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Trastuzumab as adjuvant treatment for early stage HER2-positive breast cancer — a 10 year history

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Overexpression of the receptor for human epidermal growth factor type 2 (HER2), or gene amplification for this receptor is observed in approx. 20–25% of breast cancer patients and is associated with a more aggressive course, a higher risk of recurrence and shorter survival. Trastuzumab, a monoclonal antibody, directed to the extracellular domain of the HER2 receptor, was introduced for the treatment of HER2-positive breast cancer in 1998, and its use has caused equal opportunities for patients with HER2-positive breast cancer and those with HER2-negative. In adjuvant treatment of early breast cancer the risk of recurrence is decreased and overall survival is prolonged. The results of international randomised studies, published more than 10 years ago, despite some controversies concerning optimal regimen and duration of treatment, almost immediately became the basis for a change in the standard of care. Currently we know that the optimal administration of trastuzumab is concurrent with taxane-based chemotherapy, but it should not be added to anthracyclines. Long-term observation of the patient population treated in these trials has shown that the introduction of trastuzumab to clinical practice has changed the natural history of HER2-positive early breast cancer. The benefit from this treatment lasts for many years.

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Key words: HER2-positive breast cancer, adjuvant treatment, trastuzumab, long-term outcome

Introduction

The human epidermal growth factor 2 receptor (HER 2) was identified in 1984. It soon became a significant therapeutic target in breast cancer and remained so for the next 30 years. Its overexpression or amplification of this receptor's gene occurs in about 20–25% of breast cancer patients and is connected with a more aggressive course of the disease, a larger risk of recurrence and a shorter survival period [1–3].

Trastuzumab, a monoclonal antibody, directed at the extracellular domain of the HER2 receptor, has been studied since the early 90s. [4, 5]. Initially, its value was confirmed in the treatment of the advanced stage of the disease, which resulted in its approval for the market in the USA in 1998. In 2001, Slamon et al published the results of the third phase trail, in which they proved that adding Trastuzumab to first line chemotherapy allows for the increase of the median progression-free survival period (PFS) from 4.6 to 7.4 months [4]. From 2000 onwards, the value of trastuzumab in the treatment of early stages of breast cancer was assessed. Between 2000–2001, 4 large randomised international trials (HERA, NSABP-B31, NCCTG-N9831 and BCIRG 006) as well as 2 smaller ones — Finnish (FinHer) and French (PACS-04) with a random selection, were started with almost 12 thousand patients enrolled [6–12].

In spite of the many differences concerning the construction of a trial, patient population, the chemotherapy regimens applied, methods of dosing and the duration of Trastuzumab treatment, all these studies proved there were some benefits in the application of the antibody. The first data analyses pointed to a 30% decrease in the risk of death and a decrease in recurrence risk varying between 39–52%. These results have been the most significant progress since the introduction of Tamoxifen to the treatment of breast cancer and have provided grounds for the change of the standard of adjuvant therapy [13]. All the above studies have undergone subsequent analyses and their long-term

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Table I. Characteristics of the international studies evaluating trastuzumab in adjuvant therapy

Study	HERA	B31 and N9831	BCIRG 006
Number of subjects			
Planned	5102	2043 and 2766	3222
Included	3401	1736 and 1615	3222
Age of the subjects (years median)	51	51	52
The rate of the subjects without metastases to axillary lymph nodes	32	5.7	29
The number of subjects receiving taxoids	26	100	100
Primary end-point	DFS	OS/DFS	DFS

DFS — disease-free survival; OS — overall survival

outcomes confirm the benefits of the application of Trastuzumab in adjuvant therapy of early HER2-positive breast cancer. The studies evaluated various methods of combining Trastuzumab with chemotherapy.

Studies overview

The primary endpoint of the referred international randomised trials was the disease-free survival period (DFS), and in the trials: NSABP-B31, NCCTG-N9831, additionally it was the overall survival (OS). Table I presents the most significant data concerning all the 4 above-mentioned trails.

