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The Effect of Clinical Trial Participation on Early Breast Cancer Outcomes

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The Effect of Clinical Trial Participation on Early Breast Cancer Outcomes

A dissertation submitted in partial satisfaction of the

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in Nursing

by

Meghan Brennan

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ABSTRACT OF THE DISSERTATION

The Effect of Clinical Trial Participation on Early Breast Cancer Outcomes

by

Meghan Brennan

Doctor of Philosophy in Nursing

University of California, Los Angeles, 2016

Professor Dorothy J. Wiley, Chair

Background:

Malignancy is second only to heart disease and stroke as the leading cause of death, worldwide. Invasive breast cancer is the leading malignancy and the second most common cause of cancer-related death among North American women. Support and treatment costs for cancer-affected adults are significant. There has been a dramatic increase in 5-year survival from 75.2% in 1975 to 91.0% in 2007, much of which is because of advances in technology and treatment.

Most of these improvements were achieved through basic scientific efforts translated into clinical trials. While advances such as, prevention, treatment, and management, and possible cure, may be improved by findings from clinical trials, the personal participation of adult cancer patients is low, overall, especially for potential adjuvant therapies. Experts suggest poor patient understanding, limited access, mistrust, fear, low provider engagement, and poor communication may impair recruitment to cancer clinical trials. Increasing the non-monetary

incentive for trial participation may enhance participation. Thus, determining the positive effects of trial participation may incentivize participation leading to faster development of supportive and curative therapies. Specifically, trial participation alone may improve early detection of recurrent disease, prevention or early detection of comorbidities, thereby improving survival. Participation alone may also minimize side-effects of standard therapies, and potentially improve access to effective primary and secondary prevention interventions for women diagnosed with early breast cancer.

The overall hypothesis of this study is clinical trial participation independently improves morbidity and mortality for women with early breast cancer. We will examine this through two specific aims. Specific Aim 1 will compare outcomes of women who received treatment in clinical trials (CT) and outside of a CT to one another. Specific Aim 2 will compare early breast cancer patients on randomized controlled trial (RCT), receiving standard adjuvant therapy to women reported to the U.S. population-based surveillance program: *Surveillance Epidemiology and End Results* (SEER) receiving similar therapy.

Specific Aim 1

Methods:

In this secondary analysis, all patients treated with neoadjuvant chemotherapy between 2001 and 2015 were selected. A total 1038 patients with sufficient treatment, patient and tumor characteristics data were included. A total 260 of those patientts were treated in clinical trials. We examined whether CT participation status, in addition to commonly known predictors for pCR, improves prediction of pCR. We conducted similar analyses for the outcome of rate of mastectomy. Finally, survival analyses were evaluated as part of an exploratory analysis.

Results:

Study participation was an independent predictor of pCR in addition to commonly known predictors. The adjusted OR for trial participants versus non-participants was 1.53 (95% CI, 1.03 to 2.28). Also, study participation improved the prediction of mastectomy risk. The adjusted OR for trial participants versus non-participants was 0.62 (95% CI 0.42 to 0.90). Subgroup specific differences concerning the impact of study participation could not be shown for either pCR or mastectomy rate. Formal survival comparisons could not be conducted due to large differences in follow-up data in patients participating in clinical trials versus those who did not participate; however, pCR was a predictor of prognosis in both groups.

Conclusion:

Patients taking part in neoadjuvant chemotherapy clinical trials have a higher pCR rate and a lower mastectomy risk than patients not participating in clinical trials for their cancer care. This finding is a supporting factor for trial participation in neoadjuvant chemotherapy trials.

Specific Aim 2:

Methods:

This secondary analysis included patients from one of three (3) international, adjuvant breast cancer RCT (RCT-participants) and women with similar stage breast cancer from the general U.S. population, *Surveillance Epidemiology and End Results Program* (SEER-13), the controls. Kaplan-Meier curves were generated to display differences in survival patterns between the two groups. Propensity score analysis (PSA) was calculated and applied to a Cox proportional hazard models to determine hazard ratios (HR) of trial participation on survival. Similarly, PSA was also calculated and utilized in multivariable logistic regression models to calculate the odds ratios of surgical management, mastectomy or breast conserving surgery (BCS), for RCT participation compared to the SEER-13 controls.

