

Trastuzumab for Early Breast Cancer: Current Status and Future Directions

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Abstract: The human epidermal growth factor receptor 2 (HER2) is over-expressed/amplified in up to 25% of breast cancer patients, and this feature is associated with an aggressive phenotype, a high recurrence rate, and reduced survival. Until recently, combination chemotherapy was the most effective and only adjuvant treatment for HER2-positive patients. Trastuzumab, a monoclonal antibody directed against the HER2 extracellular domain, has recently demonstrated highly reproducible and astonishing benefit in halving the recurrence rate and reducing mortality in five adjuvant breast cancer trials. But such unfettered success has come at a cost, both in terms of cardiotoxic risk and substantial financial burden. Though trastuzumab has been able to significantly improve clinical outcomes of many patients with early breast cancer, the reality is that an unacceptable proportion will still relapse. Beyond trastuzumab, what is the next step for these HER2-positive breast cancers? This review first discusses the individual results of the five adjuvant trastuzumab studies in terms of efficacy and safety, highlighting their similarities and differences. It also evaluates the current status of trastuzumab as a result of these studies and explores the possible future direction for HER2-positive breast cancers in light of recent advances in translational oncology.

Breast cancer is the most common cancer in women in the Western world and is essentially incurable when distant metastases are detected. Although the mortality rate due to breast cancer is decreasing with improvements in screening programs, adjuvant systemic therapy, and advances in locoregional control, approximately half of diagnosed patients eventually develop metastatic disease. In the United States, an estimated 40,000 women are predicted to die from breast cancer in 2007.¹

Up to 25% of women with early breast cancer have tumors that are human epidermal growth factor receptor 2 (HER2)-positive, associated with an aggressive phenotype, higher recurrence rate, and reduced survival.^{2,3} In these patients with poorer prognosis, combination chemotherapy was until recently the only treatment modality available.

Trastuzumab (Herceptin, Genentech), a monoclonal antibody directed against the extracellular domain of HER2 with proven benefit in

Keywords

Early breast cancer; trastuzumab; adjuvant therapy.

Table 1. Methods of HER2 Screening in Adjuvant Trials of Trastuzumab

	HERA ^{4,14}	B31 / N9831 ⁵	BCIRG 006 ^{6,15}	FinHer ⁷
Local laboratory	<ul style="list-style-type: none"> • IHC / FISH • 2+ / 3+ or FISH+ sent to reference lab 	<ul style="list-style-type: none"> • IHC / FISH • 3+ or FISH+ sent to reference lab 	No role	<ul style="list-style-type: none"> • IHC (any) • 2+ / 3+ sent to reference lab
Reference laboratory	<ul style="list-style-type: none"> • IHC for 3+ • FISH for 2+ • Repeat FISH for FISH+ 	<ul style="list-style-type: none"> • IHC for 3+ • FISH for 2+ 	FISH for all samples	CISH for all samples

CISH=chromogenic in situ hybridization; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry.

metastatic breast cancer, has recently been tested in HER2-positive patients with early breast cancer. In 2005, five adjuvant studies using trastuzumab demonstrated highly reproducible and astonishing benefit in halving the recurrence rate and reducing mortality.⁴⁻⁷ This degree of benefit in early breast cancer is the largest reported since the introduction of tamoxifen in hormone receptor-positive disease, and heralds a new and exciting era for molecularly targeted therapy.

In this review we discuss the individual results of the five adjuvant trastuzumab studies in terms of efficacy and safety, highlighting their similarities and differences. We also examine the clinical implications and challenges that have emerged with these results, especially for the clinician, the scientist, and healthcare authorities.

History of Trastuzumab

The *HER2/neu* gene, which encodes for a 185-kd transmembrane glycoprotein receptor involved in regulating cell proliferation, differentiation, and survival, was first identified in 1984.^{2,3} Normally only two copies of the *HER2/neu* gene encoding up to 24,000 HER2 proteins are present, but in overexpressed cells as many as 50–100 gene copies and 2 million HER2 proteins can be detected.⁸ This HER2 overexpression is found both in the primary tumor and metastatic sites.⁹

In 1986, trastuzumab was developed and was shown to inhibit neu-transformed cells.¹⁰ In 1987, Slamon and colleagues^{2,3} demonstrated a correlation between *HER2/neu* amplification and an aggressive clinical course with short disease-free intervals and reduced overall survival (OS). In 1998, trastuzumab was approved by the US Food and Drug Administration (FDA) for the treatment of metastatic breast cancer in combination with chemotherapy after demonstration of a significant survival benefit.¹¹⁻¹³

Encouraged by the results in the metastatic setting, four major international studies of adjuvant trastuzumab with a planned enrollment of over 13,000 women were launched in 2000–2001: the HERCEPTIN Adjuvant

(HERA) trial,⁴ the combined North American trials National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 and North Central Cancer Treatment Group (NCCTG) N9831,⁵ and the Breast Cancer International Research Group (BCIRG) 006 trial.⁶ In 2005, the initial results of these four trials, alongside a smaller Finnish trial, FinHer,⁷ were released, showing significant benefit with trastuzumab in reducing disease recurrence and mortality.