The objective of the HERA study was to assess the value of one and two-year therapy with Trastuzumab added to chemotherapy in comparison with chemotherapy alone in patients with early HER2-positive breast cancer after surgical treatment and standard chemotherapy (induction, adjuvant or induction and adjuvant chemotherapy). Both the patients with metastases (68%), and without metastases (32%) in the inguinal lymph nodes were included in the study; however in the latter group, the primary tumour size, as evaluated in the post-operative sample (pT) had to be larger than 1 cm. Various chemotherapy regimens were accepted which allowed for carrying out the study in many countries (Tab. II). The first results (with the median observation period of 12 months) comprised the comparison of the combination of chemotherapy with Trastuzumab administered for one year with chemotherapy solely. Some improvement in DFS was observed — a 46% decrease in the risk of tan occurrence of an event in the group of patients with combined treatment (HR 0.54, 95% CI 0.43–0.67, $p < 0.0001$) [6]. The results were confirmed in another analysis performed after almost 2 years of observation; The HR ratio was then 0.64 (Tab. III) [7]. Also the benefits in the combined therapy for overall survival were proven (HR 0.66, 95% CI 0.47–0.91, $p = 0.0115$). The results of the first analysis led to the decision to enable patients treated with chemotherapy solely to start therapy with Trastuzumab (*cross-over*). Such an opportunity was used by 884 out of 1698 patients (52%) initially treated Trastuzumab. The therapy with Trastuzumab was commenced in the cross-over cohort within a varied time period from randomisation (median: 22.8 months, scope 4.5–52.7 months) and, in spite of these differences, also in this group there was some significant decrease in the risk of recurrence observed in comparison with the group of patients who were not receiving Trastuzumab (HR 0.68, 95% CI 0.51–0.90; $p = 0.0077$). The results of the HERA trial provided grounds for the registration of Trastuzumab for adjuvant therapy.

American trials (NSABP-B31, NCCTG-N9831) had a slightly different construction with respect to the selection of adjuvant chemotherapy. In all the patients, the sequential chemotherapy with anthracyclines (doxorubicin + cyclophosphamide, AC) and taxoids (paclitaxel) was appliedThe regimens differed from each other with regards to dosage and the frequency of paclitaxel administration, comprising the regimes of administration every three weeks and every one week. The trial construction, however, concerning the comparison of the effectiveness and safety of chemotherapy alone with the Trastuzumab combined treatment was similar. Although the first of the trials had two arms whilst the second had three study arms, arm 1 and 2 in the NSABP-B31 trial and arm A and C in the NCCTG-N9831 trial were similar (Tab. II). That is why the National Cancer Institute (NCI) in the USA approved a joint evaluation of the results of these two studies, excluding arm B [9]. The first analysis (after the observation period with a 2-year median) showed a significant improvement of DFS (HR 0.48; 95% CI 0.39–0.59, $p < 0.0001$) in the group of patients treated with Trastuzumab. In this population a 33% decrease in mortality risk was also observed (HR 0.67; 95% CI 0.48–0.93, $p = 0.015$) [8]. After almost one year, the benefits remained on a similar level (Tab. III) [9]. It must be observed that the results of arm B of the NCCTG-N9831 trial were not published (sequential treatment).

The objective of the BCIRG 006 study was to evaluate the value of Trastuzumab in combination with 2 types of taxoids therapy — with anthracyclines (AC, and then docetaxel + trastuzumab) and without anthracyclines (docetaxel + carboplatin + trastuzumab – DCbT, described also as TCH). This was the outcome of a search for methods of decreasing

Table II. Therapy regimens

Study	Arm	Regimen
HERA	1	Standard chemotherapy → T every 3 weeks for 1 year
	2	Standard chemotherapy → T every 3 weeks for 2 years
	3	Standard chemotherapy
NSABP B-31	1	4 × AC every 3 weeks → 4 × Pct every 3 weeks
	2	4 × AC every 3 weeks → 4 × Pct every 3 weeks + T every one week for a year
NCCTG N9831	A	4 × AC every 3 weeks → 12 × Pct every one week
	B	4 × AC every 3 weeks → 12 × Pct every one week → T every one week for a year
	C	4 × AC every 3 weeks → 12 × pPct + T every one week → 40 × T every one week
BCIRG 006	1	4 × AC every 3 weeks → 4 × Dct every 3 weeks
	2	4 × AC every 3 weeks → 4 × Dct every 3 weeks + T for a year (with Dct every week and then every 3 weeks)
	3	6 × DCb every 3 weeks + T for a year (with DCb every week and then every 3 weeks)

AC — doxorubicin + cyclophosphamide; Dct — docetaxel; DCb — docetaxel + carboplatin; Pct — paclitaxel; T — trastuzumab

the risk of cardiotoxicity while maintaining the maximum effectiveness of the adjuvant therapy. The preliminary results of the study (an observation period median of 23 months) showed a significant improvement in the progression free survival period in both arms with (hazard ratio for DFS, [HR], 0.49; 95% CI 0.37–0.65, p < 0.0001 for the arm with anthracyclines and HR 0.61; 95% CI 0.47–0.79, p = 0.0002 for the arm with anthracyclines), whilst the difference between the arm with Trastuzumab, though clearly seen, was not significant (p = 0.16) [14]. Another analysis, after a one year observation period confirmed earlier results, yet, similarly as in the case of the HERA study, the hazard ratios were slightly higher (Tab. III) [15]. In accordance with the objective of the study, significant differences were observed in the incidence of cardiological events (a decrease of the ejection fraction by ≥ 10% was observed in 17% patients in the arm combining doxorubicin and trastuzumab, 9% in the arm with doxorubicin alone and 8% in the arm combining carboplatin and trastuzumab).

