HHS Public Access

Author manuscript

Breast Cancer Res Treat. Author manuscript; available in PMC 2018 May 08.

Published in final edited form as:

Breast Cancer Res Treat. 2018 February ; 168(1): 35–41. doi:10.1007/s10549-017-4563-3.

Characteristics and outcomes of breast cancer patients enrolled in the National Cancer Institute Cancer Therapy Evaluation Program sponsored phase I clinical trials

Filipa Lynce[1], **Matthew J. Blackburn**[1,2], **Ling Cai**[3], **Heping Wang**[3], **Larry Rubinstein**[4], **Pamela Harris**[5], **Claudine Isaacs**[6], and **Paula R. Pohlmann**[1]

[1]Lombardi Comprehensive Cancer Center, MedStar Georgetown University Hospital, 3800 Reservoir Rd NW, Podium B Room 404, Washington 20007, DC, USA

[2]University of South Carolina School of Medicine, Columbia, USA

[3]Department of Biostatistics, Bioinformatics, and Biomathematics, Georgetown University, Washington, USA

[4]Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Rockville, USA

[5]Investigational Drug Branch Cancer Therapy Evaluation Program Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Rockville, USA

[6]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA

Abstract

Purpose—Breast cancer (BC) is the most commonly diagnosed cancer and the second leading cause of cancer-related death among women. Given the availability of approved therapies and abundance of phase II and III clinical trials, historically few BC patients have been referred for consideration of participation on a phase I trial. We were interested in determining whether clinical benefit rates differed in patients with BC from other patients enrolled in phase I trials.

Methods—We performed a retrospective analysis of all Cancer Therapy Evaluation Program (CTEP) sponsored phase I trials from 1993 to 2012. We report an analysis of demographic variables, rates of response to treatment, grade 4 toxicities, and treatment-related deaths.

Results—De-identified data from 8087 patients were analyzed, with 1,376 having a diagnosis of BC. The median time from initial cancer diagnosis to enrollment in a CTEP-sponsored phase I clinical trial was 614 days for all patients. Breast cancer patients were enrolled on average 790 days after initial diagnosis, while non-BC patients had a median enrollment time of 582 days ($p <$ 0.001). Breast cancer patients had more clinical responses than non-BC patients (18.3% vs. 4.3%,

Correspondence to: Filipa Lynce.

Presented in part at the San Antonio Breast Cancer Symposium, San Antonio TX, December 9–13, 2014.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-017-4563-3) contains supplementary material, which is available to authorized users.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

respectively). Along with the higher rate of response, BC patients remained on phase I trials longer than non-BC patients with a median of 70 days while the latter were on trial for a median of 57 days. The overall rate of death related to the treatment drugs was 0.47%.

Conclusions—Our data confirm our hypothesis that when compared to a general population of patients with cancer enrolled on phase I clinical trials, BC patients tend to derive clinical benefit from these therapies with similar toxicity profile. This evidence further supports enrollment of BC patients on phase I trials.

Keywords

Breast cancer; Phase I; Clinical trials; Outcomes; Toxicity

Background

Phase I clinical trials are a critical component of the long road of innovative oncology drug development. Traditionally, the primary endpoint of these trials has been to determine the safety, tolerability, and recommended phase 2 dose (RP2D) of novel agents for further studies. As a result, the expectation of direct clinical benefit to patients participating on these trials may be perceived as being relatively low, whereas the risks and possible harms potentially substantial, given the early phase development of the drugs. Low response rates of 4–6% have historically been reported [1–9]. Although recent phase I studies have reported higher response rates [10, 11] and relatively long progression free survival [12–14], phase I studies are still typically reserved for patients who lack other treatment options.

Breast cancer (BC) is the most commonly diagnosed cancer and the second leading cause of cancer-related death among women. The 5-year relative survival for stage IV BC is 26.9% [15] and overall survival (OS) has been reported between 19 and 34 months [16–19]. Recent drug approvals by the Food and Drug Administration (FDA) have significantly improved the OS to 56.5 months in some subtypes of BC [20].

