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Clinical trials of Herceptin® (trastuzumab)

J. Baselga *

Department of Medical Oncology, Hospital General Universitari Vall d'Hebron, Psg. Vall d'Hebron, 119-129, E-08035 Barcelona, Spain

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Abstract

This report summarises the clinical efficacy and safety findings from clinical trials of the new anti-HER2 monoclonal antibody Herceptin® (trastuzumab). Data from pivotal trials indicate that trastuzumab is active when added to chemotherapy in patients with advanced metastatic breast cancer. In particular, the combination significantly prolonged the median time to disease progression, increased the overall response rate, increased the duration of response, and improved median survival time by approximately 25% compared with chemotherapy alone. Furthermore, trastuzumab is active as a single agent in women with HER2-positive metastatic breast cancer, inducing durable objective tumour responses. In total, 15% of patients who had received extensive prior treatment for metastatic disease had an objective response. The median duration of response was 9.1 months following administration of single-agent trastuzumab. Notably, 2% of patients were free of disease progression at 6 months. The safety profile of trastuzumab either given alone or in combination was favourable. © 2001 Published by Elsevier Science Ltd.

Keywords: Herceptin® (trastuzumab); Metastatic breast cancer; Survival; Efficacy

1. Introduction

Amplification of the human epidermal growth factor receptor-2 (*HER2*) gene appears to be the most common mechanism leading to overexpression of the HER2 receptor [1]. Overexpression describes an increase in the number of receptors on the cell surface by several orders of magnitude. The resultant dysregulation in the normal homeostasis of the HER system serves to trigger the cell to divide and multiply at an accelerated rate, thus contributing to tumour growth. In an attempt to inhibit tumour growth caused by this mechanism, antibodies have been developed against the extracellular domain of the HER2 receptor [2]. Studies in tumour xenografts confirmed that the murine monoclonal antibody (MAb) 4D5 inhibits the growth of human breast cancer cells overexpressing the HER2 receptor [3]. However, the immunogenic potential of using murine MAbs limits their long-term clinical use in humans.

Overcoming these immunogenicity issues has been achieved by inserting the complementarity determining regions of MAb 4D5 into the framework of a consensus human immunoglobulin G_1 (IgG_1) [4]. The resulting humanised MAb against the HER2 receptor, trastuzumab, has a higher binding affinity for HER2 ($Kd = 0.1$ nM) than murine MAb 4D5, and has a cytostatic growth inhibitory effect against breast cancer cells overexpressing HER2 [4]. In addition, trastuzumab induces antibody-dependent cellular cytotoxicity (ADCC) against human tumour cell lines in the presence of human peripheral mononuclear cells, which serves to increase anti-tumour activity [4–6]. Preclinical evidence for the anti-tumour activity of trastuzumab has been reported in detail elsewhere [7–10]. This report summarises the clinical efficacy and safety findings from clinical trials of trastuzumab in women with HER2-positive metastatic breast cancer. Trastuzumab was used both as a single agent and in combination with traditional chemotherapeutic agents in these trials. Recently updated median survival data derived from the pivotal phase III trial of trastuzumab in combination with chemotherapy are discussed.

2. Early trials with trastuzumab

Phase I trials revealed that the dose of trastuzumab (i.v. 10–500 mg single dose or once weekly) could be

* Tel.: +34-93-274-6085; fax: +34-93-274-6059.
E-mail address: baselga@hg.vhebron.es

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increased without toxicity and that pharmacokinetics were dose dependent [11]. In one of these phase I, multiple-dose studies, trastuzumab was co-administered with cisplatin (50 or 100 mg/m^2) without affecting the pharmacokinetics of trastuzumab. Furthermore, trastuzumab was well tolerated with no drug-related serious adverse events, although nausea and vomiting were frequently observed, particularly with the first dose of trastuzumab. During co-administration with cisplatin, the frequency and nature of adverse events was similar to that previously described with cisplatin alone. These trials were used to determine the optimal dose and schedule for trastuzumab in phase II/III clinical trials.