The Five Adjuvant Trials

In all these trials, HER2-positive patients (immunohistochemistry [IHC] 3+/fluorescence in situ hybridization [FISH]-positive for all except FinHer, which used chromogenic in situ hybridization [CISH]; Table 1) with invasive breast cancer were enrolled after lumpectomy or mastectomy. Patients could have node-positive (all trials) or high-risk node-negative (HERA, N9831, BCIRG 006, FinHer) disease but no locally advanced or distant disease. All patients were to receive adjuvant chemotherapy and appropriate radiotherapy and hormonal therapy. Cardiac eligibility criteria (Table 2) varied slightly, as did the timing of cardiac monitoring, between the trials: HERA patients were required to have a left ventricular ejection fraction (LVEF) above 55% after completion of all chemotherapy and radiotherapy, whereas in B31 and N9831, an LVEF above 50% after anthracycline chemotherapy was required. In the BCIRG 006 trial, LVEF needed to be above 50% after surgery. The designs of the five trials differed mainly in chemotherapy regimens and timing of trastuzumab administration (Table 3).

The HERA Trial

HERA,⁴ an international, multicenter, randomized, open-label trial, was the largest of the studies and compared 1 or 2 years of trastuzumab given every 3 weeks with observation (no trastuzumab) in patients with HER2-positive early breast cancer. Patients had either node-positive or -negative disease and completed locoregional therapy and

Table 2. Cardiac Monitoring

	HERA ^{4,14}	B31 / N9831 ⁵	BCIRG 006 ^{6,15}	FinHer ⁷
Lower-limit LVEF	55%	50%	Above that set by institution	Neither inclusion nor exclusion criteria
LVEF method	ECHO / MUGA	MUGA / ECHO	MUGA	MUGA / ECHO
Cardiotoxicity independently reviewed	Yes	Yes	Yes	Yes
Primary endpoint NYHA 3-4 CHF	Yes	Yes	Yes	No

CHF=congestive heart failure; ECHO=echocardiogram; LVEF=left ventricle ejection fraction; MUGA=multiple gated acquisition scan; NYHA=New York Heart Association.

a minimum of four courses of adjuvant chemotherapy (89%), neoadjuvant chemotherapy (5%), or both (6%) before study entry. The design of the trial was pragmatic in that it was set up to explore the potential benefit of trastuzumab given after, and independent of the type of, chemotherapy.

The primary endpoint of HERA was disease-free survival (DFS), defined as time from randomization to the occurrence of any of the following events: local/regional/distant recurrence, contralateral breast cancer including ductal carcinoma in situ, secondary nonbreast malignancy, or death without evidence of recurrence. The secondary endpoints included cardiac safety, OS, and time to distant recurrence.

The first results published compared 1 year of trastuzumab to observation, with a median follow-up of 1 year.⁴ Of the 5,090 patients enrolled, data were available for 3,387: 1,694 in the 1-year trastuzumab arm and 1,693 in the observation arm. Of these patients, the median age was 49 years, one third had node-negative disease, and nearly 50% were hormone receptor (estrogen and progesterone)-negative. Patients who were treated with trastuzumab for 1 year experienced a 46% lower risk of a first event (hazard ratio [HR] 0.54; 95% confidence interval [CI], 0.43–0.67; $P<.0001$), corresponding to an absolute DFS benefit of 8.4% at 2 years (95% CI, 2.1–14.8).

In a recently published update after a median follow-up of 23.5 months,¹⁴ 97 patients (5.7%) randomized to observation alone and 58 patients (3.4%) randomized to 1 year of trastuzumab were lost to follow-up. It was noted that 172 women had stopped trastuzumab prematurely, with 59 deaths reported for trastuzumab and 90 for the observation arm. The unadjusted HR for the risk of death with trastuzumab compared with observation was 0.66 (95% CI, 0.47–0.91; $P=.0115$), corresponding to an absolute OS benefit of 2.7%. Two hundred eighteen DFS events were reported with trastuzumab compared to 321

with observation. The unadjusted HR for the risk of an event with trastuzumab was 0.64 (95% CI, 0.54–0.76; $P<.0001$), corresponding to an absolute DFS benefit of 6.3%.

Overall, 7% of patients treated with trastuzumab experienced one or more serious adverse events, compared to 4.7% with observation (Table 4). In terms of cardiac safety (Table 5), LVEF was monitored at baseline and 3, 6, 12, 18, 24, 30, 36, and 60 months after randomization. Severe congestive heart failure (CHF; New York Heart Association [NYHA] class III/IV) occurred in 0.6% of patients treated with trastuzumab. Symptomatic CHF occurred in 1.7% and 0.06% of patients in the trastuzumab and observation arms, respectively. Fifty-one patients experienced a confirmed LVEF decrease (defined as an ejection fraction decrease of >10 points from baseline to an LVEF <50%) with trastuzumab, which recovered or stabilized within 3–6 weeks of initial treatment in 86% of cases.