Results:

Women diagnosed between 1997-2004 with invasive breast cancer, tumor (T) size 1-3, lymph node (LN) positive (LN1/2), hormone receptor positive or negative, HER2 positive or negative, treated with surgery and adjuvant chemotherapy were included in the analysis. The total sample size was 9255 patients, 1795 RCT-participants and 7460 SEER-13 controls. Multivariable analysis demonstrated reduction in risk of death by 17% [HR: 0.83 (95% CI: 0.72-0.95); p<0.001] for patients at 5-years and 21% reduction in risk for 10 years [HR:0.79 (95% CI: 0.71-0.87); p<0.001]. RCT-participants were significantly less likely to undergo mastectomy compared to SEER-13 controls [OR: 0.78 (95% CI: 0.66-0.92); p=0.03].

Conclusion:

RCT participation significantly reduces the risk of death, all cause and breast cancer specific, up to 5 and 10 years compared to the general population. RCT is associated with less morbid surgical management (mastectomy) compared to the general breast cancer population. Additionally, RCT participants have unfavorable prognostic variables compared to the general population.

Summary:

Clinical trial participation for women with early breast cancer leads to better outcomes, after controlling for other prognostic variables. The outcomes include higher probability of pCR, less risk of mastectomy and improved survival outcomes. Healthcare providers should consider this information carefully when determining their level of engagement and consideration for clinical trials and discussing participation with potential patients.

The dissertation of Meghan Brennan is approved.

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2016

DEDICATION OF THE THESIS

I dedicate this doctoral thesis to my loving husband and partner, David, and to my beloved daughter, Olivia, who give me love, joy and hope for a bright and happy future. Lastly, I would like to dedicate this work to my entire family, whom have supported, cajoled, and loved me through this very lengthy process. Without their support, I could not have reached this point. May this hard work by me, as a woman, wife and mother, be a symbol of all the possibilities for young girls and women whom desire to be better and make a difference in the lives of others.

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The manuscript entitled “The effect of participation in RCT on outcomes in patients with early breast cancer compared to the general breast cancer population” was co-authored by Dorothy

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Peer Reviewed Publications

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Submitted

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A Review of the Literature: Effect of Clinical Trial Participation on Outcomes in Adults with Cancer

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Abstract

Background: The global cancer population is increasing and the need for more effective, less toxic, safer, and cost-effective treatment increases, not just for lives saved, but, for the financial burden of cancer treatments is necessary. Clinical trials are essential to evaluate these new preventive measures, diagnostics, and therapeutic interventions to determine safety and efficacy in the adult oncology population. Data demonstrates about 5-20% of adults with cancer in North America participate in cancer clinical trials. Perhaps, if there were more compelling unequivocal data regarding the benefits of trial participation, engagement in clinical trials and enrollment would improve. There has been some research over the years exploring clinical trial participation to determine if a benefit exists for participation alone. This paper seeks to provide a comprehensive review of original studies across the adult oncology discipline examining the effect of trial participation on survival and cancer related outcomes.

Methods: A forward and backward one-generation search of the Web of Science® was conducted using three influential articles regarding oncology clinical trials and participation effect. There were 476 cited documents reviewed for consideration in this review. Duplicate citations were excluded as well as citations which did not meet inclusion criteria. The criteria for inclusion of citations were: 1) from peer reviewed journals; 2) original data regarding clinical trial participation and outcomes; 3) cancer related; and 4) adult population.

Results: A total of 38 original, peer-reviewed, articles, from 1985 to 2016, were incorporated in this review.

Conclusion: No studies demonstrated participation had a negative impact on cancer related outcomes. However, the review did not provide not unequivocal data proving participation improves outcomes for adults with cancer. Clinical trial participation should still be recommended to patients with cancer; although, discussions regarding benefits to the patients

should remain tempered based upon known risks and benefits of the treatments being studied and alternatives to participating.

Key Words: Clinical trial participation; cancer; oncology; adult; outcomes

Background and Rationale

Cancer is the second leading cause of death for adults worldwide, and the leading cause of death in developed countries.[1] The most recent global statistics demonstrate more than 14 million new cancer cases were diagnosed in 2012 with more than 8 million deaths due to malignancy in the same year, worldwide.[2, 3, 4] By 2030, the World Health Organization (WHO) estimates the global incidence of cancer will almost double (21.4 million), with the number of deaths rising to over 13.2 million individuals, due to general population growth, decreases in child mortality and an increase the population of older adults.[5] This increase in incidence and deaths has more than just emotional impact to the affected patient, friends and family. There are financial burdens of disease; and, cancer is one of the more costly.

As the cancer population increases, the need for more effective, less toxic, safer, and cost-effective treatment increases, not just for lives saved, but for the financial burden of cancer treatments. These prevention and treatment options are only realized through research and development. Clinical trials are necessary to evaluate new preventive measures, diagnostics, and therapeutic interventions to determine safety and efficacy in the oncology population. The evidence from clinical trials is not only utilized to develop and refine experimental treatments, but to establish practice standards and evidence based practice standards for management of cancer patients.