The representation of cancer patients in phase I trials has been historically low. While only 3–5% of the United States adult cancer patients are enrolled in clinical trials [21, 22] the number of those participating in phase I trials is even lower. Many factors are associated with this fact and include the misconception that phase I trials are a last-ditch effort, misinformation regarding the possibility of receiving placebo, or inconvenience of additional visits and tests. It is also our experience that patients with BC are referred to phase I trials at a late point in time on their disease natural history, possibly also related to the availability of a larger number of active standard treatment options. At that point, life expectancy, performance status, and organ function frequently preclude enrollment. In addition, in the recent years, early phase clinical trials mostly testing targeted agents or immunotherapeutic approaches presented new challenges to design [23], including limitations to the number of previous treatment lines of therapy for eligibility.

In this study, we sought to analyze a cohort of patients enrolled on phase I clinical trials over a 20-year period and to determine whether patients with BC derive similar clinical benefit

and toxicities from phase I trials when compared to enrolled patients with other malignancies.

Methods

Patient eligibility

All non-pediatric patients enrolled in phase I oncology trials sponsored by the Cancer Therapy Evaluation Program (CTEP) between 1993 and 2012 were eligible for this study. Protocols including hematologic and solid tumor malignancies were included and consisted of both single and multiagent investigational targets. These clinical trials were performed at the National Institutes of Health Clinical Center and other National Cancer Institute-sponsored academic centers within the United States.

All protocols were approved by the Protocol and Information Office (PIO) of CTEP prior to enrollment. Regular quality assurance audits were performed by the Clinical Trials Monitoring Service (CTMS) and CTEP. Data were prospectively maintained by individual trial investigators and staff of CTEP. These data were then electronically delivered to the CTMS on a bi-weekly basis for the duration of each trial. The electronic database is maintained by the CTMS which was managed by Theradex (Princeton, NJ, USA) at the time of data analysis.

Pre-enrollment characteristics

Information regarding pre-enrollment characteristics including age, sex, race, performance status (PS), hemoglobin, albumin, and primary disease site were recorded. The PS at enrollment was measured using either the Eastern Cooperative Oncology Group (ECOG) score or the Karnofsky score as specified by each protocol. For analysis, PS measured using the Karnofsky scale was directly converted to the ECOG scoring modality [24].

For the purpose of this study, patients were categorized into breast (BC) and non-breast cancer (non-BC) by using primary disease site. Data pertaining to diagnostic timelines as well as the total amount of prior medical therapies were also obtained.

Study outcomes and tolerability

Outcomes of treatment, including disease response, treatment duration, and data regarding tolerability were evaluated. We sought to analyze the beneficial effects of investigational agents for BC versus non-BC. Response to treatment was assessed using guidelines according to the World Health Organization criteria, Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, or the revised RECIST guidelines with approval from the PIO of CTEP at the time of protocol submission. The response rate in the initial trials was assessed by WHO criteria and more recent trials by RECIST or modified RECIST criteria. The disease response to treatment was categorized as complete response, partial response, less than partial response, stable disease, or progressive disease. For the purposes of our analyses, less than partial response was categorized as stable disease.

The tolerability of investigational agents among BC versus non-BC patients was of interest. Data pertinent to grade 4 and 5 toxicities were included in our study. The attribution of

adverse events (AE) was determined by pre-defined criteria outlined by the Common Terminology Criteria for Adverse Events (CTCAE) from CTEP. Attribution of each adverse event was designated as the following: definite, probable, possible, unlikely, and unrelated. For purposes of these analyses, definite, probable, possible, were grouped as related whereas all others were grouped as unrelated. Treatment-related deaths were defined as deaths determined to be at least possibly related to treatment (possible, probable, or definitive). Information regarding overall recovery status and time to recovery were also obtained. We were unable to assess survival benefit as survival data was not recorded for all patients.

Statistical methods

Descriptive statistics were provided to summarize the data. Violin plots were used for visualization of some of the continuous variables. Wilcoxon rank sum test was performed to compare continuous variables while Chi square test or Fisher's exact test was used to compare categorical variables between two groups. $p < 0.05$ is considered statistically significant.

Results

Patient characteristics

De-identified data from 8087 patients enrolled in CTEP-sponsored phase I clinical trials between 1993 and 2012 were analyzed. Patient demographic characteristics at phase I clinical trial enrollment are described in detail in Table 1. Of the total number of patients, 1376 were diagnosed with BC. Breast cancer patients had a median age of 52 years (range 23–87 years) which was younger than non-BC patients with a median age of 58 years (range 18–90). Race among BC and non-BC patients was also dissimilar in that there was a higher frequency of black patients in the BC group. The most common non-BC malignancies were gastrointestinal (43.7%), genitourinary (15.5%), and gynecologic cancer (11.2%) (Supplemental Table 1).