Combined Analysis of the NSABP B31 and NCCTG/N9831 Trials

The NSABP B31 trial compared 4 cycles of doxorubicin and cyclophosphamide followed by four 21-day cycles of paclitaxel (arm 1) with the same regimen plus 52 weeks of trastuzumab, beginning with the first cycle of paclitaxel (arm 2). The NCCTG/N9831 trial randomized patients to one of three regimens: 4 cycles of doxorubicin and cyclophosphamide followed by 12 cycles of weekly paclitaxel (arm A), the same regimen followed by 52 weekly doses of trastuzumab (arm B), or the same regimen as arm A plus 52 weekly doses of trastuzumab initiated concomitantly with paclitaxel (arm C).

Because arms 1 and 2 of B31 and arms A and C of N9831 were similar, the National Cancer Institute and the FDA approved a joint analysis with exclusion of arm B of the N9831 trial. The primary endpoint was

Table 3. Trial Designs and Patient Characteristics

	HERA ^{4,14}	B31 / N9831 ⁵	BCIRG 006 ^{6,15}	FinHer ⁷
Accrual/patients included	5,102 / 3,401	2,043 / 1,736 2,766 / 1,615	3,222 / 3,222	232 / 232
Median follow-up (months)	23.5	24	36	36
Treatment regimens	1-yr H vs Obs after any CT regimen completed (2-yr H not included in analysis)	AC × 4 → P × 4 AC × 4 → P × 4 + H P given 3-weekly AC × 4 → P × 12 AC × 4 → P × 12 + H P given weekly • starting concurrently with P (AC × 4 → P × 12 + H starting after P not included in analysis)	AC × 4 → D × 4 AC × 4 → D × 4 + H • starting concurrently with D DCb × 6 + H D given 3 weekly	V weekly × 8 or D 3 weekly × 3 with or without H weekly × 9 concurrently → then FEC 3 weekly × 3
Trastuzumab schedule	Every 3 weeks	Weekly / weekly	Weekly with CT, then every 3 weeks	Weekly
Primary endpoints	DFS	OS / DFS (DFS for combined analyses)	DFS	RFS
HER2 testing	Centralized IHC ± FISH	IHC a/o FISH in “approved” laboratories	Centralized FISH	Centralized CISH
Age < 50 years, %	51	51	52	NA
Node-negative disease, %	32*	5.7	29 [†]	16 [‡]
Grade 3 tumors, %	60	69	NA	65
Taxane-based chemotherapy, %	26	100	100	50
Planned endocrine therapy, %	46	52	54	NA
Normal cardiac function	At completion of locoregional therapy and chemotherapy	At completion of AC × 4	After surgery	After surgery
Participating countries, n	39	1	40	1

A=adriamycin; CISH=chromogenic in situ hybridization; C=cyclophosphamide; Cb=carboplatin; CT=chemotherapy; D=docetaxel; DFS=disease-free survival; E=epidriamycin; F=5-fluorouracil; FISH=fluorescence in situ hybridization; H=trastuzumab; HR=hazard ratio; IHC=immunohistochemistry; NA=not available; OS=overall survival; P=paclitaxel; RFS=recurrence-free survival; V=vinorelbine.

*Only if tumor size > 1 cm. [†]Only if other concomitant risk factors (grade > 1, hormone receptors negative).

[‡]Only if size > 20 mm and PgR negative.

DFS and secondary endpoints included OS and time to distant recurrence.

At the first planned interim analysis after a median follow-up of 2 years (March 2005; Table 4), 394 events (recurrence, second primary cancer, or death without recurrence) were reported in 3,351 patients. Patients

treated with trastuzumab experienced longer DFS with a 52% lower risk of a DFS event (HR 0.48; 95% CI, 0.39–0.59; $P < .0001$), corresponding to an absolute difference in DFS of 11.8% at 3 years and 18% at 4 years. The risk of distant recurrence was 53% lower (HR 0.47; 95% CI, 0.37–0.61; $P < .00001$) in patients treated with

Table 4. Trastuzumab Efficacy Results of All Adjuvant Trials

	HERA ¹⁴		B31 / N9831 ⁵		BCIRG 006 ¹⁵			FinHer ⁷	
Regimens	Observe	1-yr H	Control	1- yr H	AC-D	AC-DH	DCbH	Control	H 9-wk
Patients, n	1,698	1,703	1,679	1,672	1,073	1,074	1,075	115	116
Events* for DFS									
Patients* with events	321	218	261	133	192	128	142	27	12
Distant events	233	152	193	96	143	93	98	26	8
Events for OS	90	59	92	62	80	49	56	14	6
HR for DFS		0.64		0.48		0.61	0.67		0.42
95% CI		0.54–0.76		0.39–0.59		0.48–0.76	0.54–0.83		0.21–0.83
P value		<.0001		<.0001		<.0001	.0003		.00078
HR for OS		0.66		0.67		0.59	0.66		0.41
95% CI		0.47–0.91		0.48–0.93		0.42–0.85	0.47–0.93		0.47–1.08
P value		.0115		.015		.004	.0017		.07
Median follow-up	23.5 months		2 years		36 months			36 months	