A phase II, single-agent trial was conducted in 46 (43 evaluable) HER2-positive (defined as $\geqslant$25% of cells showing membrane staining on immunohistochemistry (IHC)) metastatic breast cancer patients who had failed prior cytotoxic chemotherapy. The overall response rate to trastuzumab (i.v. 250 mg initial dose on day 0 and subsequent doses of 100 mg weekly for 10 weeks, or until disease progression) was 11% (including one complete response (CR)). Duration of response ranged from 1 to >60 months [12].

A second phase II, open-label trial was undertaken to determine the overall response (CR and partial response (PR)) to trastuzumab in combination with cisplatin in 39 HER2-positive (defined as light to strong complete membrane staining on IHC using antibody 4D5) metastatic breast cancer patients who had failed prior cytotoxic chemotherapy [13]. Patients received trastuzumab i.v. on day 1 as a 250 mg initial dose followed by weekly doses of 100 mg for 9 weeks. Cisplatin was administered i.v. at a dose of 75 mg/m^2 on days 1, 29 and 57. Patients who had tumours that responded or were stable after the initial 70-day study period were eligible to receive continued trastazumab and cisplatin treatment. Of the 39 patients enrolled in the study, 37 were evaluable for efficacy, with 9 (24%) having a PR, 9 (24%) having a minor response (MR) or stable disease (SD), and the remaining 19 (51%) having progressive disease (PD). The overall response rate for all patients (in an intent-to-treat analysis) was 23% (95% confidence interval (CI), 12–40%), with a median duration of response of 5 months (range 2–18 months). The median survival time was 11 months.

Administration of trastuzumab was well tolerated in this study and there was no evidence that administration of trastuzumab altered the side-effects profile of cisplatin.

3. Pivotal phase II single-agent trial

A large, multinational, multicentre study of trastuzumab was performed in 222 women with HER2-positive metastatic breast cancer who had relapsed following one or two cytotoxic chemotherapy regimens for metastatic disease [14]. Patients with weak (2+) or complete (3+) membrane staining of >10% of tumour cells on IHC using either one of two antibodies (CB11 or 4D5) were defined as HER2-positive. This assay system constitutes the clinical trials assay (CTA). The primary efficacy endpoint of the study was the overall response rate, with secondary endpoints being duration of response, time to disease progression (TTP), quality of life (QoL), 1-year survival and time to treatment failure. Patients received i.v. single-agent trastuzumab at an initial dose of 4 mg/kg followed by 2 mg/kg weekly. The rationale for selecting this dose regimen is described elsewhere [15].

Patient demographics at entry indicate that the patients had extensive disease. All patients had either 2+ or 3+ overexpression of HER2 on IHC testing, with the majority (78%) having 3+ overexpression. Previous therapy consisted of adjuvant chemotherapy (69%), single-regimen chemotherapy for metastatic disease (32%), double-regimen (68%) or high-dose chemotherapy (26%).

The overall response rate (as determined by an independent response evaluation committee) in an intent-to-treat analysis in patients receiving trastuzumab was 15% (95% CI, 11–21%), with 8 CRs and 26 PRs (Table 1). The Kaplan–Meier estimate of the median duration of the responses was 9.1 months (range 1.6–26+months), median survival was 13 months (range 0.5–30+months) and median TTP was 3.1 months (range 0–28+months). QoL data (as determined using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30) indicated that patients with objective tumour responses following trastuzumab had clinically meaningful improvements in physical and social function, and global QoL and fatigue scale scores.

Approximately 40% of patients experienced infusion-associated symptoms, including fever and chills, which occurred primarily with the first infusion of trastuzumab. Infusion-related symptoms, as seen with other monoclonal antibody therapies, were commonly experienced during the first infusion, but were generally mild

Table 1
Efficacy of trastuzumab as a single agent in metastatic breast cancer

No. of patients (intent to treat)	222
No. of patients with overall response	34 (15%) (95% CI, 11–21%)
No. of complete responses	8
No. of partial responses	26
No. of minor responses	12
No. of stable disease lasting >6 months	47
Median duration of response (months)	9.1 (range 1.6–26+)
Median time to disease progression (months)	3.1 (range 0–28+)
Median survival (months)	13 (range 0.5–30+)

during later infusions. Two patients discontinued treatment because of adverse events. Reduction in cardiac ejection fraction was observed in 9 patients, of whom 6 were symptomatic; all had either prior anthracycline therapy or significant cardiac history at entry. One woman died of ventricular arrhythmia considered to be possibly related to the administration of trastuzumab. Toxicities commonly associated with chemotherapy, such as leucopenia, neutropenia and mouth sores, were not observed with trastuzumab. Of note, only one patient developed neutralising antibodies to trastuzumab, which was not associated with any clinical symptoms.

