

Herceptin (Trastuzumab): Adjuvant and Neoadjuvant Trials

Neora Yaal-Hahoshen MD and Tamar Safra MD

Department of Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
 Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: Herceptin, breast cancer, adjuvant and neoadjuvant chemotherapy

IMAJ 2006;8:416–421

Herceptin® (Hoffman-La Roche, Switzerland), a monoclonal antibody that specifically targets HER2neu, is currently the only approved biological agent for the treatment of HER2-positive metastatic breast cancer. Clinical trials with Herceptin in metastatic disease have shown a clear benefit in the immunohistochemistry of 3+ HER2-positive disease [1,2]. Response rates in patients with 3+ and 2+ HER2 over-expression by immunohistochemistry were 35% and 0%, respectively [3]. In combination with chemotherapy [4,5], Herceptin bestows a longer survival (median survival 25.1 vs. 20.3 months, $P = 0.046$), which translates into a 20% decrease in the risk of death and a significant (25%) improvement in overall survival.

Patients who received Herceptin and chemotherapy as their first-line treatment in metastatic disease gained greater clinical benefits compared with patients who crossed over to Herceptin after progressing on chemotherapy alone [1]. These findings support current evidence suggesting that Herceptin combined with chemotherapy should be used as first-line treatment [1,3]. Herceptin is generally well tolerated [1-5] and patients do not experience the side effects typically associated with chemotherapy, such as alopecia, myelosuppression, nausea and vomiting [1-4]. The most common side effects associated with Herceptin are infrequent mild to moderate infusion-related reaction (2%) and cardiotoxicity (4%). While they are non-desirable, both are manageable with standard treatment, although patients at risk must be identified prior to the initiation of therapy [5].

Based on the higher response rate with Herceptin and chemotherapy combinations in the metastatic setting, and taking into consideration the cardiotoxicity of combinations, several trials have been initiated to explore Herceptin in the adjuvant and neoadjuvant setting. This review will cover the adjuvant trials – four major and some smaller ones in different combinations and schedules – and briefly describe several neoadjuvant trials.

Adjuvant trials

The major trials currently underway are the NSABP (National Surgical Adjuvant Breast and Bowel Project trial B-31), NCCTG (North Cancer Center Therapy Group Inter-group trial N9831), BCIRG (Breast Cancer International Research Group trial 006), HERA (Herceptin Adjuvant Trial), and ECOG (The Eastern Collaborative Group Trial).

E2198 and FACS04 (Belgium and France)

The four large Herceptin adjuvant trials plan to enrol more than 12,000 early breast cancer patients to establish its efficacy and role in the adjuvant setting, its safety profile, and the optimal duration of therapy. They were designed to address a broad range of therapeutic strategies currently used in the adjuvant setting and to investigate the benefit that Herceptin can offer to women with HER2-positive early primary breast cancer. They are attempting to address different issues associated with Herceptin use in this patient population, i.e., its efficacy in positive and/or negative lymph nodes, its use in the adjuvant and neoadjuvant setting, its administration concomitantly or after chemotherapy, and the desired administration duration (i.e., 1 or 2 years, weekly, or every 3 weeks) [Table 1]. Finally, it must be borne in mind that some of the patients in this population can be cured with conventional treatment, such as anthracyclines and cyclophosphamide, alone or in combination with taxanes – Taxol® (Bristol-Myers Squibb, USA) or Taxotere® (Aventis Pharma, USA). Another aspect to remember is that Herceptin is a drug that has some cardiotoxicity, especially after anthracycline combination treatment and chest wall irradiation.

Table 1. Comparison of the four main Herceptin adjuvant trials

Trial	Target accrual	Patient selection	Follow-up phase (yrs)	Primary endpoint	Results interim analysis
NSABP B-31	2700	Node+, IHC3+ or FISH+	15	OS	OS (3 yrs) – HR 0.67 DFS (3 yrs) – HR 0.47
NCCTG/N9831	3300	Node+ and -, IHC3+ or FISH+	15	DFS	Results together with NSABP B-31
BCIRG 006	3150	Node+ and -, FISH+	12–15	DFS	NA
HERA trial	3192 enrolled 5090	Node+ and -, IHC3+ or FISH+	10	DFS	OS (3 yrs) – HR 0.76 DFS (3 yrs) – HR 0.51

NSABP = National Surgical Adjuvant Breast and Bowel Project trial B-31, NCCTG = North Cancer Center Therapy Group Inter-group trial N9831, BCIRG = Breast Cancer International Research Group, HERA = Herceptin Adjuvant Trial IHC = immunohistochemistry, OS = overall survival, DFS = disease-free survival, HR = hazard ratio