A=doxorubicin; C=cyclophosphamide; Cb=carboplatin; CI=confidence interval; D=docetaxel; DFS=disease-free survival; H=trastuzumab; HR=hazard ratio; NA=not available; OS=overall survival;

*Defined in all trials as breast cancer relapses, second malignancies, deaths; the FinHer trial used recurrence-free survival instead.

trastuzumab, and the risk of death was 33% lower (HR 0.67; 95% CI, 0.48–0.93; *P*=.015).⁵ Interestingly, an unplanned analysis of arms B and C of N9831 showed a 36% relative decrease in recurrence when trastuzumab was begun concurrently with paclitaxel; however, this result should be interpreted cautiously given the premature data from which it was derived. In terms of overall safety, the combined analysis showed little difference between treatment groups in the incidence of any adverse events. However, rare cases of interstitial pneumonitis were reported (4 in NSABP B31; 5 in N9831). In terms of cardiac toxicity (Table 5), LVEF was evaluated at baseline and 3, 6, and 9 months after randomization. In the NSABP B31 trial, 31 of 850 patients in the trastuzumab arm had confirmed symptomatic cardiac events, compared with 5 of 814 patients in the control arm. The 3-year cumulative incidence of cardiac events for trastuzumab-treated patients was 4.1% compared with 0.8% for the control patients. Asymptomatic cardiac dysfunction (as per Cardiac Review and Evaluation Committee criteria of >10% decline or to 55%) occurring at least once during the 52 weeks of treatment was 17% with the control group and 34% with the trastuzumab-treated group (HR 2.1; 95% CI, 1.7–2.6; *P*<.0001). In the N9831 trial, 39 cardiac events were reported in the three arms over 3 years. The 3-year cumulative incidence of

cardiac events was 0.35% in arm A, 3.5% in arm B, and 2.5% in arm C.¹⁶

The BCIRG 006 Trial

The BCIRG 006 trial evaluated the benefit of adding trastuzumab to two chemotherapy regimens, one with and one without anthracyclines, with the intention of maximizing efficacy and minimizing cardiotoxicity in both node-negative and -positive patients. The regimens included either four cycles of doxorubicin and cyclophosphamide followed by four cycles of once-every-3-weeks docetaxel (AC-D) as the control arm, four cycles of AC-D combined with 1 year of trastuzumab (AC-DH), or 6 cycles of docetaxel and carboplatin with 1 year of trastuzumab (DCbH).⁶

The primary endpoint was DFS and secondary endpoints included OS, toxicity, and evaluation of pathologic and molecular markers for predicting efficacy in these patients. Results of the first planned protocol-mandated interim analysis were reported after 322 DFS events, 84 deaths with a total recruitment of 3,222 patients (AC-D=1,073, AC-DH=1,074, and DCbH=1,075), and a median follow-up of 23 months. The two trastuzumab-containing arms showed significantly longer DFS compared to AC-D: an HR of 0.49 (95% CI, 0.37–0.65; *P*<.0001) for the AC-DH arm and an HR of 0.61 (95%

Table 5. Trastuzumab Cardiac Safety Results of All Adjuvant Trials

Treatment arms	HERA ¹⁴		NSABP B31 ¹⁵		NCCTG-N9831 ⁵			BCIRG 006 ¹⁵		
	Observe	1-yr H	AC → P	AC → PH	AC → P	AC → PH	AC → P → H	AC → D	DCbH	AC → DH
Women at risk, n	1,708	1,678	814	850	670	579	718	1,050	1,056	1,068
Cardiac deaths, n	1	0	1	0	1	0	1	0	0	0
CHF NYHA Class 3–4, n (%)	2 (0.1)	10 (0.6)	4 (0.8)	31 (4.1)	1 (0.3)	20 (3.5)	16 (2.5)	4 (0.4)	4 (0.4)	20 (1.9)

Note: no CHF class 3–4 and no cardiac death reported in the Finnish trial. Cumulative incidences at 3 years reported in NSABP B31 and NCCTG-N9831.

A=doxorubicin; C=cyclophosphamide; Cb=carboplatin; CHF=congestive heart failure; D=docetaxel; H=trastuzumab; HERA=Herceptin Adjuvant trial; NYHA=New York Heart Association; P=paclitaxel.

CI, 0.47–0.79; $P=.0002$) for the DCbH arm; there was no statistically significant difference between the two trastuzumab-containing arms ($P=.16$).⁶

At the second interim efficacy analysis,¹⁵ with median follow-up of 36 months, there were 462 DFS events and 185 deaths. For DFS, the HR was 0.61 (95% CI, 0.48–0.76; $P<.0001$) for the AC-DH arm and 0.67 (95% CI, 0.54–0.83; $P=.00003$) for the DCbH arm, compared with the AC-D arm. This translated to absolute benefits (from years 2 to 4) of 6% and 5%, respectively. The HR for OS was 0.59 (95% CI, 0.42–0.85; $P=.004$) for AC-DH and 0.66 (95% CI, 0.47–0.93; $P=.017$) for DCbH, over AC-D.