Clinical trials evaluating treatments are staged, multi-phase, step-based, organized and, in oncology, conducted in the affected cancer population, regardless of phase. Early phase (I and Ib) safety trials are carried out in this manner, as experimental therapies may be toxic and the determination of safety is best evaluated in cancer patients, as the physical condition of cancer patients may be different from “normal” or “healthy” volunteers.[6] These trials are generally open label single-arm treatment trials. The focus of early phase (I and Ib) trials is to examine safety, toxicity, determine maximum tolerated dose (MTD) and possible dosing schedules of a new

agent or agents never before used together. Phase II trials, once safety, tolerability, scheduling, and MTD are established, focus on efficacy of the novel agents alone, or in combination with standard of care (SOC), or compared to SOC alone. Efficacy, in these studies can be defined many ways; but it is usually determined by disease-free survival (DFS) or progression-free survival (PFS) intervals, tumor proliferation, response rates, pathologic complete response (pCR), and/or overall survival (OS). The Phase II trial design is determined by the primary objective(s).[7, 8, 9, 10, 11] Because often Phase II clinical trials, are multiple treatment regimens, or arms, and with placebo or SOC controls, they require a method of patient treatment assignment.

Patient treatment assignment is most commonly done by "random" assignment or "randomization". Randomized clinical trials (RCT) are considered the most superior design, as it limits enrollment issues and helps to control for confounding variables. Randomization can be done in different ways on trials: simple, block, or unequal randomization.[12, 13, 14, 15, 16, 17] Once efficacy has been established, the new agent or therapy regimen will often progress to a larger population in a Phase III setting. Most Phase III trials are conducted in a randomized fashion, as these trials usually compare SOC treatments (control), based upon Phase II studies and government approval, or SOC coupled with novel therapies to SOC alone (control) in a large population. Most Phase II and III trials are conducted to determine the superiority of one treatment arm over the other, or equivalence of the treatments.[18, 19]

Clinical study execution is complex and further challenged by lack of patient engagement and enrollment. Many trials will never be completed or completed in a timely manner whereby they can alter medical practice.[20] While pediatric oncology trial enrollment remains high, approximately 80%, adult enrollment is poor at best.[21, 22] Data demonstrates less than 18% of adults with cancer in the United States and Canada (7%) participate in clinical trials.[23, 24, 25, 26, 27, 28] Phase III participation is estimated to be even less, between 1-5%.[29] Even more alarming is the under-representation of minority populations and women in cancer trials in North America.[28,

[30, 31] This poor accrual to trials and lack of diversity in RCT further draws concern about the generalizability and application of their findings.[32, 33]

There has been considerable study of reasons adult cancer patients participate or decline clinical trial, including studies focused on women and minority populations, in addition to the general cancer population. Trial participation is a decision-making process involving clinicians, nurses, patients, and families. Consequently, it has been demonstrated each group of individuals involved in the process impacts participation. The literature has demonstrated barriers to patient participation vary from patient mistrust of the clinical trial treatments, time commitment, fear of treatment assignment (randomization process), placebo, drug side-effects, concern regarding medical processes involved, insurance coverage, and a general misunderstanding and miscommunication about trial participation. [34, 35, 36, 37, 38, 39,] Furthermore, it has also been shown, the physician is generally at the center of enrollment and non-participation and it is related to 1) patient/physician relationships; 2) lack of commitment of physicians to the trials; 3) physicians failing to offer trials to every eligible patient; and 4) clinician-to-clinician relationships which may put physicians at odds with colleagues by offering trials or enrolling patients on a trial. [39, 40, 41, 42, 43, 44] Similarly, a meta-analysis of over 40 different studies examining barriers to cancer clinical trial participation identified all of these same patient and physician barriers, with the addition of: access to trials, general patient misunderstanding of the research process and the importance or relevance in serious diseases, such as cancer.[45]

Perhaps, if there were more compelling unequivocal data regarding the benefits of trial participation, beyond access to earlier or potentially better treatments, engagement in clinical trials and enrollment would improve. If patients whom participated on clinical research could have improved outcomes, such as survival or symptom management, perhaps both patients and healthcare providers would be more inclined to consider their involvement. There has been research over the years examining clinical trial participation, across many different health

disciplines and domains, attempting to determine if a benefit exists for participation in clinical trials. [46, 47, 48, 49, 50] While this area of study has been explored, it is not extensive nor exhaustive. Some studies have demonstrated survival benefit either short-term, long-term or both, while others have not demonstrated any survival differences. What has been determined is clinical trial participation does not, overall, appear to be harmful for patients, even cancer patients.[51, 52, 53] This paper seeks to provide a comprehensive review of original studies across the adult oncology discipline examining the effect of trial participation on survival and cancer related outcomes.