The FinHer study was initially planned with an objective to compare 2 regimens of adjuvant chemotherapy — 3 cycles of docetaxel every 3 weeks and 9 weekly doses of vinorelbine followed by 3 cycles of $FE_{50}C$ (5-fluorouracil + epirubicin 50 mg/m^2 + cyclophosphamide) every 3 weeks in both arms. Out of 1010 patients included in the study, 232 of them had a diagnosis of HER2-positive cancer. With regards to the available knowledge concerning the value of trastuzumab in the adjuvant treatment, these patients were additionally randomised, with an administration of 9 weekly doses of trastuzumab at the same time with docetaxel or vinorelbine or chemotherapy alone. A significant decrease in the risk of breast cancer recurrence was observed (median

Table III. Preliminary and long-term results of international studies evaluating trastuzumab in adjuvant therapy

Study			HERA	B31 and N9831	BCIRG 006	
					AC→Dct+T	DCb+T
Preliminary results	DFS	HR	0.64	0.48	0.61	0.67
		(95% CI)	(0.54–0.76)	(0.39–0.59)	(0.48–0.76)	(0.54–0.83)
		p value	< 0.0001	< 0.00001	< 0.0001	0.0003
	OS	HR	0.66	0.65	0.59	0.66
		(95% CI)	(0.47–0.91)	(0.51–0.84)	(0.42–0.85)	(0.47–0.93)
		p value	0.0115	0.0007	0.004	0.0017
Median follow-up period (months)			23.5	34.8	36	
Long-term results	DFS	HR	0.76	0.60	0.70	0.76
		(95% CI)	(0.68–0.86)	(0.53–0.68)	(0.60–0.83)	(0.65–0.90)
		p value	< 0.0001	0.001	< 0.001	< 0.001
	OS	HR	0.74	0.63	0.64	0.76
		(95% CI)	(0.64–0.86)	(0.54–0.73)	(0.52–0.79)	(0.62–0.93)
		p value	< 0.0001	0.001	< 0.001	0.0081
Median follow-up period (years)			11	8.4	10.3	

observation period: 3 years) under the influence of the application of Trastuzumab (HR 0,46; p = 0,0078) [11].

The PACS-04 study comprising 528 patients (including those with axillary lymph nodes metastases), was the only study which did not show any significant reduction in disease recurrence in the patients receiving trastuzumab [12]. Nevertheless, in this study a 14% decrease in the recurrence risk was also observed (HR 0.66; p = 0.41) and an improvement of the 3-year progression-free survival rate (78% in the group of patients treated with chemotherapy alone in comparison with 81% in the group with trastuzumab administered additionally).

Long-term study results

An integral element of the studies concerning adjuvant treatment is the long follow-up period, which provides remote study results for evaluation. The long term results concern not only effectiveness, but also safety, which is especially important in the case of radical treatment. The data from the study concerning the efficiency of trastuzumab in the treatment of early breast cancer confirm that trastuzumab provides equal chances for the patients with HER2-positive breast cancer and the patients with HER2--negative breast cancer [16].

A long-term (median period of 11 years) observation of the patients in the HERA study presented in December 2015 at the San Antonio conference, point to a ongoing benefit in treatment with Trastuzumab [17]. In spite of the above-mentioned *crossover*, which took place after the first analysis in 2005 and included 884 subjects out of 1698 patients treated ith the arm with chemotherapy alone, there is still a relative risk of recurrence (HR 0.76; 95% CI 0.68–0.86, p < 0.0001) and of death (HR 0.74; 95% CI 0.64–0.86, p < 0.0001) although the indicators are slightly lower than in earlier studies (Tab. III, Fig. 1a and 1b). This benefit is observed both in patients with the expression of steroid receptors and without them. The results of the Trastuzumab study, which was prolonged to 2 years, point to a lack of additional benefit in such methods (DFS – HR 0.77; 95% CI 0.69–0.87, p < 0.0001 and OS — HR 0.72; 95% CI 0.62–0.83, p < 0.0001). This confirms the observation that the optimum duration of the adjuvant treatment with trastuzumab is 1 year.

