Trastuzumab tolerability in the treatment of advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress HER2/neu

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Abstract

Objective: Due to previously reported trastuzumab safety concerns and the scant data available in endometrial cancer patients, we sought to assess the safety, tolerability and toxicity profile of trastuzumab in patients with advanced/recurrent uterine serous carcinoma (USC) that overexpress HER2/neu in our multicenter randomized phase II trial.

Methods: Patients were randomized 1:1 to receive carboplatin/paclitaxel (C/P) for 6 cycles ± trastuzumab (T) with the experimental arm continuing to receive single agent trastuzumab maintenance treatment until disease progression/toxicity. Progression-free-survival was the primary endpoint; overall-survival and toxicity were secondary endpoints. Adverse events (AEs) were compared between treatment arms.

Results: There were 28 patients in the C/P arm and 32 patients in the experimental (C/P+T) arm. Fifty-eight patients (97%) experienced 977 treatment-related AEs of which 875 (89.6%) were low-grade (grade 1–2) and 102 (10.4%) were high-grade (grade 3–5). The mean±standard deviation of AEs per patient was 15.5±16.3 in the C/P arm and 17.0±16.0 in the C/P+T arm. Gastrointestinal AEs were the most common in both arms (n=155, 15.7%) of which 94.2% were low-grade (n=146). Importantly, no significant difference between treatment arms was detected

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in any system-organ class of AE including cardiac AE. Five (17%) of 29 patients who received prolonged trastuzumab maintenance therapy had no sign of cumulative toxicity after an average (range) of 5.1 (4.2 – 6.3) years.

Conclusions: Trastuzumab appears to be safe and has a manageable toxicity profile both when used in combination with chemotherapy and when used for single agent maintenance in patients with HER2/neu positive USC. This safety profile is reassuring given the proven efficacy of trastuzumab in advanced/recurrent HER2/neu positive USC.

Keywords

Trastuzumab; uterine serous carcinomas; HER2/neu; tolerability; side effects

INTRODUCTION

In the United States, endometrial cancer is the most prevalent of all gynecologic malignancies, accounting for an estimated 65,620 cases and 12,590 deaths in 2020 alone [1]. Endometrial cancer remains one of the only malignancies in which both the incidence and deaths continue to rise [1–3]. Uterine serous carcinoma (USC) is an aggressive, high-grade histologic subtype of endometrial cancer that portends a poor clinical prognosis. In fact, approximately 70% of patients with USC present with stage III or IV disease [4,5]. Although USC accounts for only 10% of all endometrial carcinomas, it is responsible for a disproportionate 39% of all uterine cancer-related deaths and has an overall 5-year survival rate of 45%, compared to 91% for those with the more common histologic subtype, endometrioid adenocarcinoma [6–8].

HER2/neu, the molecular target of the monoclonal antibody trastuzumab, is a tyrosine kinase receptor that plays an integral role in the coordination of the complex ErbB signaling network that is responsible for the regulation of cell growth, survival and proliferation [9]. HER2 overexpression and amplification is present in approximately 30% of USC and appears to be a poor prognostic factor similar to that seen in breast cancer [10–18]. Traditionally, USC has been treated with hysterectomy and surgical staging followed by platinum/taxane combination chemotherapy [19–22]. However, initial response rates to the most commonly used chemotherapy regimen, carboplatin and paclitaxel, can be as low as 20–60% for previously untreated advanced stage disease and an even worse response rate of 10–15% for those with recurrent disease [23].

A recent multicenter randomized phase II trial demonstrated that trastuzumab in combination with carboplatin/paclitaxel resulted in a significant improvement in both progression-free survival and overall survival for patients with both advanced and recurrent HER2/neu-positive USC [24,25]. As a result, the National Comprehensive Cancer Network's Uterine Neoplasm Guidelines endorses the addition of trastuzumab to standard cytotoxic chemotherapy as the preferred regimen for the treatment of HER2/Neu-positive, advanced or recurrent USC [26].