The NSABP Trial B-31

The NSABP trial B-31 is investigating the addition of Herceptin to paclitaxel following postoperative administration of adriamycin/cyclophosphamide in node-positive, Her-2neu-positive breast cancer patients. Eligible patients must have normal cardiac function at baseline and no prior history of cardiac disease. The use of adriamycin/cyclophosphamide followed by a taxane is standard treatment for node-positive primary breast cancer, while the role of taxanes in postmenopausal women with positive hormone receptors (estrogen/progesterone) tumors is debatable [unpublished data, San Antonio, USA, 2004]. Recruitment of the expected 2700 women began in March 2000, and the study is now closed.

In patients with axillary lymph node-positive breast cancer who over-express HER-2 (IHC 3+ or FISH amplified at the level of ≥ 2.1), trastuzumab should be incorporated into the adjuvant therapy. Trastuzumab should also be considered for patients with lymph node-negative tumors ≥ 1 cm.

Study objectives. The primary objective of stage I of the study is to compare the cardiotoxicity of four cycles of AC followed by four cycles of Taxol with or without Herceptin in patients who have node-positive breast cancer with over-expressed Her-2 protein. The primary endpoint of stage II of the study is to determine whether the addition of 1 year of weekly Herceptin to AC followed by Taxol with or without Tamoxifen improves overall survival. The secondary endpoint is to determine if the addition of 1 year of Herceptin changes disease-free survival. The study also intends to evaluate the prognostic and predictive value of phosphorylated HER2 receptor, the prognostic and predictive value of shed extracellular domain, concordance between different HER2 assays (i.e., immunohistochemistry versus fluorescent in situ hybridization), changes in HER2-phosphorylated receptor, the extracellular domain levels, and the extent of HER2neu over-expression upon relapse.

Study inclusion criteria. Patients with histologically/cytologically proven invasive adenocarcinoma of the breast with at least one positive axillary node and known hormone receptor sta-

Table 2. Herceptin adjuvant trials: interim safety analyses

Trial	
NSABP	First cardiac safety analysis, October 2001 (n=200)
	Second cardiac safety analysis, November 2002 (n=600)
NCCTG	First analysis, June 2002 (n=1,052)
BCIRG	First cardiac safety analysis, March 2003 (n=300)
	Second cardiac safety analysis, September 2003 (n=900)
	Third cardiac safety analysis, February 2004 (n=1,500)
HERA	First safety analysis, June 2003 (n=300)
	Second safety analysis, September 2003 (n=600)
	Third cardiac safety analysis, November 2003 (n=900)

NSABP = National Surgical Adjuvant Breast and Bowel Project trial B-31, NCCTG = North Cancer Center Therapy Group Inter-group trial N9831, BCIRG = Breast Cancer International Research Group, HERA = Herceptin Adjuvant Trial

tus (estrogen/progesterone receptors) in HER2 over-expressed (immunohistochemistry 3+ or FISH+) would be enrolled.

Study design. Women with operable breast cancer HER2-positive tumor and pathologically positive axillary nodes were randomized into one group receiving AC x4 plus paclitaxel x4 and one group receiving AC x4 plus paclitaxel x4 + Herceptin. Herceptin will be administered according to the usual recommendation: a loading dose of 4 mg/kg in week 1 followed by a maintenance dose of 2 mg/kg weekly (up to 1 year of treatment).

Study analysis. The first interim analysis of the trial (n=1000) was designed to establish the incidence of cardiotoxicity and determine the safety profile of paclitaxel plus Herceptin following AC therapy. Interim safety cardiac analysis was planned following accrual of 100, 300 and 500 patients to each treatment arm. The protocol dictated that if the incidence of cardiotoxicity was within set limits, the trial would proceed to step II, when a further 1700 patients would be recruited for evaluation. Interim efficacy analyses were planned after 96, 192 and 384 events. The main efficacy analysis already took place after the 480th event. The trial was also designed to determine the prognostic and predictive value of phosphorylated HER2 and shed HER2 extracellular domain, and the concordance between immunohistochemistry and FISH for HER2 status determination. An independent Data Monitoring Committee conducts interim safety analyses every 6 months [Table 2]. At the first one, the incidence of adverse events was similar in both arms of the trial: the incidence of grade 2 toxicity was slightly higher in patients who received paclitaxel plus Herceptin compared with patients who received paclitaxel alone (47% vs. 40%, respectively); grade 3 toxicity was similar in both arms (31% vs. 32%) and grade 4 was lower in the paclitaxel plus Herceptin arm compared with the paclitaxel arm (2% vs. 6%, respectively) [6]. Following the first two interim cardiac

NSABP = National Surgical Adjuvant Breast and Bowel Project
AC = adriamycin/cyclophosphamide

FISH = fluorescent in situ hybridization

safety analyses, the committee concluded that the incidence of cardiotoxicity in both arms of the study remains within acceptable limits.