The result of long-term joint analysis (median observation period was 8.4 years) of the American studies (NSABP-B31, NCCTG-N9831) also confirmed a permanent benefit in combining trastuzumab with adjuvant therapy (synchronous administration of trastuzumab with taxoids following a previous anthracycline therapy). A relative improvement in theoverall survival of 37% was observed (HR 0.63; 95% CI 0.54–0.73; p = 0.001) and an increase in the 1 year survival rate from 75.2% with chemotherapy alone to 84% in the combined treatment with trastuzumab (Tab. III, Fig. 2a and 2b). A similar benefit was observed in disease free survival (HR 0.60; 95% CI 0.53–0.68, p = 0,001, an increase of the 10-year DFS rate DFS from 62.2% to 73.7% respectively). Trastuzumab improved the treatment results in all the analysis subgroups, whereas synchronous administration of trastuzumab with taxoids is proven to be more effective than sequential treatment [18].

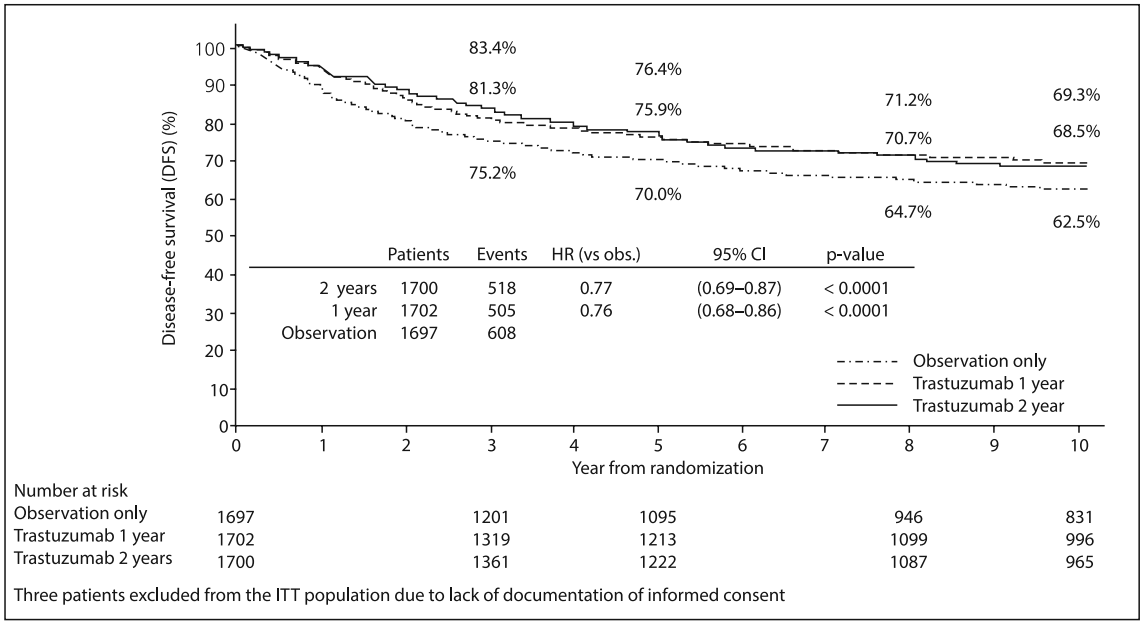

Figure 1a. Long-term study results: HERA — DFS [17]