HER2/neu amplification or overexpression is present in approximately 15 percent of primary invasive breast cancers [27]. Women with both early-stage and metastatic HER2-positive

breast cancer are treated with trastuzumab-containing regimens because of several studies demonstrating substantial clinical benefit for these patients [28–31]. Large randomized trials of adjuvant trastuzumab for HER2-positive breast cancer reported an increase in the risk of cardiac toxicities, including congestive heart failure (0.6% to 3.8%) and left ventricular ejection-fraction declines (4.1% to 30.1%) [28,33–36]. Additionally, 20%−40% of breast cancer patients have an infusion reaction during the first treatment with trastuzumab, although most are mild, and only 0.3% exhibiting features suggestive of anaphylaxis [37–41]. Other rarer side effects of trastuzumab (less than 1%), are acute respiratory distress syndrome (ARDS), subacute interstitial pneumonia, and organizing pneumonia [42–44]. Although pulmonary toxicity is infrequent, it may be life-threatening, and discontinuation of trastuzumab is advised if such pulmonary side effects are present [45–47].

Despite the vast amount of information present in the literature regarding the safety, tolerability, and toxicity profile of trastuzumab in breast cancer patients, there is very limited information available on those with endometrial cancer in general and USC in particular who are treated with trastuzumab. In fact, GOG 181B, which was a phase II trial evaluating trastuzumab in women with advanced or recurrent HER2-positive endometrial carcinoma, is the only study to date that reports on the side-effect profile of treatment with trastuzumab for HER2-positive endometrial cancer [48]. In this study, Fleming et al. found a total of 33 adverse effects in their HER2-positive cohort of 34 patients. There were two deaths that were thought to be attributed to trastuzumab treatment, and both were associated with cardiovascular events (one infarction and one cardiopulmonary arrest) [48]. Other grade-3 and −4 adverse events included anemia and other hematologic events, plus gastrointestinal, metabolic, pain, and pulmonary issues [48]. Nevertheless, patients in GOG 181B were on study only for a few months before trial closure, highlighting the fact that there is no information available on the long-term tolerability of trastuzumab in USC patients, who tend to be older in age than Type I endometrial cancer patients. An important secondary objective of the randomized phase II trial was "to assess the safety profile of trastuzumab in USC patients" [24,25]. In this report, we fulfill that objective by characterizing the tolerability and toxicity profile of trastuzumab treatment found in our randomized phase II trial of patients treated with trastuzumab for advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress HER2/neu.

METHODS

Study design and conduct

The patient eligibility criteria and study design for this investigator-initiated randomized phase II study (NCT01367002) have been previously described in detail [24]. In brief, at a total of 11 participating academic institutions within the United States, patients were randomized 1:1 by the lead study institution using minimization to balance the treatment arms for study site, disease status (advanced versus recurrent uterine serous carcinoma), and residual tumor after debulking within the advanced-disease group [26]. Patients were scheduled to receive intravenous carboplatin area under the curve (AUC) 5 and paclitaxel 175 mg/m^2 over 3 hours every 21 days with or without trastuzumab at 8mg/kg for the first dose and 6 mg/kg in subsequent cycles until disease progression or prohibitive toxicity. The

first subject was enrolled in August of 2011, after which (1) the accrual rate was slower than planned, and (2) observed progression-free survival exceeded original expectations. The study was closed to further accrual in March of 2017 with a total of 61 enrolled subjects. Efficacy analysis commenced in August of 2017. The current updated analysis was performed at the time of 43 progressions and 38 deaths (Figure 1).

Eligibility

All patients were 18 years or older and had FIGO 2009 stage III-IV recurrent (any previous stage) HER2/Neu-positive uterine serous carcinoma as defined by an immunohistochemistry score of 3+ or 2+ with gene amplification confirmed by fluorescence *in situ* hybridization (FISH). HER2/Neu-positive status was determined using paraffin-embedded tumor tissue from either primary surgery or from recurrent disease [49]. Scoring was performed according to guidelines set forth by the 2007 American Society of Clinical Oncology/ College of American Pathologists for breast cancer [50]. Specimens were centrally reviewed for HER2/Neu+ and confirmed to contain 10% uterine serous carcinoma by two gynecologic pathologists. Patients may have been either optimally or suboptimally debulked after primary surgery. Patients were enrolled within 8 weeks after surgery or diagnosis of recurrent disease. Patients were required to exhibit an Eastern Cooperative Oncology Group performance status of 0 to 2, adequate bone marrow, renal function, and hepatic function. All patients diagnosed with recurrence were required to have measurable disease, defined as at least one target lesion per RECIST v1.1 [50,51]. A treatment-free interval of >6 months from last carboplatin/paclitaxel was required in those with recurrent disease. Patients with recurrent disease may not have received >3 prior chemotherapies for treatment of their uterine cancer. The schemata for treatment modification are provided in the full protocol.