4. Pivotal phase III comparative trial

A randomised, placebo-controlled, phase III trial was performed to determine the efficacy and safety of adding trastuzumab to chemotherapy in women with HER2-positive metastatic breast cancer who had not previously received chemotherapy for metastatic breast cancer. All patients enrolled had to have 2+ or 3+ HER2 overexpression on IHC testing using the CTA, measurable disease and Karnofsky performance score $\geqslant 60$. The primary efficacy endpoints of the study were TTP and safety. Secondary endpoints of the study were overall response rate, duration of response, QoL, survival and time to treatment failure (TTF).

A total of 469 women received doxorubicin (60 mg/m^2) or epirubicin (75 mg/m^2) plus cyclophosphamide (600 mg/m^2) as first-line i.v. chemotherapy or, if they had received prior adjuvant anthracycline therapy, paclitaxel (175 mg/m^2 as a 3-h infusion). All agents were given every 3 weeks for six cycles, although patients could receive more than six cycles at the investigators' discretion. Half the patients (stratified by previous chemotherapy) were randomised to receive i.v. trastuzumab (4 mg/kg initial dose followed by 2 mg/kg weekly). Of the women enrolled, 143 (30%) received an anthracycline plus trastuzumab, 138 (29%) received an anthracycline alone, 92 (20%) received paclitaxel plus trastuzumab and 96 (20%) received paclitaxel alone. Patient characteristics, including mean age, performance status, prior therapy, HER2 status (2+ versus 3+) and number of metastatic sites, were similar among the 4 subgroups. However, the median number of positive lymph nodes tended to be higher in the paclitaxel subgroups and the median disease-free interval was shorter in the paclitaxel-treated subgroup than any other subgroup.

4.1. Efficacy

Assessments of TTP, response rate and 1-year survival showed a significant improvement in the chemotherapy effect in patients receiving trastuzumab (Table 2 and Fig. 1). TTP was defined as the time from randomisation to disease progression or death (whichever occurred first). The prospectively defined, primary intent-to-treat analysis indicated that the combination of trastuzumab plus chemotherapy prolonged TTP significantly. The overall absolute increase in TTP with trastuzumab was also evident in both treatment subgroups, but was greater for those receiving paclitaxel. Based on Kaplan–Meier estimates of TTP, 28% of the patients treated with trastuzumab plus chemotherapy were free of disease progression at 12 months compared with 9% of the patients treated with chemotherapy alone. Similar differences were seen in subgroup analyses: patients receiving trastuzumab plus an anthracycline (28%) compared with 13% in those receiving an

Table 2
Efficacy of trastuzumab when given in combination with chemotherapy in metastatic breast cancer

	Trastuzumab + AC ($n=143$)	AC alone ($n=138$)	Trastuzumab + paclitaxel ($n=92$)	Paclitaxel alone ($n=96$)	Trastuzumab + chemotherapy ($n=235$)	Chemotherapy alone ($n=234$)
Median TTP (months)	7.8	6.1 ($P=0.0004$)	6.9	3.0 ($P=0.0001$)	7.4	4.6 ($P=0.0001$)
Response rate (%)	56	42 ($P=0.0197$)	41	17 ($P=0.0002$)	50	32 ($P<0.0001$)
Median duration of response (months)	9.1	6.7 ($P=0.0047$)	10.5	4.5 ($P=0.0124$)	9.1	6.1 ($P=0.0002$)
Median TTF (months)	7.2	5.6 (P = 0.0014)	5.8	2.9 ($P=0.0001$)	6.9	4.5 ($P=0.0001$)
1-Year survival (%)	83	72 (P = 0.0415)	72	60 ($P=0.0975$)	79	68 ($P=0.008$)
Median survival (months)	26.8	22.8	22.1	18.4	25.4	20.3 ($P=0.025$)

AC, anthracycline; TTP, time to disease progression; TTF, time to treatment failure.

