TRASTUZUMAB-RELATED CARDIOTOXICITY

RISK FACTORS:

Baseline left ventricular ejection fraction (LVEF) less than 55%; post-AC (doxorubicin-cyclophosphamide) LVEF less than55%; age greater than 50, and hypertension.
Reference: Tan-Chiu E, et al. *J Clin Oncol* 2005;23:7811 - 9.

POSTULATED MECHANISM OF CARDIOTOXICITY

The exact mechanism of trastuzumab-induced cardiotoxicity is unknown. Animal data indicates that unlike anthracyclines trastuzumab does not cause structural damage. HER2 (also called erbB2) can heterodimerise with erbB3 and erbB4 and form a receptor for neuregulins. Neuregulin signaling in the heart leads to protein synthesis, stabilization of contractile proteins, and promotes cell survival by inhibiting apoptosis. It is postulated that by inhibiting HER2 these benefits are lost and thus induces a toxic cardiomyopathy. This theory is supported by the fact that LVEF recovers upon trastuzumab discontinuation and treatment with CHF medications (including ACE-inhibitors and beta-blockers).
References: Ewer MS, et al. *J Clin Oncol* 2005;23:7820 - 6; Guarneri V, et al. *J Clin Oncol* 2006;24:4107 - 15; Schneider JW, *Semin Oncol* 2001;28(5 Suppl 16):18 - 26.

CLINICAL TRIAL DATA

Trastuzumab therapy has been shown to result in the development of ventricular dysfunction and congestive heart failure (CHF) in several trials including the NSABP B-31 trial and the HERA trial.

TABLE 1: CARDIOTOXICITY IN NSABP B-31 AND HERA TRIALS

	NSABP 31 (at 3 years)		HERA	
Incidence of cardiac events	4.1%	0.8%	NR	NR
Asymptomatic decrease in LVEF	NR	NR	7.08%	2.21%
CHF symptoms	NR	NR	1.73%	0.06

References: Tan-Chiu E, et al. *J Clin Oncol* 2005;23:7811 - 9; Piccart-Gebhart MJ, et al. *N Engl J Med* 2005;353:1659 - 72.

The NSABP B-31 trial compared AC followed by trastuzumab to AC with weekly trastuzumab therapy. Among the evaluable trastuzumab-treated patients, the cumulative incidence of cardiac events at three years was 4.1% compared to 0.8% in the control arm. Trastuzumab was permanently discontinued in 28% patients due to asymptomatic decrease in LVEF (14%), CHF symptoms (4%), adverse events (2%), patient withdrawal (4%), or other reasons (3%). Left ventricular function should be evaluated in all patients prior to and during treatment with trastuzumab (see table 2 for current NSABP B-31 dose modification recommendations).
Reference: Tan-Chiu E, et al. *J Clin Oncol* 2005;23:7811 - 9.

The HERA trial compared three groups: women who had observation alone; those treated with trastuzumab, given as adjuvant treatment (at a dose of 8 mg per kilogram of body weight intravenously once, then at a dose of 6 mg per kilogram every three weeks) for two years; and those treated with trastuzumab at the same dose and on the same schedule for one year. Nine patients (0.54%) receiving trastuzumab developed severe congestive heart failure compared to none in the observation arm. Confirmed significant reductions in LVEF occurred in 7.08% trastuzumab treated patients compared to 2.21% in the observation arm.
Reference: Piccart-Gebhart MJ, et al. *N Engl J Med* 2005;353:1659 - 72.

TABLE 2: CURRENT NSABP B-31 DOSE MODIFICATION RECOMMENDATIONS

Relationship of LVEF to LLN	Asymptomatic decrease in LVEF from baseline		
	↓ of less than 10%	↓ of 10-15%	↓ of greater than 16%
Within Normal	Continue T	Continue	Hold[a]
1-5% below LLN	Continue T	Hold[a]	Hold[a]
≥ 6% below LLN	Continue T and repeat MUGA after 4 weeks	Hold[a]	Hold[a]

T=trastuzumab; LLN=lower limit of normal.
[a]Repeat LVEF assessment after 4 weeks. If criteria for continuation were met, trastuzumab was resumed. If 2 consecutive holds or total of 3 holds occurred, trastuzumab was discontinued.
Reference: Tan-Chiu E, et al. *J Clin Oncol* 2005;23:7811 - 9.

REVERSIBILITY OF CARDIOMYOPATHY

Thirty-eight patients with HER2/neu-positive breast cancer treated with trastuzumab were evaluated for cardiomyopathy over a course of 4 years. All patients had received prior chemotherapy (100% treated with anthracycline, 92% with cyclophosphamide, and 71% with a taxane). Patient's left ventricular ejection fractions (LVEF) were evaluated prior to administration of trastuzumab, upon treatment with trastuzumab, and after discontinuation. 37 patients discontinued treatment with trastuzumab due to development of CHF symptoms or LV dysfunction.

Table 3 - Mean LVEF in Relation to Treatment with Trastuzumab:

Prior to Trastuzumab	During treatment (@ 4.5 months - median)	Upon Recovery	Time to LVEF Recovery
0.61 +/- 0.13	0.43 +/- 0.16	0.55 +/- 0.11	1.5 months

Twenty patients experienced symptomatic CHF, but showed LVEF recovery and symptomatic improvement upon trastuzumab discontinuation. Thirty-two patients were treated with standard CHF medications and 6 were observed (based treating physician discretion). 25 patients that were treated with CHF medications were re-introduced to trastuzumab (while on ACE-I and Beta-blockers). Twenty-two patients tolerated re-treatment without recurrence of CHF symptoms.
Reference: Ewer MS, et al. *J Clin Oncol* 2005;23:7820 - 6.

CLINICAL MONITORING

Patients typically obtain evaluation of LVEF with either MUGA or echocardiogram at baseline, after completion of AC (prior to trastuzumab) and then every 3 months during the first year of therapy. Thereafter, monitoring occurs every 6 months for 5 years and then annually while on therapy or as clinically indicated.

References: Tan-Chiu E, et al. *J Clin Oncol* 2005;23:7811 - 9; Piccart-Gebhart MJ, et al. *N Engl J Med* 2005;353:1659 - 72; Romond E, et al. *N Engl J Med* 2005;353:1673 - 84.