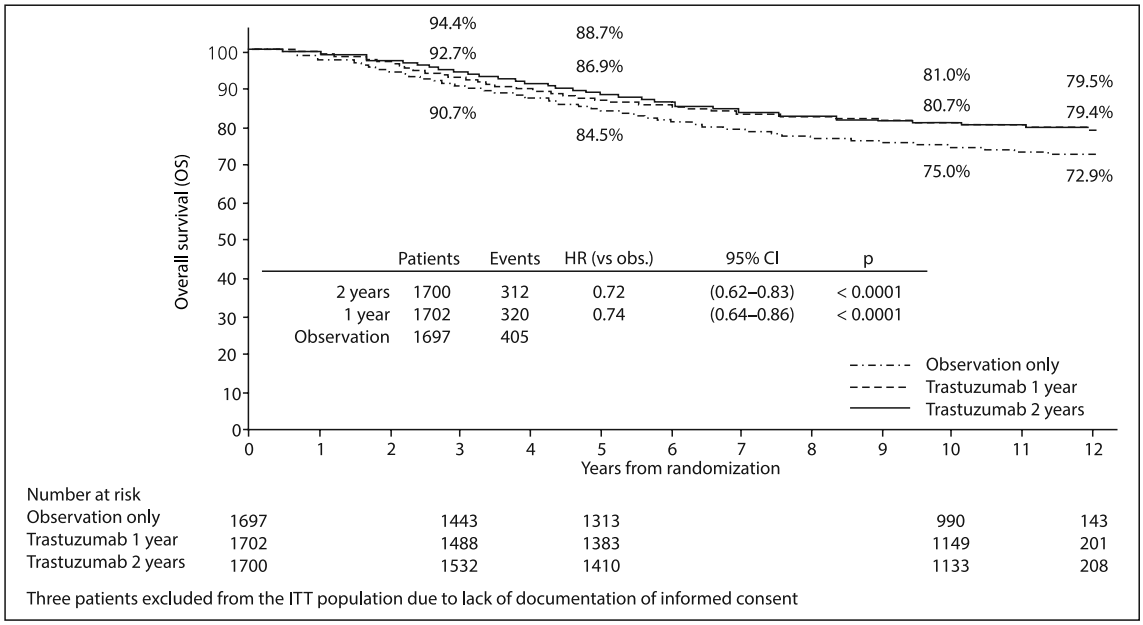

Figure 1b. Long-term study results: HERA — OS [17]

Similar results were obtained within a long observation period (median observation period: 10.3 years) of the patients from the BCIRG 006 study. A significant improvement of survival periods was observed (DFS and OS) in both study arms with combined therapy in comparison with chemotherapy alone [19]. In the arm with anthracyclines, for the disease free survival (AC→Dct+T) the obtained HR value was 0.70 (95%CI 0.60–0.83, p < 0.001), whilst in the arm without anthracyclines (DCbT) — HR 0.76 (95% CI 0.65–0.90, p < 0.001), and the rates were slightly lower than in the previous analysis (then it was 0.61 and 0.67 respectively, Table III, Figure 3a and 3b). Also a decrease in the relative risk by 36% was observed in the AC→Dct+T arm (HR 0.64; 95%CI 0.52–0.79, p < 0.001) and by 24% in the DCbT arm (HR 0.76; 95% CI 0.62–0.93, p = 0. 0081). With regards to the survival rate, no significant differences between the two study arms were observed (with anthracyclines and without anthracyclines) and this concerns also the patients with a high risk of recurrence (metastases to more than 3 axillary lymph nodes), which confirms the value of the DCbT regimen in the patients with u pN+. In the arm with anthracyclines, the incidence of congestive heart disease was five times higher (21 cases — 2.0% in comparison with 4 cases — 0.4%; p = 0.0005) and also there was a twofold increase in the incidence of the reduction of the left ventricular ejection fraction 2 (LVEF) above 10% (206 in comparison with 97 respectively; p < 0.0001). In the group of patients treated with chemotherapy alone, there were 8 cases of symptomatic heart failure (0.8%). The long term results of the BCIRG study suggest that in patients with early HER2--positive breast cancer treated with adjuvant trastuzumab, chemotherapy without anthracyclines is not worse than with anthracyclines, as it brings about a much lower risk of cardiological complications.

The final results of the FinHer study were published in 2009, after a follow-up period with the median period of 5.2 years [20]. In the subgroup of patients with HER2-positive breast cancer, it was shown that the addition of trastuzumab (9 weekly doses) to chemotherapy decreased the relative risk of the cancer spreading by 35% in comparison with chemotherapy alone, yet this difference proved to be insignificant — distant disease-free survival (DDFS); HR 0.65, 95% CI 0.38–1.12, p = 0.12). In the subgroup analysis one significant advantage of the Dct+T→FEC treatment over other arms was proven without increasing cardiotoxicity.

Controversies

The differences in the treatment methods of the presented studies (the duration of the trastuzumab treatment, immediate or sequential combination of trastuzumab and taxoids) led to some controversies, the majority of which were resolved within the course of the follow-up or on the basis of additional studies.