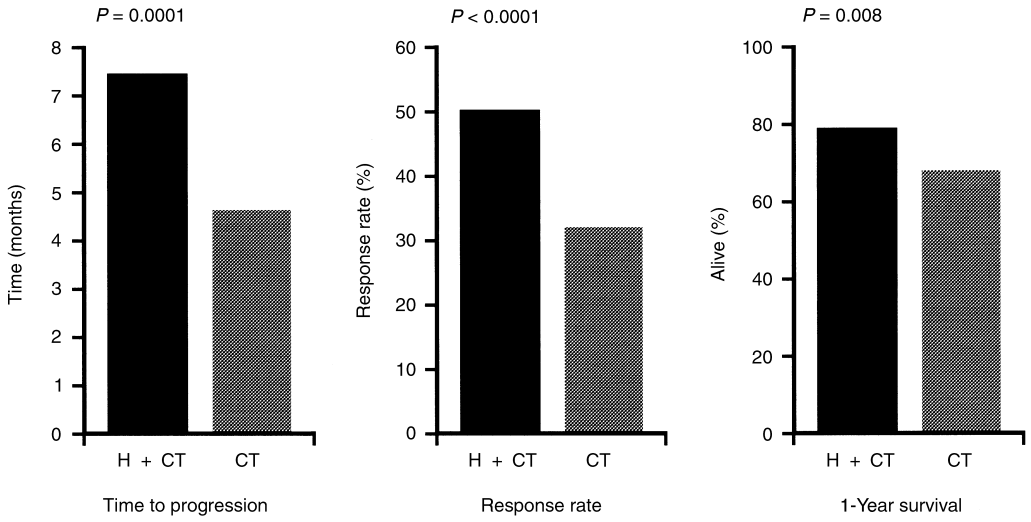

Fig. 1. Key 1-year efficacy results for pivotal phase III trial comparing cytotoxic chemotherapy with or without trastuzumab in metastatic breast cancer. H, trastuzumab; CT, chemotherapy.

anthracycline alone, and 25% in those treated with trastuzumab plus paclitaxel versus 3% in those receiving paclitaxel alone. Addition of trastuzumab to chemotherapy resulted in an absolute increase in the objective response rate from 32 to 50% ($P < 0.0001$), corresponding to a 56% relative increase in the rate reported for the chemotherapy alone treatment. The addition of trastuzumab significantly increased the median duration of response by 3 months (49%) for all patients who achieved an objective response. At the time of data cut-off (29 months follow-up), 8/12 patients in the trastuzumab plus anthracycline subgroup and 4/6 of those receiving trastuzumab plus paclitaxel who had a complete response were free of progressive disease. These results indicate that the combination of trastuzumab and chemotherapy increased both the percentage of patients having an objective response and the duration of the response. The addition of trastuzumab prolonged the time to treatment failure significantly compared with chemotherapy alone. This effect was also observed in the anthracycline and paclitaxel subgroups.

One-year survival data were presented at ASCO 1998 for a median follow-up of 14 months (Table 2) [16]. Significantly more patients treated with trastuzumab plus chemotherapy had survived at 1 year (79%) compared with those receiving chemotherapy alone (68%). This was equivalent to a 16% survival improvement at 1 year. Median survival data were presented at ASCO 1999 [17]. Data cut-off on 1 April 1999 yielded data for 451 of 469 patients (96%) for a median follow-up of 29 (range 21–42) months. The Kaplan–Meier plot (Fig. 2) showed an approximate 25% increase in median survival. It is important to realise that, at 25 months of follow-up, 65% of patients whose disease progressed on chemotherapy alone were switched to trastuzumab with or without chemotherapy at 25 months of follow-up, which generated a potential bias against the trastuzumab-treated group as the study progressed. The percentages of patients switched between these groups over time is shown in Fig. 2.

A total of 401 patients completed the QoL questionnaire at baseline and during at least one follow-up assessment. Health-related QoL scores declined at week 8 while patients were receiving chemotherapy. There was no significant difference in health-related QoL scores among patients treated with trastuzumab up to week 32 compared with those receiving chemotherapy alone. However, there were trends towards maintained health-related QoL at weeks 20 and 32 for patients treated with trastuzumab plus chemotherapy compared with the decreased QoL for those receiving chemotherapy alone. Similar favourable trends were observed in the trastuzumab plus anthracycline and trastuzumab plus paclitaxel subgroups.