Endpoints

All adverse events were classified using the Medical Dictionary for Regulatory Activities version 20.0 and onward. The severity of any toxic effect was graded in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 [51]. All adverse events and serious adverse events were collected and documented for each patient from the day informed consent was obtained until their end-of-treatment visit. New serious adverse events (including deaths) were collected for 30 days after the last dose of study treatment. To assess the safety profile of trastuzumab in USC patients enrolled on NCT01367002, we performed two analyses First, we analyzed the adverse events reported by patients in both treatment arms and evaluated the overall tolerability of the addition of trastuzumab to the standard chemotherapy regimen of carboplatin and paclitaxel for the treatment of advanced-stage and recurrent uterine serous carcinoma. Second, we analyzed the adverse events reported by patients in Arm 2 who received single-agent-trastuzumab maintenance after chemotherapy. All data were entered into our OnCore clinical-trials management system using case report forms specifically for NCT01367002 and collecting TRAEs (treatment related adverse events), grade, and drug attribution information.

Statistical analyses

Descriptive statistics were used to summarize and describe the basic features of the data collected. The number and proportion of patients who experienced at least one AE was

reported in each treatment arm. For each patient, the number of AEs of any grade, of low grade (Grades 1 or 2), and of high grade (Grades 3, 4, or 5) was counted, and these three counts per patient were summarized by treatment arm as the sum, mean, standard deviation, and the "five-number summary" consisting of the mean, quartiles, and range.

RESULTS

As previously published by Fader et al., between August 2011 and January 2017, sixty-one subjects were enrolled, of which three participants were excluded due to withdrawal of consent (n=1) or failure to confirm HER2/Neu positivity by FISH following 2+ immunohistochemistry (n=2) at the time of central review. This left 58 subjects (28 in the carboplatin/paclitaxel (C/P) arm and 30 in the carboplatin/paclitaxel +trastuzumab (C/P+T) arm) evaluable for response to treatment [24] (Figure 1). Treatment arms did not differ significantly in regard to race, ethnicity, study site, or disease status (advanced versus recurrent disease), radiation or optimal debulking among advanced-disease subjects, or number of prior lines of chemotherapy among recurrent-disease subjects. However, the patients in the trastuzumab arm were seven years younger (median 66 years; interquartile range of 64–69 years) compared to the control arm (median 73 years; interquartile range of 68–78 years) [24]. Nonetheless, there was no statistically significant difference in the number of patients who experienced any adverse event due to treatment when stratified by age 70 years and age <70 years. Additionally, although most of the patients in both study arms were Caucasian, there were no significant differences in race or ethnicity between treatments arms, as previously published [24].

For our final analysis of adverse events due to treatment, we included the two aforementioned patients with immunohistochemical HER2/Neu positivity that were ultimately found to be FISH-negative upon central review. This was deemed acceptable for two reasons: the primary outcome of the current manuscript is toxicity and these two patients received trastuzumab. Thus, there were 60 patients evaluable for toxicity, 28 of whom received C/P and 32 of whom received C/P+T. Fifty-eight (97%) of them reported at least one treatment-related adverse event (AE) during the chemotherapy phase of treatment, including 27 (96%) on the C/P arm versus 31 (97%) on the C/P+T arm. These 58 patients experienced a total of 977 treatment-related AEs during chemotherapy (Tables 1A, 1B, and 1C), of which 875 (89.6%) were low-grade (grade 1–2) and 102 (10.4%) were high-grade (grade 3–5). The number of AEs per patient had a mean ±SD [standard deviation] of 15.5 ±16.3 on the C/P arm and 17.0 ±16.0 on the C/P+T arm (Table 1A). Of the 977 AEs, 433 (44.3%) were in the C/P arm and 544 (55.7%) were in the C/P+T arm (Table 1B). When grouped by system-organ class, the most common AE in both arms consisted of gastrointestinal disorders (n=155, 15.7%), the overwhelming majority of which (n=146) were low-grade (Table 1C). Gastrointestinal disorders also showed the most treatment-arm imbalance for any AEs per patient, with a mean ±SD of 3.16 ±3.20 on the C/P+T arm versus 1.93 ±2.67 on C/P alone, but this 64% increase in the presence of trastuzumab failed to attain statistical significance. Importantly, none of the other 18 system-organ classes showed a noteworthy treatment-arm imbalance in the number of AEs of any grade per patient (range in p-values: 0.17 – 0.84).

