and Adverse Reactions

Nausea was the mostly commonly reported adverse event in the first month of study, with 8.9% of the patients in the letrozole 0.5 mg arm, 10.5% of the patients on the letrozole 2.5 mg arm, and 10.8% of the patients on the aminoglutethimide arm. In the second month of study the incidence of nausea was about one-fourth that reported in the first month for each treatment arm. Musculoskeletal pain was reported in the first month by 11.5% of the patients on the letrozole

0.5 mg arm, 8.6% of the patients on the letrozole 2.5 mg arm, but in only 2.3% of the patients on aminoglutethimide arm. On the AG arm besides nausea the most common adverse events during the first month of therapy were rash occurring in 10.1% of patients and somnolence in 6.2% of patients. These adverse events occurred much less frequently in the second month of study: nausea - 3.0%, rash - 1.8%, and somnolence - 2.4%. Few patients reported new adverse events after six months on study. Many of the reported AEs were probably related to the underlying disease process rather than to treatment.

Premature Discontinuations due to Serious Adverse Events

Twenty-one serious adverse events were reported for 18/192 (9.4%) patients on the letrozole 0.5 mg arm, twenty-nine serious adverse reactions were reported for 27/185 (14.6%) patients on the letrozole 2.5 mg arm, and twenty-eight serious adverse events were reported for 19/179 (10.7%) patients on the aminoglutethimide arm. Nine patients reported more than one serious adverse reaction: three patients on the letrozole 0.5 mg arm each reported two serious adverse reactions; one patient of the letrozole 2.5 mg arm reported three serious adverse reactions; on the AG arm two patients reported two serious adverse drug reaction; two patients reported three serious adverse events; and, one patient reported four serious adverse events. No statistically significant difference was found between the incidence of serious adverse reactions on the three treatment arms. Study discontinuations occurred in 6/193 (3.1%) patients on the letrozole 0.5 mg arm, in 7/185 (3.8%) patients on the letrozole 2.5 mg arm, and in 7/178 (3.9%) patients on the aminoglutethimide arm (Table AR/BC3-S6). Four patients on the letrozole 0.5 arm, reportedly removed from study for AEs, were judged on review to have been removed from study for disease progression headache due to frontal bone metastasis; treatment discontinued for progression; jaundice due to choledocholithiases, treatment continued;: hypoadrenalism due to metastatic disease in the hypophyseal stalk. cardiomyopathy which was diagnosed two days prior to progression which resulted in study removal) followed by CHF two-three days later). Four patients were added based on information in the study report On the letrozole 2.5 mg arm the following patients which the sponsor included in the list of study discontinuations due to SAEs were not removed from study due to the SAE according to the clinical narratives. was withdrawn due to "progression of metastatic disease"; did not have study drug discontinued at time of episode of probable septic shock; Adverse event of nausea and vomiting was due to cerebellar metastases (disease progression) for which study med was discontinued. Four patients treated with letrozole 2.5 mg were discovered on review to have been discontinued for adverse events On the aminoglutethimide arm patient was not, as noted in the Ciba study report, discontinued for cervical pain and patient was removed for disease progression. On the aminoglutethimide arm, after review of the CRFs and narratives, the following additional patients were judged to be discontinued due to a serious adverse event.

Table AR/BC3-S6. Study Discontinuation Due to Serious Adverse Events

Treatment	Patient No.	Type of Serious Adverse Reaction	Relationship to Study Drug
L 0.5		Death due to shock s/p talc sclerosis with sepsis	No
		Severe bony pain	No
		Conjunctival irritation, fatigue, mucositis - Drug Allergy	Yes
		DVT	Probable
		Increased bone pain	No
		Fx. Left Clavicle	No
L 2.5		Advanced Colon Cancer diagnosed	No
		Hypercalcemia, without documented progression w/in six wks of entry	No
		Death due to acute pulmonary edema	No
		Death, Cause Unknown	Unlikely
		Quadriplegia	No
		CVA	Possible
		Hypercalcemia	Possible
AG		Disease Progression	No
		Erythematous Rash due to study drug	Yes
		Erythematous rash	Yes
		Gastric carcinoma	No
		Acute Renal Failure	Yes
		Rash	Yes
		Stupor, Coma, Death -Cause not documented	No

Review of Table AR/BC3-S6 indicates that most study discontinuations for serious adverse events were not related to study treatment. Case report forms were submitted for twenty-three patients who discontinued study due to an adverse event or who died within six weeks of removal from study. CRFs for the four patients on the letrozole 0.5 mg arm

the nine patients on the letrozole 2.5 mg arm

and for the nine patients on the aminoglutethimide arm

were reviewed. Appendix V lists the reason for the inclusion of the CRF in the submission. No case report forms were submitted for patients

but short clinical narratives which describe the SAE(s) in these patients were included in the study report (Sec. 9.3). Again no deaths and very few SAEs were related to study drug.

Ninety-seven serious adverse events were described in narratives in the study report. The narratives were evaluated for potential relationship to study drug. Table AR/BC3-S7 summaries the serious adverse events described in the narratives. The number in parenthesis indicates those SAEs which *may be related to drug treatment in the FDA reviewer's opinion even though not identified as such by the sponsor.* Three patients developed DVT's soon after study drug therapy was initiated and one was removed from study due to this adverse event. For the three patients with CVAs relationship to study drug is possible. The retinal artery occlusion occurred within six weeks of initiation of study drug. Hypertension appears to have been worsened by use of study drug in three patients Postural hypotension was observed in one patient on AG. Simple partial seizure in one patient occurred after initiation of study drug and are possibly related to treatment. Five patients on the aminoglutethimide arm developed rash related to study drug and in two patients the persistence of the rash resulted in removed from study Two patients on the letrozole 0.5 mg arm and one patient on the aminoglutethimide arm had severe fatigue with a flu-like syndrome. Patient on the L- 0.5 arm complained of fatigue developed conjunctivitis and mucositis, which appeared to be an allergic reaction to letrozole, and was removed from study. Patient on the aminoglutethimide arm developed nausea, vomiting and diarrhea related to initiation of study drug. These adverse events resolved within two - three days and the patient remained on study. Hypercalcemia in one patient on the letrozole 2.5 mg arm may have been related to "tumor flare" associated with the use of the study drug treatment. The majority of serious adverse events reported in this study were not related to drug, but were related to estrogen deprivation, underlying disease process (breast cancer), or intercurrent illness in an relatively elderly population.

Table AR-BC3 - S7: Serious Adverse Events Included in Study Report Narratives

Serious Adverse Events	Letrozole 0.5	Letrozole 2.5	Aminoglutethimide
Cardiovascular			
Deep Venous Thrombosis	2 (2)	1 (1)	1
CVA	1 (1)	2	
Sinus Bradycardia	1		
Retinal Artery Occlusion	1 (1)		
Uncontrolled Hypertension	1 (1)	2 (2)	
Heart Failure	1		
Near Syncope		1	
A-V Block		1	
Angina / Chest Pain of Cardiac Origin			2
Postural Hypotension			1 (1)
Pulmonary			
Cough with Chest Pain		1	
Pulmonary Edema, Acute, ? Etiology		1	
Asthma / Status Asthmaticus		1	1
Pneumothorax			1