NCCTG Inter-Group Trial N9831

The NCCTG Inter-Group Trial N9831 is investigating the addition of Herceptin to 12 weekly paclitaxel infusions after 4xAC in women with early node-positive and high risk node-negative breast cancer tumor with HER2 over-expression (immunohistochemistry 3+ or FISH positive). The trial plans to recruit 3300 women over a period of 4.5 years.

Objectives. The primary objectives are disease-free survival and cardiotoxicity, and the secondary objectives are overall survival, evaluation of whether HER1 or HER2 levels at baseline are prognostic for disease-free survival and overall survival, and concordance of immunohistochemistry (HercepTest[®]) with FISH (Vysis[™]).

Trastuzumab may be given concurrently with paclitaxel as part of the AC followed by the paclitaxel regimen, or alternatively after the completion of chemotherapy, for 1 year, with cardiac monitoring and on a weekly or 3 weekly schedule

Study design. Taxanes as adjuvant treatment will be given weekly (and not once every 3 weeks). This randomized three-arm trial, led by the NCCTG, proposes to investigate standard doxorubicin (60 mg/m²) plus cyclophosphamide (600 mg/m²) every 3 weeks for four cycles followed by weekly paclitaxel for 12 weeks, weekly paclitaxel for 12 weeks followed by weekly Herceptin for 52 weeks, and weekly paclitaxel plus Herceptin for 12 weeks followed by weekly Herceptin for 40 weeks.

Study analysis. The trial was designed to assess disease-free survival in the three arms with a final follow-up at 15 years. The trial will also enable the incidence of cardiotoxicity to be determined in patients receiving Herceptin immediately following AC therapy compared with those receiving Herceptin following Taxol. The AC followed by paclitaxel plus Herceptin arm of the Inter-group trial was temporarily suspended in January 2002 and restarted following completion of the first interim safety analysis in June 2002 (n=1052). This analysis demonstrated that the rate of congestive heart failure between each treatment arm and the control arm was below the pre-specified limit of 4%. Thus, the Data Monitoring

Committee recommended continuation of accrual to the three original arms. Further cardiac safety analysis was planned to be based on the pre-specified plan when 100, 300 and 500 patients have been followed for 6 months after completion of AC chemotherapy. Safety analyses are based on a three-way comparison between the control versus each investigational treatment, and between the two investigational Herceptin arms. The information that has been collected to date on cardiotoxic events from previous investigations is limited. Unpublished data on a combined analysis of the above two studies, i.e., NSABP B-31 and NCCTG N9831, were presented at the ASCO meeting 2005 (Orlando, Florida, USA). They were based on a median follow-up of 2 years, with disease-free survival as the primary endpoint and overall survival and first distant recurrence as secondary endpoints. The first interim analysis was to take place after 355 disease-free events and the final analysis after 710 events. The results presented in a special session of the ASCO meeting were very impressive [Table 3].

The BCIRG Trial 006

This is a global multicenter randomized phase III trial that is investigating Herceptin in the adjuvant setting in 3150 women (1050 per treatment arm). This study is looking into the use of docetaxel (Taxotere), and not paclitaxel (the drug commonly administered in the U.S.), as well as the inclusion of the very innovative arm that includes docetaxel, platinum and Herceptin (detailed arms will be mentioned later). The protocol consists of weekly Herceptin concurrently with docetaxel for six courses followed every 3 weeks thereafter until 1 year of therapy has been completed. The trial began recruiting patients in March 2001 and is now closed.

Objectives. The primary objective is to compare disease-free survival in each arm. The secondary objectives include comparison of overall survival, cardiotoxicity, safety and quality of life between the three treatment arms.