The low-grade AEs per patient had means ±SDs of 14.07 ±15.31 and 15.03 ±13.68, respectively, on the C/P and C/P+T arms Table 2). When low-grade AEs were subgrouped by system-organ class, gastrointestinal disorders revealed the most treatment-arm imbalance. The average number of low-grade gastrointestinal AEs per patient was 1.6-fold higher with C/P+T(mean ±SD = 2.97 ±3.07) than with C/P alone (mean ±SD = 1.82 ±2.58), but this increase was considered clinically inconsequential given that these AE were low grade and secondary to the prolonged duration of treatment in the trastuzumab arm. None of the 18 other system-organ classes revealed an appreciable treatment-arm imbalance in the number of low-grade AEs per patient.

For high grade AEs per patient, the means ±SDs on the C/P and C/P+T arms were 1.39 ±2.39 and 1.97 ±3.43, respectively (Table 3). When high-grade AEs were subgrouped by system-organ class, the blood and lymphatic-system disorders demonstrated the most treatment-arm imbalance. The average number of high-grade blood-and-lymph AEs per patient was 3.3-fold higher with C/P+T (mean ±SD = 0.59 ±1.01) than with C/P alone (mean ±SD = 0.18 ±0.55). This difference was however clinically inconsequential and likely related to chemotherapy and the prolonged duration of treatment in the trastuzumab arm. Importantly, none of the other system-organ-class comparisons for high-grade adverse events demonstrated a noteworthy significant imbalance between treatment arms.

Regarding cardiovascular AEs, four patients experienced a total of four AEs, all of which were low-grade. There was only one in the C/P arm and only three in the C/P+T arm (Table 4). There were also no instances of congestive heart failure. There was one investigation for a grade-3 left ventricular dysfunction deemed to be unrelated to study drug by both the patient's cardiologist and the study's Principal Investigator.

Of the thirty-two patients that were randomized to the C/P+T arm and treated with trastuzumab during their chemotherapy, twenty-nine of them (91%) received single-agent maintenance trastuzumab after finishing frontline chemotherapy. Of the three patients who did not, two were the HER2/neu 2+ but FISH-negative patients who were excluded from the original efficacy analysis. All except two of the 29 patients began single-agent trastuzumab on Cycle 7. The two exceptions both had recurrent measurable disease, received carboplatin and paclitaxel through Cycle 9, and began their single-agent trastuzumab on Cycle 10. The 29 patients have experienced 617 post-chemotherapy cycles up through June 24th, 2020 and have received trastuzumab during 615 of them to yield an average of 21.2 cycles (range: 1–94 cycles) of trastuzumab thus far (Table 4). At the time of this writing (mid-March of 2021), 5 (17%) of the 29 USC patients who began maintenance treatment with single-agent trastuzumab continue to receive it every 3 weeks per protocol. These 5 patients have been on trastuzumab maintenance for 4.2, 4.7, 4.9, 5.5, and 6.3 years. One subject skipped trastuzumab on Cycles 41 and 50 and received late paclitaxel instead. Another patient received late paclitaxel concurrently with trastuzumab from Cycle 25 through Cycle 29 of her trastuzumab-alone treatment. Those 5 cycles are counted as single-agent trastuzumab for purposes of this analysis. No other patient received a second agent during their trastuzumab alone post chemotherapy segment.

DISCUSSION

In a previous multicenter randomized phase II trial, the addition of trastuzumab to carboplatin and paclitaxel resulted in a significant improvement in PFS and OS in advanced/recurrent HER2/neu-positive USC [24,25]. Due to previous safety concerns regarding trastuzumab and its reported adverse cardiac events, we evaluated the safety of the addition of trastuzumab to carboplatin and paclitaxel followed by maintenance trastuzumab in elderly patients with advanced or recurrent USC, as a follow up analysis of the original phase II study [24,25, 28, 33–35]. Our data suggest both the safety and tolerability of trastuzumab, which has been shown to improve oncologic outcomes for HER2/Neu 3+ patients with advanced or recurrent USC. Thus far, five of 29 patients who began trastuzumab maintenance have remained on treatment for an average (range) of 5.1 (4.2 – 6.3) years.