In four large trials the treatment duration was empirically defined for 1 year. In the HERA study, the addition of an arm with a 2-year study period was intended to show whether the prolongation of the treatment with trastuzumab would increase the benefits in the use of this drug. Some shorter periods of trastuzumab were also studied. The first study of such a type was the FinHer trial conducted in Finland. The benefits in a 9-week treatment, observed in the initial results (in the subgroup receiving docetaxel

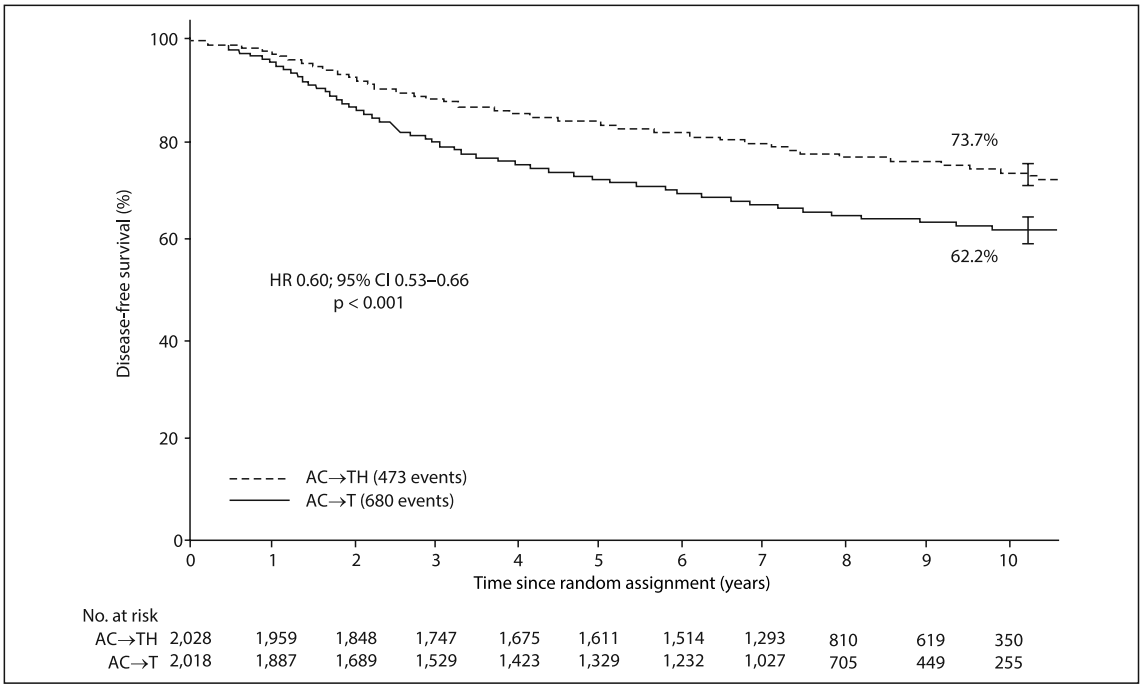

Figure 2a. Long-term study results: NSABP-B31, NCCTG-N9831 — DFS [18]

with trastuzumab, the share of the patients without distant metastases was significantly lower than in the group receiving chemotherapy alone, p = 0.029) were, for a few years, the subject of some controversies concerning the optimal duration of the treatment with trastuzumab. Some further studies comparing shorter and longer administration of the drug (PHARE, PERSEPHONE, Short-HER), as well as the long-term results of the 2-year long treatment in the HERA study allowed for the final determination of the standard treatment to be a 1-year duration therapy [21–24].