Most patients had an ECOG PS of 0 (31.7%) or 1 (59.9%). The BC cohort had a greater frequency of patients with a PS of 0 (35.8%) than those without BC (31.2%). Regarding pretreatment laboratory values, hemoglobin levels were similar between BC and non-BC patients. Platelet count was slightly lower in BC patients. Albumin was mildly lower in non-BC patients than in BC patients.

Pre-enrollment characteristics

The median time from initial cancer diagnosis to enrollment in a CTEP-sponsored Phase 1 clinical trial was 614 days for all patients (Table 2). Breast cancer patients were found to be enrolled on average 790 days after initial diagnosis while non-BC patients had a median enrollment time of 582 days ($p < 0.001$). Along with this longer time to enrollment, BC patients were also found to be more heavily pretreated with a median of 4 (range 1–26) prior medical treatments than those with other cancers at 3 prior treatments (range 1–19).

Treatment

Of the 8087 patients enrolled, 84 did not receive any dose of study drug and were thus removed from further analysis. While on phase I study, the best response to treatment was evaluated (Table 3). Disease progression was the best response in slightly less than 40% of all patients. Breast cancer patients had more clinical responses (complete and partial responses) than non-BC patients (18.3% vs. 4.3%, respectively). In addition, 42.7% of BC patients achieved stable disease compared to 57.2% of non-BC patients. Along with the higher rate of response, BC patients were found to be on phase I trials longer than non-BC patients with a median of 70 days while the latter were on trial for a median of 57 days (Table 4).

Treatment tolerability and toxicity

Among the 8003 patients that received treatment, 1680 patients experienced at least one grade 4 or 5 adverse event representing 25.9 ($n = 353$) and 20.0% ($n = 1327$) of BC and non-BC patients respectively (Table 5). The overall rate of death related to the treatment drugs was 0.47% ($n = 38$) and was similar between BC and non-BC patients (0.58 and 0.45% respectively). Of the 38 deaths thought to be related to study drug, 26 were considered “possible”, 3 as “probable” and 9 as “definite”. Of the 3887 grade 4 AEs in which attribution data was recorded, 2790 were treatment-related. Of these, 24.9% occurred in BC patients and 75.1% in patients without BC (Table 6). Breast cancer patients more often had a full recovery of grade 4 AE then non-BC patients (78.5% vs. 54.1%, respectively). The median time to recovery for all grade 4 AEs was 7 days. Breast cancer patients seem to experience a slightly quicker recovery time with a median of 6 days. Statistical significance was not evaluated in here as several patients had multiple AEs and not all AEs were independent events.

Discussion

To our knowledge this study is the first to compare enrollment characteristics, response rates and toxicity between BC and other patients enrolled on the same phase I trials. In our study we confirmed that patients with BC enrolled in CTEP-sponsored phase I trials are more heavily pretreated, have higher response rates and have a similar toxicity profile compared to non-BC patients enrolled on the same trials. Our results also confirm that patients with BC are enrolled in phase I clinical trials later in the course of their disease when compared to patients diagnosed with other malignancies, based on number of previous lines of therapy and time from initial diagnosis to enrollment.

The reported high response rates of BC patients (18.3%) suggest a higher benefit from phase I oncology trials than previously reported. Historically, patients treated on phase I studies have response rates of 4–10.6% [11, 25]. In a small retrospective study of 78 patients with metastatic breast cancer (MBC) treated in phase I trials at MD Anderson [26], there were no complete or partial responses. On another study from the same institution, 8.2% (8 of 98) of evaluable patients with MBC achieved complete (n = 1) or partial response (n = 7) [10], and if treated on matched therapy had improved rate of stable disease for 6 months and partial or complete response when compared with those on nonmatched therapy (33% vs. 8%, $p =$

0.018). However, our data are derived only from trials sponsored by the CTEP. Although the program is a major sponsor of phase I oncology trials in the United States, there may be differences in terms of response rate with other phase I trials that were not captured in this study.

The overall rate of toxicity-related deaths on phase I trials has remained stable [1–9]. Breast cancer patients experienced more grade 4 toxicities while on study than other patients, but fewer were treatment-related and more BC patients had complete resolution of toxicities compared to non-BC patients. These findings, along with a similar rate of treatment-related deaths, confirm that despite being more heavily pretreated, BC patients do not experience increased toxicity. However, one important limitation of this study is the lack of detailed information on patient-specific reported data on grade 4 and 5 events.