Though most of the patients were Caucasian, the treatment arms were well-balanced in regard to ethnicity and race, as previously published [24]. Elderly patients (70 years old in this analysis) were more likely to experience a high-grade AE in both arms. Although the average number of high-grade AEs per patient was 3.3-fold higher in Arm II (mean = 0.59 high-grade AEs per patient) compared to Arm I (mean = 0.18 high-grade AEs per patient) this increase was clinically inconsequential since no patient discontinued therapy due to these AEs and such an increase in number was likely related to the prolonged duration of treatment in the trastuzumab arm. Our adverse-events investigation suggest that trastuzumab is very well-tolerated in elderly patients with USC. In that respect, it differs from the published results in breast cancer, a tumor where patients often receive cardiotoxic agents (i.e. anthracyclines) as standard of care, and where trastuzumab treatment has been shown to increase the incidence of adverse events. It is worth noting that the median age in a large Cochrane review was 49 years, which is much younger than the median age (67 years) of our experimental arm [30,24]. Thus, despite our much more elderly population, our data suggests that trastuzumab was not only efficacious but also highly tolerable in this group of patients not previously exposed to Adriamycin (doxorubicin).

In addition, even though the majority of patients in our study had at least one AE, either during treatment or during post-treatment maintenance with trastuzumab, the majority of these adverse events were low-grade AEs, most commonly being fatigue, nausea, and constipation. These are all extremely common AEs with most chemotherapeutic regimens, each with their own available treatments and prophylactic regimens to decrease their incidence. There was an investigation due to decreased EF in a patient with a history of complete heart block with a pacemaker and cardiologic workup including LVEF monitoring every 3 months per protocol revealed the cause as pacemaker-induced cardiomyopathy. Thus it was not deemed to be a direct toxicity of trastuzumab.

Most of the available literature in breast cancer has limited the window of usage of trastuzumab to 1 year in the adjuvant setting [28–30]. Though there is insufficient evidence based on a small number of trials, a shorter duration of therapy was associated with lower cardiotoxicity in the aforementioned Cochrane review [34]. Despite this, even though our cohort of patients received an average of 21.2 cycles and maximum of 94 (at the time of

this writing, five patients continue to receive trastuzumab treatment every 21 days), there was no clinically significantly increase in toxicity, particularly cardiac toxicity. Based on the limited data currently available, one would anticipate a greater number of adverse effects due to the cumulative number of cycles in combination with the elderly median age of our population, which we unexpectedly did not find. As mentioned above, an important difference between our study and the existing literature in breast cancer is that most trials reporting significant cardiac toxicity with trastuzumab included anthracyclines, which are an important contributor to cardiac toxicity. Both a history of prior anthracycline receipt and, especially, concurrent anthracycline use are known to increase cardiac toxicity, so much that the NCCN recommends the latter be avoided [53]. Standard first line chemotherapy (both adjuvant and neoadjuvant) consists of carboplatin and paclitaxel in USC; anthracyclines were avoided altogether, and patients were excluded from this study if they had a prior malignancy, thus this would not confound our results [24]. In our patient cohort there was only one patient that had a grade 3 event while receiving maintenance trastuzumab and this event was not considered related to treatment. Thus, we found no evidence of increased cardiac toxicity of trastuzumab in this elderly cohort of patients with USC.

Our study has several important limitations. The sample size could impact the rate of adverse events, as they were not the primary endpoint and thus our analysis was not powered to detect them. This was due to slow patient accrual and unexpected efficacy in the parent trial [24]. Additionally, the patients in the control arm had a higher median age than the experimental arm; however, the high-grade AE rate was higher in the older population, thus indicating that this did not confound our results.

The safety demonstrated herein is particularly promising given the proven utility of trastuzumab in advanced and/or recurrent HER2/neu positive USC. Pertuzumab will be used in combination with trastuzumab in an upcoming NRG/CTEP trial in the same population and we are hopeful that results will not be limited by patient toxicity (NCT01367002). In conclusion, trastuzumab appears to be very well-tolerated treatment when used in combination with standard chemotherapy and as single-agent maintenance in patients with HER2/neu positive advanced/recurrent uterine serous carcinoma.

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Highlights

- Our patients received an average of 21.2 and maximum of 94 cycles of Trastuzumab without significant toxicity.

- The majority of adverse events were low-grade, most commonly fatigue, nausea, and constipation.