4.2. Safety

All patients who received treatment during the study ($n = 464$) were evaluable for safety. Of these, 235 (51%) received trastuzumab. As expected, adverse events were reported commonly in this population of chemotherapy-treated patients with metastatic breast cancer. The incidence of many adverse events that were mild to moderate in severity was increased among patients receiving trastuzumab. In particular, patients experienced a greater incidence of infusion-associated signs and symptoms and infection versus chemotherapy alone. Treatment with trastuzumab did not increase the overall incidence of severe adverse events. A total of 162 deaths have been reported, although there were fewer on-study deaths in the trastuzumab plus chemotherapy

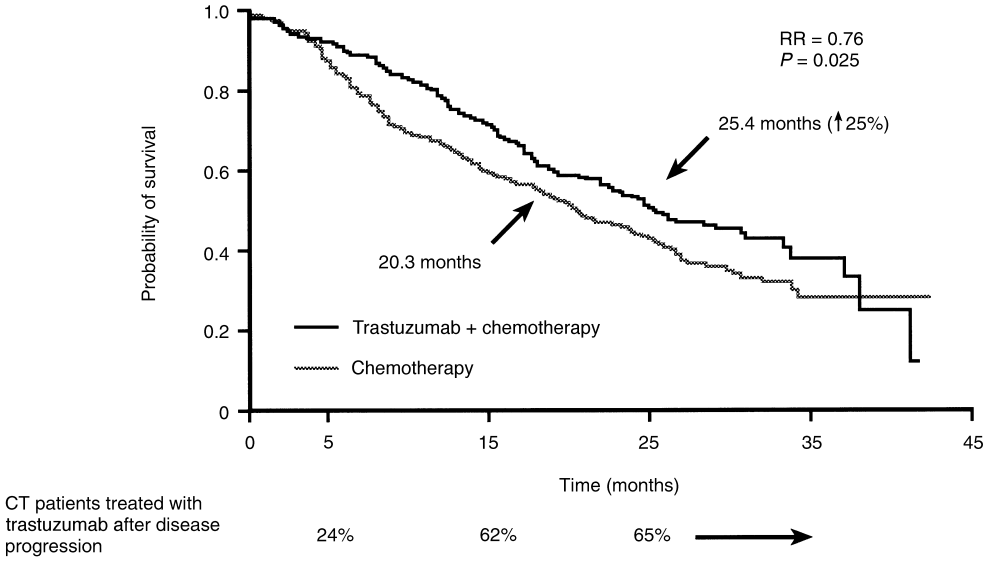

Fig. 2. Updated median survival data for pivotal phase III trial comparing cytotoxic chemotherapy with or without trastuzumab in metastatic breast cancer.

group compared with the group receiving chemotherapy alone. Of these, three deaths were considered to be related to trastuzumab, with causes of death being cardiac dysfunction ($n=1$), septic shock ($n=1$) and acute viral hepatitis B infection ($n=1$). A total of 26/235 (11%) patients (20 in the anthracycline combination group, 6 in the paclitaxel combination group) discontinued trastuzumab because of an adverse event.

The addition of trastuzumab to chemotherapy did not cause significant changes in the laboratory analysis results. Furthermore, laboratory tests for hepatic function were less frequently abnormal among patients receiving trastuzumab plus chemotherapy compared with those receiving chemotherapy alone. No patients enrolled in the study developed antibodies against trastuzumab.