There were significant differences between the arms in the incidence of grade 3/4 nonhematologic adverse events, with DCbH-treated patients having less arthralgia, myalgia, hand-foot syndrome, stomatitis, and vomiting than AC-D-treated patients.¹⁵ In terms of grade 3/4 hematologic adverse events, patients receiving AC-DH had significantly more anemia and thrombocytopenia than those receiving AC-D. Clinically symptomatic cardiac events were detected in 0.38% of patients in the AC-D arm, 1.87% in the AC-DH arm, and 0.37% in the DCbH arm (Table 5). There was also a statistically significant higher incidence of asymptomatic and persistent decreases in LVEF in the AC-DH arm than in either the AC-D or DCbH arms. No cardiac deaths were reported in the BCIRG 006 trial.

The FinHer Trial

Despite enrolling only 232 patients with HER2-positive disease, the FinHer trial has generated quite provocative results. In this trial, 1,010 patients with node-positive or

high-risk node-negative disease were randomized to three cycles of docetaxel (once every 21 days) or 8 weekly cycles of vinorelbine followed by three cycles of 5-fluorouracil, epirubicin, and cyclophosphamide, with the primary aim of comparing treatment using docetaxel or vinorelbine. The subset of HER2-positive patients was further randomized to either receive ($n=116$) or not receive ($n=116$) 9 weeks of trastuzumab, given upfront with the first three cycles of docetaxel or vinorelbine.

The primary endpoint was recurrence-free survival and secondary endpoints included OS, adverse events, cardiac safety, and time to distant recurrence. At a 3-year median follow-up (Table 4) there was a significant reduction in distant recurrence (HR 0.29; 95% CI, 0.13–0.64; $P=.002$), an improved 3-year DFS (HR 0.42; 95% CI, 0.21–0.83; $P=.01$), and a statistically nonsignificant trend toward improved OS (HR 0.41; 95% CI, 0.16–1.08; $P=.07$) favoring the patients treated with trastuzumab. In terms of overall toxicity, there was no significant difference in adverse events with or without trastuzumab. In addition, none of the patients who received trastuzumab in the FinHer trial experienced clinically significant cardiac events. In fact, LVEF was preserved in all of the women receiving trastuzumab (Table 5).

Critical Review of the Five Adjuvant Trials

Trial Designs and Patient Characteristics

Although a total of 13,365 patients were accrued in these trials, a large proportion has not been discussed in the published analyses: 1,694 patients in the 2-year trastuzumab arm of HERA, 842 patients in arm B of N9831 (which was not suitable for direct comparison with the

B31 study), and those still pending follow-up (325 in the combined B31 and N9831 studies and 9 in HERA). A further 152 patients from N9831 were excluded during the temporary closure of the study. In total, data for 10,192 patients has been analyzed thus far.

In terms of patient characteristics, similarities included young age (median age approximately 50 years), a large proportion of high-grade tumors (60–69%), and a high percentage of patients (46–54%) planning endocrine therapy. Conversely, there were notable differences in the percentage of patients with high-risk node-negative disease enrolled in the trials: 32% in HERA (if tumor >1 cm), 29% in BCIRG 006 (if hormone receptor–negative), 5.7% in the combined analysis of B31 and N9831, and 16% in FinHer (if tumor >2 cm and progesterone receptor–negative).

The use of taxanes also differed among the trials, with all patients in BCIRG 006 and the combined US trials (B31 and N9831) receiving taxanes, but only 26% in HERA and 50% in FinHer receiving taxanes. The type of taxanes used also varied, with paclitaxel in B31 and N9831 and docetaxel in BCIRG 006.

Notably, because HERA allowed many types of chemotherapy regimens, its results have far-reaching implications for women with HER2-positive disease worldwide. The BCIRG 006 trial, which compared anthracycline-based to nonanthracycline-based regimens, showed no difference between the two and is provocative in suggesting that the risk of cardiotoxicity may be minimized without compromising efficacy by using trastuzumab with a nonanthracycline such as carboplatin. However, this option of a trastuzumab-based nonanthracycline regimen, although seemingly attractive for the treatment of women with pre-existing cardiac risk factors, should be considered very cautiously because patients with any cardiac disease were excluded from all of the five trials.