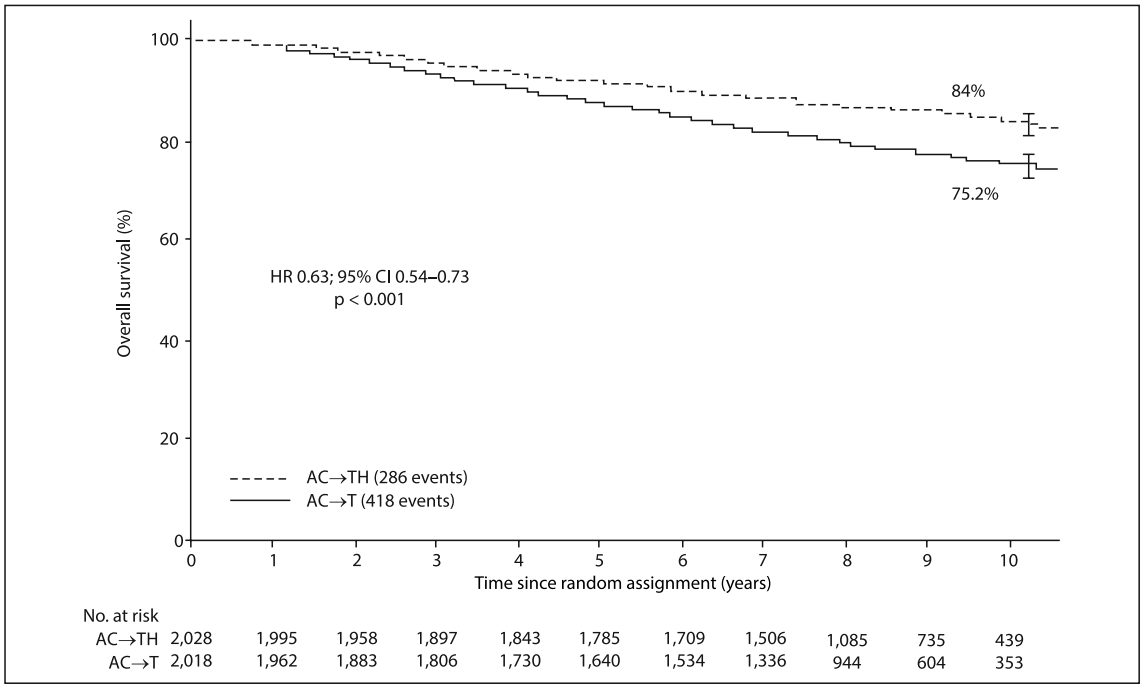

Figure 2b. Long-term study results: NSABP-B31, NCCTG-N9831 — OS [18]

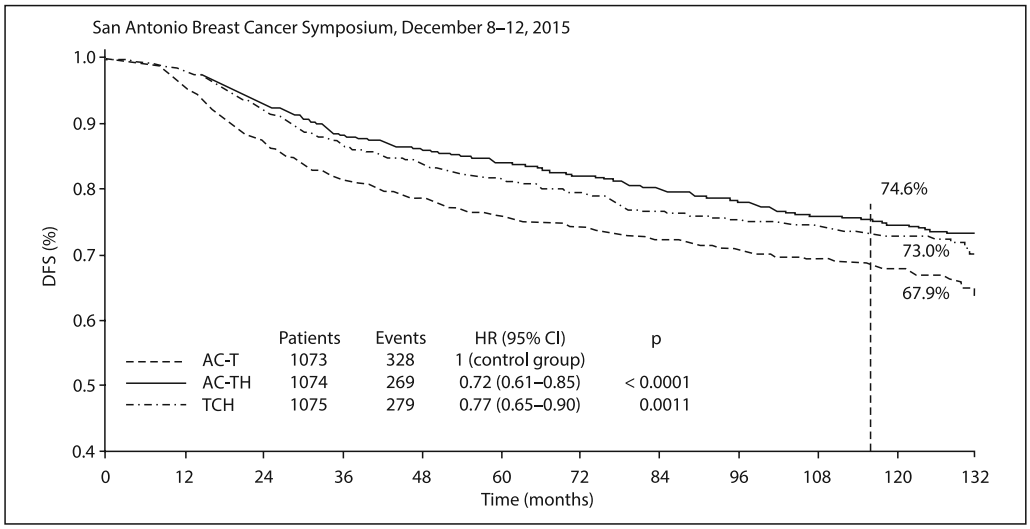

Figure 3a. Long-term study results: BCIRG 006 — DFS [19]

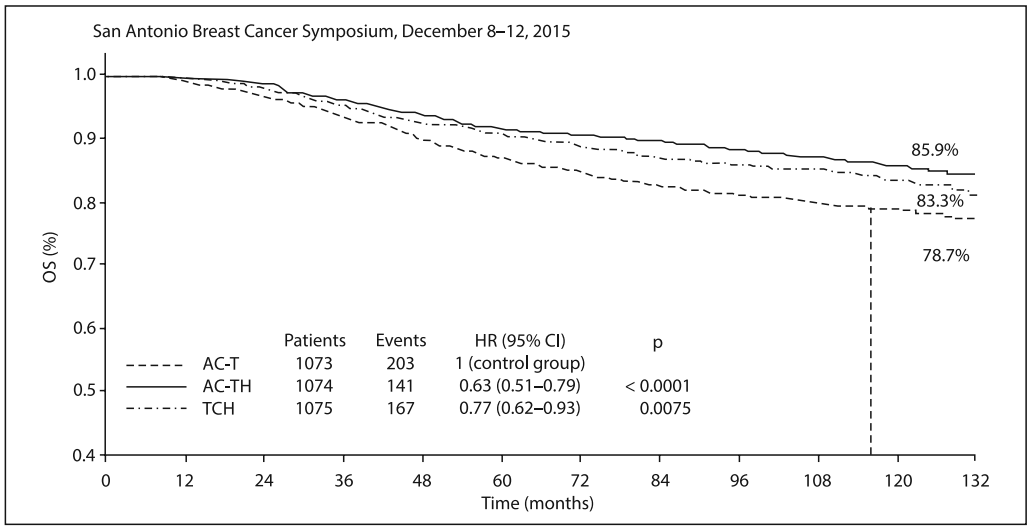

Figure 3b. Long-term study results: BCIRG 006 — OS [19]