Finally, our findings suggest that BC patients are enrolled in phase I clinical trials later in the course of their diseases when compared to non-BC patients. It is unclear whether this reflects the natural history of breast cancer and the fact that there are many available standard therapies for breast cancer. Between 1993 and 2012, eleven drugs received accelerated or regular FDA approval for advanced BC which makes BC the oncologic disease with the most FDA drug approvals in the last decades [27, 28]. Other factors may contribute to this pattern of late referrals, including the type of institution where BC treatment is delivered and the availability of early phase trials, or health provider/patients stigma against phase I clinical trials. Lack of participation by BC patients on phase I trials may represent missed opportunities to detect early signals of response of promising drugs for this disease.

In summary, we showed that phase I clinical trials are associated with clinical benefit in a significant number of BC patients with similar toxicity profile of other non-BC patients, despite being enrolled later in the course of their diseases. Multiple factors are possibly associated with the pattern of late referrals of BC patients to participation in phase I clinical trials and are worth further exploring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

AE	Adverse events
BC	Breast cancer
CTCAE	Common terminology criteria for adverse events
CTEP	Cancer therapy evaluation program
CTMS	Clinical trials monitoring service
ECOG	Eastern cooperative oncology group

MBC	Metastatic breast cancer
OS	Overall survival
PIO	Protocol and information office
PS	Performance status
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended phase 2 dose

References

1. Itoh K, Sasaki Y, Miyata Y, et al. Therapeutic response and potential pitfalls in phase I clinical trials of anticancer agents conducted in Japan. Cancer Chemother Pharmacol. 1994; 34:451–454. [PubMed: 7923553]
2. Estey E, Hoth D, Simon R, et al. Therapeutic response in phase I trials of antineoplastic agents. Cancer Treat Rep. 1986; 70:1105–1115. [PubMed: 3527410]
3. Decoster G, Stein G, Holdener EE. Responses and toxic deaths in phase I clinical trials. Ann Oncol. 1990; 1:175–181. [PubMed: 2148104]
4. Bachelot T, Ray-Coquard I, Catimel G, et al. Multivariable analysis of prognostic factors for toxicity and survival for patients enrolled in phase I clinical trials. Ann Oncol. 2000; 11:151–156. [PubMed: 10761748]
5. Han C, Braybrooke JP, Deplanque G, et al. Comparison of prognostic factors in patients in phase I trials of cytotoxic drugs vs new noncytotoxic agents. Br J Cancer. 2003; 89:1166–1171. [PubMed: 14520440]
6. Roberts TG Jr, Goulart BH, Squitieri L, et al. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. JAMA. 2004; 292:2130–2140. [PubMed: 15523074]
7. Sekine I, Yamamoto N, Kunitoh H, et al. Relationship between objective responses in phase I trials and potential efficacy of non- specific cytotoxic investigational new drugs. Ann Oncol. 2002; 13:1300–1306. [PubMed: 12181255]
8. Smith TL, Lee JJ, Kantarjian HM, et al. Design and results of phase I cancer clinical trials: three-year experience at M.D Anderson Cancer Center. J Clin Oncol. 1996; 14:287–295. [PubMed: 8558210]
9. Von Hoff DD, Turner J. Response rates, duration of response, and dose response effects in phase I studies of antineoplastics. Invest New Drugs. 1991; 9:115–122. [PubMed: 1827432]
10. Ganesan P, Moulder S, Lee JJ, et al. Triple-Negative Breast Cancer Patients Treated at MD Anderson Cancer Center in phase I trials: improved outcomes with combination chemotherapy and targeted agents. Mol Cancer Ther. 2014; 13(12):3175–3184. [PubMed: 25253784]
11. Horstmann E, McCabe MS, Grochow L, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. N Engl J Med. 2005; 352:895–904. [PubMed: 15745980]
12. Agus DB, Gordon MS, Taylor C, et al. Phase I clinical study of pertuzumab, a novel her dimerization inhibitor, in patients with advanced cancer. J Clin Oncol. 2005; 23:2534–2543. [PubMed: 15699478]
13. Phillips GDL, Fields CT, Li G, et al. Dual Targeting of HER2 positive cancer with trastuzumab emtansine and pertuzumab: critical role for neuregulin blockade in antitumor response to combination therapy. Clin Cancer Res 15. 2013; 20(2):456–468.
14. Nanda R, Chow QL, Dees EC, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase ib keynote-012 study. J Clin Oncol. 2016; 34(21):2460–2467. [PubMed: 27138582]
15. Howlader, N.Noone, AM.Krapcho, M., et al., editors. SEER Cancer Statistics Review, 1975–2014. National Cancer Institute; Bethesda, MD: Apr, 2017 https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site

16. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front- line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol. 2003; 21:588–592. [PubMed: 12586793]
17. Cresta S, Grasselli G, Mansutti M, et al. A randomized phase II study of combination, alternating and sequential regimens of doxorubicin and docetaxel as first-line chemotherapy for women with metastatic breast cancer. Ann Oncol. 2004; 15(3):433–439. [PubMed: 14998845]
18. Conte PF, Guarneri V, Bruzzi P, et al. Concomitant versus sequential administration of epirubicin and paclitaxel as first-line therapy in metastatic breast carcinoma: results for the Gruppo Oncologico Nord Ovest randomized trial. Cancer. 2004; 101:704–712. [PubMed: 15305399]
19. Alba E, Martin M, Ramos M, et al. Multicenter randomized trial comparing sequential with concomitant administration of doxorubicin and docetaxel as first-line treatment of metastatic breast cancer: a Spanish Breast Cancer Research Group (GEI-CAM-9903) phase III study. J Clin Oncol. 2004; 22:2587–2593. [PubMed: 15226326]
20. Swain SM, Baselga J, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015; 372:724–734. [PubMed: 25693012]
21. Tejeda HA, Green SB, Trimble EL, et al. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. J Natl Cancer Inst. 1996; 88:812–816. [PubMed: 8637047]
22. Go RS, Frisby KA, Lee JA, et al. Clinical trial accrual among new cancer patients at a community-based cancer center. Cancer. 2006; 106:426–433. [PubMed: 16353206]
23. Postel-Vinay S, Aspeslagh S, Lanoy E, et al. Challenges of phase 1 clinical trials evaluating immune checkpoint-targeted antibodies. Ann Oncol. 2016; 27:214–224. [PubMed: 26578728]
24. Ma C, Bandukwala S, Burman D, et al. Interconversion of three measures of performance status: an empirical analysis. Eur J Cancer. 2010; 46(18):3175–3183. [PubMed: 20674334]
25. Kurzrock R, Benjamin RS. Risks and benefits of phase 1 oncology trials, revisited. N Engl J Med. 2005; 352:930–932. [PubMed: 15745986]
26. Wheler J, Tsimberidou A, Moulder S, et al. Clinical Outcomes of patients with breast cancer in a phase I clinic: the MD Anderson Cancer Center Experience. Clinical Breast Cancer. 2010; 10(1): 46–51. [PubMed: 20133258]
27. Verma S, McLeod D, Batist G, et al. In the end what matters most? A review of clinical endpoints in advanced breast cancer. Oncologist. 2011; 16(1):25–35.
28. FDA Hematology/Oncology (Cancer) Approvals & Safety Notifications. 2015. https://wayback.archive-it.org/7993/20170111231726/http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm381452.htm. Accessed on 5 May 2017