The timing of trastuzumab initiation also varied considerably in the five trials. The design of the HERA trial delayed the start of trastuzumab for a median of 8 months after surgery, in contrast to a median of 4 months in the combined B31 and N9831 group and 1 month in the FinHer trial and the platinum-taxane arm of BCIRG 006. Whether the timing of trastuzumab has an impact on overall efficacy is unknown, but the rationale for its early administration concurrent with chemotherapy lies in the hypothesis that there may be the possibility of synergism between certain chemotherapy agents and trastuzumab.^{17,18}

Even the schedule of trastuzumab administration varied between the trials, with the 3-week cycle used in HERA, the weekly cycle used in B31 and N9831, and both cycles used in BCIRG 006. Whether one schedule is better than the other is unknown, but both have been tested in the metastatic setting, with good efficacy.^{19,20}

The FinHer trial was particularly provocative in testing whether a shorter course of trastuzumab treatment could be used. In this trial, trastuzumab was given over 9 weeks as compared with the empirical 52 weeks in the other trials. Although the FinHer results are certainly intriguing, it should be noted that the confidence intervals were wide for efficacy (HR for recurrence 0.42; 95% CI, 0.21–0.83; $P=.001$) and death (HR 0.41; 95% CI, 0.16–1.08; $P=.07$), and the small study population gives limited confidence in safety. Thus, 9 weeks of trastuzumab should not be regarded as the standard of care, but it indeed generates interesting hypotheses for the design of future studies. In the meantime, the 1-year-versus-2-year results from the HERA trial and the PHARE (Protocol of Herceptin Adjuvant with Reduced Exposure) trial evaluating 6 months versus 1 year of trastuzumab in HER2-positive early breast cancer are eagerly awaited.²¹

Efficacy

Despite differences in patient populations and trial designs—including chemotherapeutic regimens, the timing of trastuzumab initiation, and the schedule and duration of trastuzumab administration—highly reproducible and impressive results have been produced across the five trials: 39–52% reductions in recurrence rates and 33–41% reductions in mortality. This degree of benefit in early breast cancer is the largest reported since the introduction of tamoxifen in hormone receptor–positive disease. As promising and astonishing as these results are, the median follow-up times ranged from 23.5 to 38 months and, thus, much longer follow-up will be needed to evaluate whether trastuzumab's effect is maintained over time.

Safety

Hypersensitivity is the most common adverse effect of trastuzumab and usually occurs with the first infusion. Unexpected short-term side effects did not emerge in any of the five trials with the exception of nine cases of interstitial pneumonitis in B31 and N9831, though the relationship to trastuzumab is not clearly defined. Longer follow-up is needed to assess for the emergence of late toxicities, including secondary leukemias.

Cardiotoxicity remains the most important adverse effect of trastuzumab. In studies of metastatic disease, the rates of trastuzumab-induced cardiotoxicity were 3–7% when given alone, 13% when administered with paclitaxel, and 27% when administered with concurrent anthracyclines.²² In a retrospective analysis of seven phase II/III metastatic trials, the risk for cardiotoxicity was increased with greater age and concurrent anthracycline use.²²

It should be noted that in the adjuvant trials, the definitions for cardiac events, schedules for cardiac monitoring, analyses of cardiac endpoints, and follow-up times

differed. Thus, cross-trial comparisons, if done, require reasonable caution.

Even with these variables in mind, it can still be generally concluded that the incidence of cardiac events with trastuzumab in the adjuvant trials was not high, ranging from 0.4% in the BCIRG 006 trial to 4.1% in the B31 trial. Within the control arms of all studies the incidence of cardiac events ranged from 0 to 0.8%.

In looking more closely at the cardiac safety analysis of the NSABP B31 trial,²² the 3-year cumulative incidence of cardiac events was 4.1% (95% CI, 2.9–5.8), corresponding to a difference of 3.3% (95% CI, 1.7–4.9) from the control arm. Asymptomatic drops in LVEF occurred in 11.3% of patients, and two thirds showed a significant improvement in their cardiac function over time. Women with hypertension, borderline LVEF (50–54%), or greater age at entry appeared at higher risk for CHF, but no apparent increase occurred among patients with left-sided lesions receiving radiotherapy. In HERA, risk factors associated with cardiac side effects of trastuzumab were a higher mean cumulative dose of doxorubicin (287±58 mg/m² vs 257±54 mg/m²; *P*<.02) or epirubicin (480±119 mg/m² vs 422±105 mg/m²; *P*<.01), a lower screening LVEF (55–60 vs >60), and a higher body mass index (>25 vs 20–25).²³

The Future

These five adjuvant trials, despite short follow-up, have provided compelling evidence for the use of trastuzumab in patients with early breast cancer. However, even with the unfettered success of these trials, not all patients will respond to trastuzumab. Single-agent trastuzumab produces objective responses in approximately one third of patients only, and when combined with chemotherapy can produce responses up to 72%.^{11,12,24} With low, albeit real, cardiotoxic risks, better selection of patients for trastuzumab therapy should allow us to choose those patients with the best chance of cure, and spare those who are less likely to respond.