Trastuzumab was added into the treatment immediately with taxoids (after 4 cycles of anthracyclines) or at the moment of initiation of adjuvant chemotherapy in the arm without anthracyclines (BCIRG 006 study), after 3 AC chemotherapy cycles (American trials) or after the completion of chemo- and, alternatively, also radiotherapy (the HERA study). The above studies did not evaluate the immediate combination of trastuzumab with anthracyclines, as such combinations were evaluated in the neoadjuvant treatment. Currently, in the case of the application of chemotherapy with anthracyclines, it is recommended to include trastuzumab as late as after the completion of the treatment with chemotherapy with anthracyclines. Sequential combination is safer with regards to cardiotoxicity than immediate combination. Trastuzumab, however, should be administered immediately with taxoids, as the long term study results show that such a combination is more beneficial than the administration of trastuzumab sequentially after taxoids [8, 25, 26]. The exemplary regimens are, for example: 4 × AC → Pct + T lub Dct + T; 3 × FEC → 3 × Dct and, the DCbT (TCH) regimen, which was evaluated in the BCIRG 006 study.

Cardiotoxicity connected with trastuzumab consists mostly in cardiac muscle failure and LVEF decrease. These adverse events are studied in detail in each study evaluating the use of trastuzumab. The Cochrane Collaboration For the Cochrane Collaboration meta-analysis proved an increased risk of cardiac failure: relative risk (RR) 5.11; $p < 0.00001$) and of LVEF reduction (RR 1.83; $p = 0.0008$), whereas it must be

stressed that for this meta-analysis, the third arm of the 3 BCIRG 006 was not included [27]. It was numerously proven that cardiotoxicity caused by trastuzumab is reversible, provided that the administration of the drug is discontinued. Nevertheless, patients for such treatment must be carefully selected, taking into account their history of circulatory diseases and an evaluation of the left ventricle ejection fraction. It should be stressed that the adjuvant treatment of patients with HER2-positive breast cancer with chemotherapy without anthracyclines has a documented value [14].

The authors of the meta-analysis from 2011 observed more frequent incidence of breast cancer recurrence in the central nervous system in patients treated with trastuzumab, which is probably related to the life prolongation in this group of patients [28].

The majority of the randomised clinical studies do not include the patients with very early breast cancer, in particular those with so-called "small nodules", whose size, in pathomorphological evaluation do not exceed 1 cm (pT1a/bN0). Although retrospective data suggest that the patients with the advancement stage pT1a/bN0 benefit from adjuvant therapy with trastuzumab, these data are still insufficient [29]. In the above studies, such patients made up a small share of the population and the results of the studies in such a sub-population were usually not reported. The patients with HER2-positive breast cancer in the pT1a/bN0M0 stage, however, have a higher recurrence risk and shorter survival than the patients with HER2-negative breast cancer with the same advancement stage; this may suggest that in this case the cancer biology may be more significant than the tumour size and thus the cancer biology should be the factor that determines the treatment choice [30, 31].

Conclusions

The use of trastuzumab in the adjuvant treatment of patients with early HER2-positive breast cancer, decreases the risk of recurrence and has a positive influence on life prolongation. The results of the discussed studies, published more than 10 years ago, in spite of some controversies concerning the optimum regimen and duration of treatment, almost immediately provided the grounds for changes in the standard treatment. The years of studies on the use of trastuzumab helped to reduce doubts concerning the duration of treatment and the optimum method of combining trastuzumab with chemotherapy and provided thorough knowledge bases about the drug's safety. In accordance with the current state of knowledge, adjuvant therapy with trastuzumab should last one year (or until the recurrence of the disease, if the recurrence occurs earlier). Trastuzumab should be administered together with taxoids, as such a combination is more effective than its administration after taxoids, and there are no medical contraindications for immediate administration of trastuzumab with post-operative radiotherapy. In order to reduce cardiotoxicity, it seems worthwhile to consider chemotherapy excluding anthracyclines (DCbT) also in patients with pN+.

Many years of observation of patients with HER2-positive breast cancer showed that the introduction of trastuzumab to clinical practice changed the natural course of HER2-positive early breast cancer and the benefits from the treatment continue for many years.

Conflict of interest: none declared

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