The most significant adverse event observed in studies of trastuzumab was cardiac dysfunction similar to that observed with anthracyclines. An independent Cardiac Review and Evaluation Committee (CREC) determined the occurrence of cardiac dysfunction up to 14 months of follow-up in a retrospective fashion. The signs and symptoms of patients with cardiac dysfunction included a decline in cardiac ejection fraction, S3 gallop, dyspnoea on exertion, orthopnoea, cardiomegaly, cough, tachycardia and peripheral oedema. Cardiac dysfunction cases were most frequently seen among patients enrolled in the pivotal phase III combination study who received trastuzumab plus an anthracycline. The majority of the events occurred after patients had received a cumulative dose of $\geqslant 360$ mg/m^2 of doxorubicin. Cardiac dysfunction in patients receiving the trastuzumab plus paclitaxel combination was less common and less severe than that observed in patients treated with trastuzumab plus an anthracycline. A total of 11/91 patients treated with paclitaxel plus trastuzumab compared with 1/95 of those receiving paclitaxel alone experienced cardiac dysfunction. Corresponding figures for patients receiving anthracycline plus trastuzumab or anthracycline alone were 38/143 and 10/135, respectively. The number of patients with symptomatic heart failure (NYHA class III/IV) as a result of cardiac dysfunction was low. Furthermore, the majority of patients with symptomatic disease improved following the use of standard therapies. Two deaths secondary to cardiac dysfunction were reported (1 patient receiving trastuzumab plus anthracycline, 1 patient receiving anthracycline alone). When the impact of such cardiac adverse events on net clinical benefit of trastuzumab was determined via an analysis of time to disease progression, death or CREC-determined cardiac dysfunction, the results indicated that the median time to undesired clinical outcomes was still longer with trastuzumab plus chemotherapy than with chemotherapy alone.

5. Conclusions

Data from pivotal trials indicate that trastuzumab is active when added to chemotherapy, increasing clinical benefit markedly, as indicated by increases in TTP, response rate and median survival. The combination of trastuzumab with chemotherapy (anthracycline or paclitaxel) was active for the treatment of patients with HER2-positive metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. In particular, the combination significantly prolonged the median TTP (from 4.6 to 7.4 months), increased the overall response rate (from 32 to 50%), increased the duration of response (from 6.1 to

9.1 months), and improved 1-year survival times (from 68 to 79%) compared with chemotherapy alone. Median survival was improved by approximately 25%. These benefits of using trastuzumab were observed both in combination with an anthracycline and in combination with paclitaxel. There was also a trend towards maintenance of QoL among patients treated with trastuzumab plus chemotherapy compared with chemotherapy alone.

Furthermore, trastuzumab is active as a single agent in women with HER2-positive metastatic breast cancer, inducing durable objective tumour responses. In total, 15% of patients who had received extensive prior treatment for metastatic disease had an objective response. The median duration of response was 9.1 months (range 1.6–26+) following administration of single-agent trastuzumab. Notably, 21% of patients were free of disease progression at 6 months. The safety profile of trastuzumab either given alone or in combination was favourable. However, data indicate that there is a risk of cardiac dysfunction in patients receiving trastuzumab. This appears to be related to previous or concomitant anthracycline exposure, and it is recommended that women with pre-existing heart disease or high cumulative anthracycline exposure are treated with caution. Regular cardiac monitoring while treating patients with trastuzumab is also recommended.

The clinical trials discussed above have led to the approval by the US Food and Drug Administration (FDA) of trastuzumab for use in women with metastatic breast cancer with HER2-positive tumours. The treatment is indicated in the USA as a single agent for patients having failed earlier therapy and as first-line treatment for metastatic disease when used in combination with paclitaxel.

One prerequisite for using trastuzumab is that the HER2 status of all patients being considered for therapy must be established. The best test to use for this purpose has been the subject of some discussion, with a variety of immunohistochemistical techniques having been used in clinical trials and elsewhere. Fluorescence *in situ* hybridisation has been proposed to be a useful alternative to IHC, but is less widely available, requires specialised equipment and has not been correlated with clinical outcomes. Therefore, IHC currently appears to be the best option for HER2 testing, and the HercepTest® (DAKO) is the most widely used and best standardised immunohistochemical assay. In addition, the concordance between the HercepTest® and the CTA used in the pivotal trials is high [18], supporting the use of this test to select those patients most likely to respond to trastuzumab therapy.

Based on the successful outcome of these and other trials, further studies are underway to assess the benefit of trastuzumab when used in different combinations and at different stages of therapy. Such trials are examining the efficacy and safety of trastuzumab as a single agent in previously untreated metastatic disease, in combination with other anthracyclines and taxanes or with different dose schedules of these agents, with agents such as vinorelbine, and as adjuvant therapy.

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