Table 3. DFS significantly longer among doxorubicin/cyclophosphamide + paclitaxel/trastuzumab patients vs. doxorubicin/cyclophosphamide + paclitaxel patients

3 and 5 year survival (%)	Doxorubicin/cyclophosphamide + paclitaxel/trastuzumab	Doxorubicin/cyclophosphamide + paclitaxel	Hazard ratio (2-sided P value)
NSABP B-31 Trial			
3 yrs	87	74	0.45 (1 x 10 ⁻⁹)
5 yrs	85	66	
NCCTG N9831 Trial			
3 yrs	87	78	0.55 (.0005)
5 yrs	86	68	
NSABP B-31 + NCCTG N9831			
3 yrs	87	75	0.48 (3 x 10 ⁻¹²)
5 yrs	85	67	

NCCTG = North Cancer Center Therapy Group
BCIRG = Breast Cancer International Research Group

Study Inclusion Criteria. The study cohort consists of women with node-positive and high risk node-negative HER2-positive primary breast cancer (tested by FISH in two laboratories, one in North America and one in Europe).

Study Design. The patients were randomized to one of three treatment arms: a) AC x4 every 3 weeks followed by docetaxel x4 every 3 weeks, b) AC x4 followed by docetaxel x4 every 3 weeks (over 21 weeks) plus Herceptin for 1 year, and c) docetaxel plus carboplatin x6 every 3 weeks (over 18 weeks) followed by Herceptin for 1 year. Herceptin was administered on a weekly basis in combination with chemotherapy for 1 year and once every 3 weeks thereafter. The unique docetaxel, carboplatin and Herceptin arm is based on the observed synergies of these chemotherapeutic agents with Herceptin *in vitro* [7,8]. The addition of a platinum analogue to Herceptin in combination with paclitaxel has been shown to improve outcome in patients with metastatic breast cancer [9] and can prevent the associated cardiotoxicity.

Study analysis. Interim and main efficacy analyses were planned to take place after 654 and 1308 events had been observed, respectively. In addition, cardiac safety analyses would be carried out after 100, 300 and 500 patients had been randomized to each treatment arm. A final follow-up at 10 years following recruitment of the last patient is also planned.

Study Inclusion Criteria. The study population consists of women with early breast cancer with positive or negative nodes, HER2 over-expression (immunohistochemistry 3+ or FISH positive), and known hormonal receptor status after acceptable adjuvant chemotherapy

Study Design. Herceptin monotherapy will be investigated for 1 or 2 years in comparison with observation after acceptable adjuvant chemotherapy. The follow-up period will last 10 years starting from the time the last patient is enrolled. Unlike the other studies, acceptable chemotherapy includes a large variety of combinations according to each center's therapeutic protocol, but with some limitations. It is the only adjuvant trial investigating Herceptin treatment administered every 3 weeks (8 mg/kg loading dose followed by 6 mg/kg) from the onset, a schedule that is feasible based on the Herceptin half-life of 28.5 days.

Study Analysis. Also unlike the other three major adjuvant trials, the patients entered into the HERA trial had received one of a number of prior adjuvant anthracycline-based or non-anthracycline-based regimens. Since enrollment of the first patient in December 2001, an interim analysis of cardiac endpoints was planned after the first 300, 600 and 900 patients had been enrolled and treated for 6 months. Interim and final efficacy data analyses are planned after 475 and 951 events. In addition to the main protocol, a cardiac sub-study (n=800) will correlate the presence of natriuretic peptides and pro-inflammatory cytokines with changes in left ventricular ejection fraction and congestive heart failure. Furthermore, a pharmacokinetics substudy (n=60) will investigate and compare the pharmacokinetics of Herceptin administered every 3 weeks for 1 or 2 years.

The unique features of the HERA study are: investigating the role of Herceptin independent of the chemotherapy regimen, evaluating 2 years of Herceptin treatment, and administering the drug at a schedule of every 3 weeks from the start, which is more convenient than once weekly and gives the patient a similar exposure to Herceptin as weekly administration of lower doses.

Unpublished data were presented at the last ASCO meeting (2005) [Table 3]. With a median follow-up of 2 years, the interim analysis results were as follows:

- Trastuzumab given every 3 weeks for 1 year following adjuvant chemotherapy significantly prolongs disease-free survival (hazard ratio = 0.54, $P = 0.0001$) and relapse-free survival (hazard ratio = 0.50, $P = 0.0001$) for women with HER-2-positive early breast cancer
- Trastuzumab therapy is associated with a low incidence of severe symptomatic congestive heart failure; longer follow-up is needed to better quantify this risk
- All patients continue to be followed for long-term safety: patients in the observation arm will be offered trastuzumab (a very unusual procedure)
- Results on optimal trastuzumab duration (1 vs. 2 years) should be available by 2008.