Table 1

Patients demographics

	BC	Non-BC	Total	*p*-value
Total number	1376	6711	8087	
Age				< 0.001
Range	23–87	18–90	18–90	
Median	52.0	58.0	57.0	
Mean	51.9	57.0	56.1	
SD	10.8	12.3	12.3	
Gender				< 0.001
Male	9 (0.7%)	3788 (56.4%)	3797 (47.0%)	
Female	1367 (99.4%)	2923 (43.6%)	4290 (53.1%)	
Race				< 0.001
White	1006 (83.7%)	5487 (89.9%)	6493 (88.9%)	
Native Hawaiian or other Pacific Islander	19 (1.6%)	21 (0.3%)	40 (0.6%)	
Black	148 (12.3%)	435 (7.1%)	583 (8.0%)	
Asian	21 (1.8%)	149 (2.4%)	170 (2.3%)	
American Indian or Alaskan native	8 (0.7%)	13 (0.2%)	21 (0.3%)	
Missing	174	606	780	
ECOG PS				0.001
0	482 (35.8%)	2078 (31.2%)	2560 (31.7%)	
1	766 (57.0%)	4074 (61.1%)	4840 (59.9%)	
2	96 (7.1%)	514 (7.7%)	610 (7.5%)	
3	1 (0.1%)	0	1 (0.0%)	
Missing	31	45	76	
Hemoglobin (g/dL)				0.862
Range	6.7–41.8	4.7–36.4	4.7–41.8	
Median	12.2	12.1	12.2	
Mean	12.2	12.2	12.2	
SD	2.0	1.9	1.9	
Platelets ($\times 10^9$/L)				< 0.001
Range	34-821	14-1229	14-1229	
Median	250	261	259.0	
Mean	263.9	282.9	279.0	
SD	94.0	117.1	113.1	
Albumin (g/dL)				< 0.001
Range	1.8–5.3	0.9–8.4	0.9–8.4	
Median	4.1	3.8	3.8	
Mean	3.9	3.8	3.8	
SD	0.5	0.6	0.6	

BC breast cancer, *ECOG*, eastern cooperative oncology group, *PS* performance status, *SD* standard deviation

Table 2

Pre-enrollment characteristics

	BC	Non-BC	Total	*p*-value
Days from diagnosis to entry				< 0.001
Number analyzed	547	2862	3409	
Range	1–8684	1–10122	1–10122	
Median	790	582	614	
Mean	1334	894.9	965.4	
SD	1530.6	1053.0	1154.2	
Prior treatment				< 0.001
Number analyzed	1364	6639	8003	
Range	1–26	1–19	1–26	
Median	4	3	3	
Mean	4.9	3.3	3.6	
SD	3.5	2.3	2.6	

BC breast cancer, *ECOG* eastern cooperative oncology group, *PS* performance status

Table 3

Best treatment response

	BC	Non-BC	Total*	*p*-value
Number analyzed	1364	6639	8003	< 0.001
CR	29 (2.6)	30 (0.5%)	59 (0.9%)	
PR	178 (15.7)	220 (3.9%)	398 (5.9%)	
SD	484 (42.7)	3215 (57.2%)	3699 (54.8%)	
PD	442 (39.0)	2152 (38.3%)	2594 (38.4%)	

*Missing information in 1253 (15.7%) of total; 231 (16.9%) BC and 1022 (15.4%) non-BC

BC breast cancer, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 4

Days on study

	BC	Non-BC	Total	*p*-value
Number analyzed	1364	6639	8003	< 0.001
Range	0–2786	0–3206	0–3206	
Median	70	57	58	
Mean	135.9	95.6	102.4	
SD	225.1	136.3	155.5	

BC breast cancer, *SD* standard deviation

Table 5

Adverse events (AEs)

	BC (*n* = 1364)	Non-BC (*n* = 6639)
Number of grade 4 incidences (N)	1064	2936
Number of grade 5 incidences (N)	63	350
Number of treatment-related deaths (N)	8	30
Person days on study	181664	633138
Person years on study	497	1733
Grade 4 incidence rates[a]	2.1/person-year	1.7/person-year
Grade 5 incidence rates[a]	0.1/person-year	0.2/person-year
Treatment-related deaths incidence rates[a]	0.02/person-year	0.02/person-year
Average number of grade 4 AEs per patient[b]	0.8	0.4
Average number of grade 5 AEs per patient[b]	0.047	0.053
Average number of treatment-related deaths[b]	0.006	0.005

[a]Incidence rate is defined as number of incidences divided by person time

[b]Average number is defined as number of incidences divided by total number of patients

Table 6

Grade 4 adverse events attribution, recovery and time to recovery

	BC (*n* = 1064)	Non-BC (*n* = 2936)	Total
Attribution			
Related	696 (65.4%)	2094 (71.3%)	2790
Non-related	263 (24.7%)	834 (28.4%)	1097
Not recorded	105 (9.9%)	8 (0.0%)	113
Recovery			
Yes	835 (78.5%)	1588 (54.1%)	2423
No	143 (13.4%)	797 (27.1%)	940
Not recorded	86 (8.1%)	551 (18.8%)	637
Days to recovery			
Range	0–373	0–1100	0–1100
Median	6	7	7
Mean	10.7	11.1	10.9
SD	30.7	35.1	33.8

BC breast cancer, *SD* standard deviation