The first step in improving selection of HER2-positive patients lies in the accurate and reproducible testing of HER2 status. This is reflected in new guidelines from the American Society of Clinical Oncology and the College of American Pathologists,²⁵ in which a positive result is considered IHC staining of 3+ (with uniform, intense membrane staining of >30% of invasive tumor cells), a FISH result of more than six *HER2* gene copies per nucleus, or a FISH ratio (*HER2* gene signals to chromosome 17 signals) of more than 2.2. A negative result, on the other hand, is an IHC staining of 0 or 1+, a FISH result of less than four *HER2* gene copies per nucleus, or a FISH ratio of less than 1.8. Importantly, equivocal

results must have additional action for final determination. The recommendation for laboratory validation and standardization represents a concerted effort to improve the accuracy of HER2 testing and its utility as a predictive marker, thereby restricting the use of HER2-targeted therapies to the population that would have the greatest benefit-risk ratio.

Indeed, other new promising biomarkers of adjuvant trastuzumab benefit have emerged with progress in translational oncology, and these may serve to define the HER2 patient population into even smaller subgroups, allowing for better tailoring of treatment within the one population.

An example of this is the topoisomerase II alpha (*TOP2A*) gene, which is known to be located in close proximity to the *HER2/neu* oncogene on chromosome 17q12-q21. This gene is deleted or amplified in 40% to nearly 90% of *HER2/neu*-amplified primary breast tumors, and this range may reflect methodologic and cut-point differences between the studies.²⁶ It is believed that amplification and/or deletion of *TOP2A* may account for the relative chemosensitivity and resistance to anthracycline therapy, depending on the specific genetic defect at the locus.²⁷ Indeed, since 2002, there have been at least six published studies demonstrating this association between *TOP2A* amplification and improved anthracycline response.

In the BCIRG 006 trial, *TOP2A* was assessed in protocol-specified subgroup analyses. Although neither the first nor second interim analysis showed a statistically significant relationship between *TOP2A* coamplification and benefit from anthracyclines, it is interesting to note that among the 35% of patients with coamplification, there was no apparent incremental benefit from the addition of trastuzumab.²⁶

Therefore, the predictive value of *TOP2A* for anthracycline response is still undetermined and warrants further evaluation. If this predictive value proves to be true in future studies, the scenario that HER2-positive patients without *TOP2A* coamplification may indeed be better off with nonanthracycline-based regimens with trastuzumab is appealing, due the cardiotoxicity-sparing implications.

Other promising biomarkers potentially predictive of trastuzumab activity have also been examined in studies other than these five adjuvant trials. In the NSABP B28 trial, 27 genetic loci were analyzed for the presence of amplified genes in 1,900 cases of node-positive breast cancer.²⁸ Using multivariate analysis, it was found that *c-myc*, *HER2/neu*, and *HTPAT* amplicons were associated with a poor prognosis. Furthermore, coamplification of *c-myc* and *HER2/neu* was correlated with worse outcome than when *HER2/neu* alone or *c-myc* alone was amplified. Subsequent analysis of NSABP B31 data found *c-myc*

coamplification was indeed present in 30% of patients. These patients had a worse outcome if they were treated with chemotherapy alone but had a 4-year recurrence-free survival rate of 90% if treated with chemotherapy and trastuzumab, suggesting an exquisite sensitivity to trastuzumab and its possible role in turning on the proapoptotic function of deregulated *c-myc*.²⁹

Other new markers with predictive potential are PTEN (phosphatase and tensin homolog) and p95HER2 (a truncated HER2 receptor lacking the external domain). Recent studies with PTEN have demonstrated that resistance to trastuzumab treatment depended on the level of PTEN present^{30,31} and that PTEN was, in fact, lost or reduced in expression in 40% of HER2-overexpressing breast cancers.

With respect to p95HER2, Saez and colleagues³² showed that, in HER2-positive patients, p95HER2 correlates with reduced 5-year DFS (HR 2.55; 95% CI, 2.13–8.01; $P < .0001$) and, with multivariate analysis, demonstrated that p95HER2 overexpression is an independent predictor of recurrence or death from any cause (HR 1.59; 95% CI 1.246–1.990; $P = .0004$). One study found evidence of p95HER2 in approximately 10% of breast cancer samples.³³ Very recently, a study using MCF-7 and T47D breast cancer cells showed that breast tumors that expressed p95HER2 were resistant to trastuzumab and, of 46 patients with metastatic breast cancers who were treated with trastuzumab, only 1 of 9 patients (11.1%) expressing p95HER2 responded to trastuzumab (with a partial response), whereas 51% (19 of 37) of patients with full-length HER2 achieved a response (complete or partial; $P = .029$).³⁴

As exciting as their potential may be, the clinical utility of these new predictive biomarkers needs to be rigorously tested in large, prospective, well-designed, and well-conducted trials before they can be confidently implemented into clinical practice.

Another equally important consideration is cost. The recommendation of 1-year of adjuvant trastuzumab therapy—as a direct result of these trials—by many regulatory authorities has had significant economic implications that must be acknowledged. This financial burden is best illustrated by the cost of drugs and drug administration estimated for each patient within these trials: \$19,750 for FinHer, \$61,064 for HERA, and \$79,417 for the N9831 trial using weekly paclitaxel.