In neoadjuvant chemotherapy trastuzumab should be considered.

The HERA Trial

The HERA Trial is an international (non-USA) randomized three-arm study involving approximately 600 participating centers that is being managed by the Breast International Group and Hoffman-La Roche, Ltd. The recruitment of the anticipated 3192 (1064 per arm) patients has been completed.

Study Objectives. The primary objective is to compare disease-free survival in patients treated with Herceptin for 1 and 2 years compared with patients who receive no drug therapy other than standard chemotherapy during the same period. The secondary objectives are overall survival, relapse-free survival and distant disease-free survival as well as 1 year of Herceptin versus observation compared to 2 years of Herceptin versus observation. The two patient groups will be compared for safety and tolerability and incidence of cardiac dysfunction, and the efficacy and safety will be compared between 1 and 2 years of Herceptin treatment.

HERA = Herceptin Adjuvant Trial

Neoadjuvant Trials

Preoperative chemotherapy is a well-established strategy in the treatment of early breast cancer. Its main purpose is to decrease the need for major surgery (lumpectomy instead of mastectomy), and its benefit for survival has been extensively investigated. Several ongoing trials are investigating the potential role for Herceptin in the neoadjuvant setting, enabling the evaluation of biological as well as clinical endpoints. Using Herceptin in the neoadjuvant setting for patients with HER-2-positive disease could reduce the extent of major surgery even further and provide insight into the biology of HER-2-positive disease. It may also lower the risk of treatment failure and improve survival in women with HER-2-positive disease. Data from initial Herceptin neoadjuvant trials are promising.

The NOAH Trial

The NOAH (NeoAdjuvant Herceptine) randomized trial is investigating doxorubicin plus paclitaxel followed by paclitaxel followed by cyclophosphamide methotrexate 5-FU with or without Herceptin every 3 weeks for 1 year after surgery in women with operable HER-2-positive T1-3, N0-1, M0 breast cancer. The study objectives are to compare pathologic complete response rates in breast and axilla following chemotherapy alone or followed by Herceptin. The endpoints of this trial include clinical response, progression-free survival, overall survival, and safety of the two regimens.

An unscheduled review board met in October 2003 to investigate the impressively high complete pathologic response of 47%. Their findings showed that the pathologic complete response was 25% for the treatment arm of chemotherapy alone. Following that meeting, it was decided to close the trial because of the compelling evidence that showed higher chances of pathologic complete response in the treatment arm of chemotherapy plus Herceptin: the addition of Herceptin to taxane and anthracyclines significantly increased the pathologic complete response rates in patients with HER-2-positive breast cancer. There was no observable clinical cardiac toxicity.

Herceptin and paclitaxel with and without carboplatin [9]

In a phase 3 comparative study patients with HER-2-positive (2+ or 3+ by immunohistochemistry) stage II or III breast cancer received preoperative Herceptin (4 mg/kg x mg/kg/week x 11) in combination with paclitaxel (175 mg/m² every 3 weeks) with or without carboplatinum. The patients then received adjuvant doxorubicin and cyclophosphamide chemotherapy following definitive breast surgery. The clinical and pathologic response rates were determined after preoperative therapy. LVEF and circulating levels of HER-2 extracellular domain were measured serially. Trastuzumab+paclitaxel+carboplatinum was superior to trastuzumab+paclitaxel in terms of response and time to progression, and had acceptable toxicity.

M.D. Anderson Trial – (Dr. A. Budzar [10])

This study on neoadjuvant chemotherapy, comparing chemotherapy

LVEF = left ventricular ejection fraction

Table 4. Adverse events: cardiac safety data

Events	Pac → FEC alone (n=19)	Pac → FEC plus Her (n=23)
Congestive heart failure	0	0
> 10% decrease in LVEF	5	7
Decrease on paclitaxel	0	4
Decrease on FEC	5	3
Improvement in LVEF on follow-up evaluation	2	3
Abnormal troponin T levels	0	1

Pac→FEC = paclitaxel followed by 5FU epirubicin cyclophosphamide

alone with the same chemotherapy combined with Herceptin in operable breast cancer with HER-2-positive disease is the most impressive. The overall complete pathologic response rate was 25% for chemotherapy alone and 66.7% for chemotherapy plus Herceptin. There was no unexpected treatment-related non-cardiac toxicity. Four patients developed grade 2 cardiotoxicity (asymptomatic declines in their LVEF). It should be noted that Herceptin was administered concurrently with paclitaxel and epirubicin, a possible cardiotoxic combination. The baseline HER-2 extracellular domain was elevated in two patients and declined to normal values with the preoperative therapy [Table 4].