- Patients who received trastuzumab maintenance had no sign of increased toxicity after an average of 5.1 years of continued treatment.

- Elderly patients (70 years old) were more likely to experience a high-grade adverse event in both treatment arms.

- Trastuzumab in combination with chemotherapy appears to be safe and has a manageable toxicity profile in patients with HER2/Neu-positive USC.
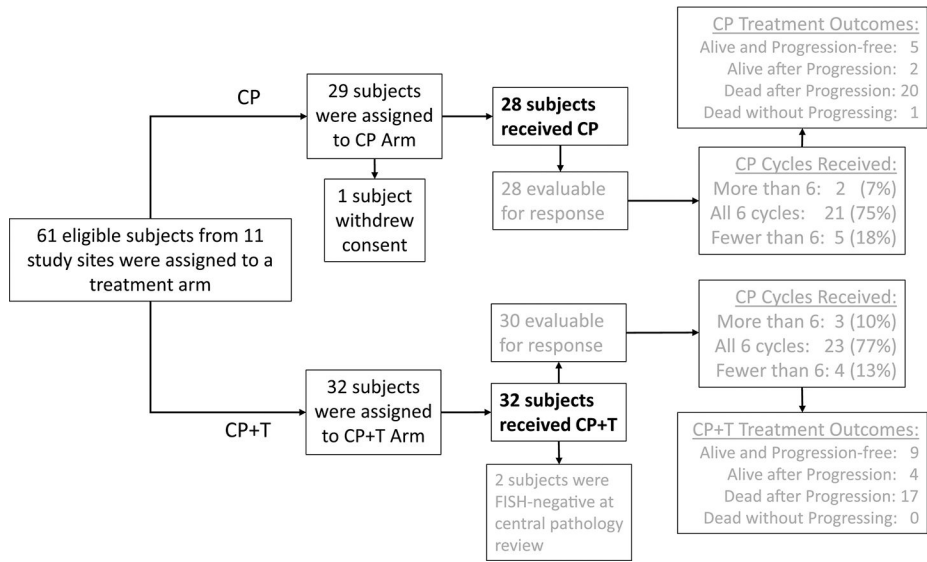
Figure 1:
CONSORT diagram. Adapted from Fader AN, Roque DM, Siegel E, et al. Randomized phase II trial of carboplatin-paclitaxel compared to carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress HER2/Neu (NCT01367002): updated overall survival analysis.

Table 1.

Demonstrates all adverse events for both Arm I and Arm II Please note in Table 1c the investigations category can best be described as abnormal lab findings, or other abnormal procedural findings (i.e. ejection fraction decreased is categorized here as well as urine output decreased).

A. Distribution of AEs Per Patient (any grade) During Chemotherapy								
Treatment Arm	**Sum**	**Mean**	**Standard Deviation**	**Minimum**	**First Quartile**	**Median**	**Third Quartile**	**Maximum**
Carboplatin/Paclitaxel only (C/P)	433	15.46	16.26	0	6.5	8.5	18	73
Carboplatin/Paclitaxel +Trastuzumab (C/P+T)	544	17.00	16.01	0	8	10.5	25.5	72
BOTH ARMS	977	16.28	16.01	0	7	10	20.5	73

B: Adverse Events (AEs) by Grade and Treatment Arm						
	Number of AEs by Grade					**Number of AEs, All Grades**
TREATMENT ARM	**1**	**2**	**3**	**4**	**5**	
Carboplatin/Paclitaxel only (C/P)	273	121	34	3	2	433
Carboplatin/Paclitaxel +Trastuzumab (C/P+T)	343	138	52	11	.	544
BOTH ARMS	616	259	86	14	2	977

C: Adverse Events (AEs) by Grade and System Organ Class						
	Number of AEs by Grade					**Number of AEs, All Grades**
SYSTEM ORGAN CLASS (CATEGORY)	**1**	**2**	**3**	**4**	**5**	
Gastrointestinal disorders	109	37	9	.	.	155
Investigations	74	44	25	4	.	147
Blood and lymphatic system disorders	38	27	17	7	.	89
General disorders and administration site conditions	65	23	.	.	.	89
Skin and subcutaneous tissue disorders	47	33	1	.	.	81
Metabolism and nutrition disorders	54	16	10	.	.	80
Musculoskeletal and connective tissue disorders	54	21	1	.	.	76
Nervous system disorders	59	8	1	.	.	68
Respiratory, thoracic and mediastinal disorders	33	10	3	1	.	47
Vascular disorders	10	8	9	.	2	29
Infections and infestations	12	11	4	2	.	29
Renal and urinary disorders	14	11	3	.	.	28
Psychiatric disorders	21	1	2	.	.	24