Interestingly, a reanalysis of the HERA trial conducted in the UK showed an absolute reduction in recurrence at 1 year of 5.5% with trastuzumab, and the need to treat 18 patients in order to avoid one recurrence, meaning that 94% of those treated will derive no benefit yet will be exposed to side effects.³⁵ With these numbers in mind, it is important that the forward evolution toward

tailored therapy considers both the human burden (ie, adverse effects, recurrence risk, and mortality) and the financial burden.

This consideration is particularly important because the future direction for HER2-positive breast cancer patients needs to move beyond predictive markers toward the continued development of new anticancer drugs because, even with trastuzumab's success so far, the reality is that not all patients will respond and a fair proportion will eventually die from their disease. Enabled by the advances in molecular oncology and a better understanding of tumor biology, many such new drugs, targeting different levels of the mitogenic signaling pathways, have recently been developed and evaluated.

These drugs have variable but interesting properties, including dual inhibition against epidermal growth factor receptor (EGFR) and HER2 (eg, lapatinib, pertuzumab, HKI-272); antiangiogenesis (eg, bevacizumab, pazopanib); anti-mTOR action (eg, temsirolimus); and heat shock protein 90 inhibition (eg, 17-AAG). Most of these agents are currently being investigated in the metastatic setting either in combination with trastuzumab, in combination with cytotoxic chemotherapy, or as single agents.

Lapatinib (Tykerb, GlaxoSmithKline) deserves special mention because of its potential adjuvant benefit, which is currently being investigated. Lapatinib is a small molecule tyrosine kinase inhibitor capable of dual inhibition of EGFR and HER2. In the metastatic setting, lapatinib caused objective responses in 4.3–7.8% of HER2-positive patients who had progressed on multiple trastuzumab-containing regimens, with a substantial number having stable disease at 4 months (34–41%) and 6 months (18–21%).³⁶

More recently, a phase III trial evaluated the administration of capecitabine (Xeloda, Roche) with or without lapatinib in the treatment of 321 patients with HER2-positive locally advanced or metastatic breast cancer refractory to trastuzumab (study EGF100151).³⁷ The results showed a significant improvement in median time to progression for patients receiving lapatinib and capecitabine compared with patients treated with capecitabine alone (8.4 vs 4.4 months, respectively; $P = .00032$), and suggested that the HER2 receptor remains a viable target even after initial trastuzumab failure.

Whether simultaneous administration of lapatinib and trastuzumab can produce improved outcome has been suggested in preclinical studies, with encouraging but still preliminary results generated in a phase I study of the combination (EGF10023).³⁸ With promising preclinical and metastatic data, the efficacy of lapatinib in HER2-positive patients is now being tested in the adjuvant setting. The ALTO (Adjuvant Lapatinib and Trastuzumab Treatment Optimisation) trial is an international col-

laboration between the Breast International Group and the North Central Cancer Treatment Group evaluating this possible synergistic effect by comparing the efficacy of trastuzumab and lapatinib given alone, sequentially, or in combination. It is a randomized, 4-arm, phase III trial that will enroll 8,000 adjuvant breast cancer patients with HER2-positive disease. Patients will be randomized to receive one of the following treatments: 1) lapatinib for 52 weeks; 2) trastuzumab for 52 weeks; 3) trastuzumab for 12 weeks followed by a washout period of 6 weeks and 34 weeks of lapatinib; or 4) lapatinib in combination with trastuzumab for 52 weeks. This trial aims to improve upon the success of trastuzumab thus far, and started recruiting patients worldwide in mid-2007.³⁹

Conclusion

There is no doubt that adjuvant trastuzumab can impressively reduce the recurrence rate and improve survival in patients with HER2-positive early breast cancer. This observation was demonstrated consistently across the five adjuvant trials, and many countries have now implemented the use of trastuzumab into clinical practice. But where do we go from here?

The year 2005 was particularly successful, with the publication of these results, which certainly have been practice-changing. But the very real cardiotoxic risk and the huge financial burden of such clinical implementation should be equally acknowledged.

Part of the answer perhaps lies within the recent progress made with translational oncology, with the development of new predictive biomarkers enabling better selection of HER2-positive patients who are more likely to respond to treatment. In tailoring the prescription of trastuzumab to well-selected subgroups of the HER2-positive population, both the incidence of cardiotoxicity and the overall healthcare costs may be minimized.

Certainly, the importance of translational and molecular oncology goes far beyond the initial success with trastuzumab. As new molecular targets are increasingly identified and corresponding therapeutics are developed, the ability to select appropriate patient groups will become even more important. Research and healthcare costs must be economically sustainable, and thus with the discovery of new molecular targeted therapies must also emerge the discovery of translational tools that can select those patients who are most likely to derive benefit.

The ALTTO trial is an example of such an effort to evaluate the potential clinical benefit of a new adjuvant drug like lapatinib in relation to an established adjuvant drug like trastuzumab in tandem with translational research that may be able to refine treatment decisions based on an improved knowledge of tumor biology. This shift from the empirical treatment of the whole breast

cancer population to tailored treatment will ultimately minimize unnecessary adverse effects while maximizing clinical benefit at optimal economic cost.

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