Conclusions

HER2NEU-positive breast cancer is an aggressive form of disease that is associated with a particularly poor outcome. Clinical trials have shown that the anti-HER2 monoclonal antibody, Herceptin, is an effective treatment for HER-2-positive metastatic breast cancer: it is known that the earlier the drug is administered, the better its effect. Based on this concept, it is logical to apply the use of Herceptin in the primary setting (adjuvant and neoadjuvant treatment). Currently, there is no gold standard adjuvant breast cancer treatment. While AC followed by a taxane is standard for node-positive disease in North America, the role of Taxol in postmenopausal women with positive lymph nodes is controversial, and many alternative regimens are being used in Europe and the rest of the world. This is the first major difference between the American Joint analysis and the European trial (HERA). The four main Herceptin adjuvant trials take into account the number of possible regimens in current use and will go far to ensure that the efficacy and safety of Herceptin in the adjuvant setting will be determined as expediently as possible. Several years will be needed for completion of these studies due to the large number of participants. The interim analysis of the first three studies is very impressive and, for the first time in the history of breast cancer treatment, we have in the therapeutic arsenal a targeted drug that improves the results of the classical hormonal treatment and chemotherapy. It is anticipated that Herceptin will offer women with HER-2-positive primary disease enhanced overall survival without significantly compromising their quality of life. Not enough time has elapsed to determine the effect of 2 years of treatment with Herceptine: this will be the second contribution of the HERA trial.

The question concerning the neoadjuvant setting is more complicated: although the published studies are very impressive, especially the ones on the complete pathologic response in the breast and a lesser response in the lymph nodes as well as those showing that the toxicity is not different from other regimens, the numbers of these studies are very few and they include relatively few treated patients in randomized trials.

As far as we know, trastuzumab given every 3 weeks following chemotherapy significantly prolongs disease-free survival and relapse-free survival and significantly reduces the risk of distant metastases for women with HER-2-positive early breast cancer, independent of the patient's baseline characteristics (e.g., nodal status, hormone receptor status) and we have enough data to strongly recommend the use of Herceptin in the adjuvant setting in this high risk population. Secondly, trastuzumab therapy is associated with some risk of cardiac toxicity; longer follow-up is needed to better quantify this risk. Thirdly, it is currently not possible to recommend the use of combined treatment in the neoadjuvant setting.

Acknowledgment. Esther Eshkol is thanked for editorial assistance and Limor Alon-Baron for technical assistance.

References

- Salmon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 positive metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783-92.
- Baselga J. Herceptin alone in combination with chemotherapy in the treatment of HER2 positive metastatic breast cancer: pivotal trials. *Oncology* 2001;61(Suppl 2):14-21.
- Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first line treatment of HER2 overexpressing metastatic breast cancer. *J Clin Oncol* 2002;20:719-26.
- Colbeigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti HER2 monoclonal antibody in women who have HER2 overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999;17:2639-48.
- Cook-Bruns N. Retrospective analysis of the safety of Herceptin immunotherapy in metastatic breast cancer. *Oncology* 2001;61(Suppl 1):57-63.
- Tan-Chui E, Piccart M. Moving forward: Herceptin in the adjuvant setting. *Oncology* 2001;63(Suppl 1):57-63.
- Pegram M, Hsu S, Lewis G, et al. Inhibitory effects of combinations of HER1/neu antibody and chemotherapeutic agents used for the treatment of human breast cancers. *Oncogene* 1999;18:2241-51.
- Konecny G, Pegram M, Beryt M, et al. Therapeutic advantage of chemotherapy drugs in combination with Herceptin against human breast cancer cells with HER2/neu overexpression. *Breast Cancer Res Treat* 1999;57:114 (Abstract 467).
- Robert N, Leyland-Jones B, Asmar L, et al. Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER2/neu positive advanced breast cancer. *Breast Cancer Res Treat* 2002;76(Suppl 1):S37 (Abstract 35).
- Budzar AU, Ibrahim NK, Francis D et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol* 2005;23:3676-85.

Correspondence: Dr. N. Yaal-Hahoshen, Dept. of Oncology, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel.

Phone: (972-3) 697-3413

Fax: (972-3) 697-4828

email: neora@tasmc.health.gov.il, neora@barak.net.il