Reproductive system and breast disorders	7	4	.	.	.	11
Eye disorders	5	2	.	.	.	7
Ear and labyrinth disorders	5	.	.	.	.	5
Injury, poisoning and procedural complications	4	.	.	.	.	4
Immune system disorders	1	3	.	.	.	4
Cardiac disorders	4	.	.	.	.	4
ALL SYSTEM-ORGAN CLASSES	616	259	86	14	2	977

Table 2:

Demonstrates grade 1–2 adverse events for both Arm I and Arm II

A. Distribution of Low-Grade (1–2) AEs Per Patient During Chemotherapy

Treatment Arm	Sum	Mean	Standard Deviation	Minimum	First Quartile	Median	Third Quartile	Maximum
C/P	394	14.07	15.31	0	5.5	8.5	17	68
C/P+T	481	15.03	13.68	0	7	10	20.5	57
Both arms	875	14.58	14.35	0	6	9	18	68

B. Number of Low-Grade AEs reported

System-Organ Class	Grade 1	Grade 2	Sum
Gastrointestinal disorders	109	37	146
Investigations	74	44	118
Blood and lymphatic system disorders	38	27	65
General disorders and administration site conditions	65	23	88
Skin and subcutaneous tissue disorders	47	33	80
Metabolism and nutrition disorders	54	16	70
Musculoskeletal and connective tissue disorders	54	21	75
Nervous system disorders	59	8	67
Respiratory, thoracic and mediastinal disorders	33	10	43
Vascular disorders	10	8	18
Infections and infestations	12	11	23
Renal and urinary disorders	14	11	25
Psychiatric disorders	21	1	22
Reproductive system and breast disorders	7	4	11
Eye disorders	5	2	7
Ear and labyrinth disorders	5	0	5
Injury, poisoning and procedural complications	4	0	4
Immune system disorders	1	3	4
Cardiac disorders	4	0	4
ALL System-Organ Hasses	616	259	875

Table 3:

Demonstrates grade 3–5 adverse events for both Arm I and Arm II

A. Distribution of High-Grade (3–5) AEs Per Patient During Chemotherapy								
Treatment Arm	**Sum**	**Mean**	**Standard Deviation**	**Minimum**	**First Quartile**	**Median**	**Third Quartile**	**Maximum**
C/P	39	1.39	2.39	0	0	0	1.5	10
C/P+T	63	1.97	3.43	0	0	0.5	3	15
Both arms	102	1.70	2.98	0	0	0	2	15

B. Number of High-Grade AEs reported				
System-Organ Class	**Grade 3**	**Grade 4**	**Grade 5**	**Sum**
Gastrointestinal disorders	9	0	0	9
Investigations	25	4	0	29
Blood and lymphatic system disorders	17	7	0	24
General disorders and administration site conditions	1	0	0	1
Skin and subcutaneous tissue disorders	1	0	0	1
Metabolism and nutrition disorders	10	0	0	10
Musculoskeletal and connective tissue disorders	1	0	0	1
Nervous system disorders	1	0	0	1
Respiratory, thoracic and mediastinal disorders	3	1	0	4
Vascular disorders	9	0	2	11
Infections and infestations	4	2	0	6
Renal and urinary disorders	3	0	0	3
Psychiatric disorders	2	0	0	2
Reproductive system and breast disorders	0	0	0	0
Eye disorders	0	0	0	0
Ear and labyrinth disorders	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	0
Immune system disorders	0	0	0	0
Cardiac disorders	0	0	0	0
ALL System-Organ Classes	86	14	2	102

Table 4:

Adverse cardiac events for both Arm I and Arm II

Table (Supp) Cardiac AEs			
	Any Cardiac AE (During Chemotherapy)		
Arm	Yes	No	
1	1	27	
2	3	29	
	Cardiac AE Type* (N) (During Chemotherapy)		
Arm	Palpitations	Sinus Tachycardia	Vent. Arrhythmia
1	0	1	0
2	2	0	1
	Any Cardiac AE (Trastuzumab Maintenance)		
Arm	Left Ventricular systolic dysfunction		
	Yes	No	