Methods:

A forward and backward one-generation search on the Web of Science® was conducted using two influential articles concerning oncology clinical trials and participation effect. The first article by Davis et al, published in 1985, studied survival outcomes based upon participation in RCT for patients with lung cancer compared to those who did not participate.[54] An additional review by Peppercorn, examining a conceptual framework and research in this area, was used to further identify additional references.[47] A forward (n=98) and backward one-generation (n=41) search of the Davis paper identified 139 documents from the core collection. A forward and backward one-generation search of Peppercorn identified 184 and 52 sources, respectively. Based upon the forward searches of Davis and Peppercorn, a third manuscript, by Unger et al, published in 2013, was identified and used for identification of additional citations regarding this topic.[55] Again, a forward and backward one-generation search was conducted, revealing 101 citations (n=79 backward citations; and n=22 forward citations). A total of 476 cited documents were identified and considered for inclusion in this comprehensive review. Several citations were excluded based upon inclusion criteria and some were duplicates. Citations which met all of the 4 following inclusion criteria: 1) published in peer reviewed journals; 2) articles with original data regarding patient clinical trial participation and outcomes based upon participation; 3) oncology related; and 4) adult population. Therefore, studies in the pediatric population and

other health disciplines (i.e. cardiology, infectious disease, or internal medicine) were excluded from the review. **Figure 1** diagrams the articles included in the review. A total of 38 original, peer-reviewed, articles, from 1985 to 2016, are incorporated in this review of the effect of clinical trial participation on outcomes for adults with cancer. A table is included as well with details regarding the 38 studies reviewed (**Table 1**).

Literature Review

Breast Cancer

While overall, participation in adult oncology remains low, breast cancer patients tend to participate more in clinical trials compared to other cancer patients.[26] Perhaps because it is the most common cancer for women or one of the deadliest, breast cancer clinical trial participation has been given some attention with regards to participation and outcomes. Importantly, studies concentrating on trial participation and outcomes in breast cancer, specifically, have not demonstrated survival disadvantages for trial participants compared to non-participants. In this review, we evaluated 6 original studies concentrating only on breast cancer patients and outcomes associated with clinical trial participation. Additionally, there were 3 studies including breast cancer with other histologies which are reported in the section, “Multiple Histologies”. These studies of breast cancer patients included in this review regarding trial participation and outcomes have shown equivocal results.

As early as 1996, this idea of studying trial participants compared to non-participants took hold in breast cancer.[56] This early retrospective analysis examined the effect of participation in a surgical trial (comparing modified radical mastectomy to breast quadrantectomy, axillary dissection, followed by radiation therapy) compared to receipt of the same therapy subsequent to the trial ending (non-participants) on survival, overall, and disease free, for “early breast” cancer patients. In this study, crude Kaplan-Meier survival curves demonstrated non-participants had worse all-cause mortality, disease-free relapse and distant metastases

compared to participants. However, in the adjusted analysis, only relative risk of local relapse was significantly reduced for trial participants compared to non-participants. These findings were similar to a study conducted by Mayers which explored the effect of participation in an adjuvant chemotherapy [cyclophosphamide, methotrexate and 5-fluorouracil (CMF)] trial or supportive care trial on survival outcomes. [57] Again, crude survival estimates demonstrated a significant difference in OS (p=0.02) for participation compared to no participation; however, when adjusted for confounding variables (e.g. hormonal status, lymph node status, tumor size and therapy), trial participation was not significantly associated with differences in OS.

Likewise, Hébert-Croteau and colleagues from Quebec, Canada examined the value of participating in clinical trials for early stage breast cancer patients.[58] In this retrospective study, they studied women diagnosed with lymph node negative early stage breast cancer on clinical trials and compared them to patients treated according to guidelines and not treated according to guidelines. In the simple survival estimates, they demonstrated an OS advantage for participants compared to non-participants (guideline adherent and non-adherent). Similarly, the adjusted analysis, also demonstrated significant (p=0.001) OS advantage of trial participants compared to non-participants who did not receive guideline consistent treatment outside of a clinical trial. They did not, however, compare participants to non-participants treated according to guidelines to determine survival differences based upon participation; moreover, they did not control for systemic therapy.

Ejlertsen and colleagues in Denmark also examined study participation in pre-menopausal women with early breast cancer to determine effect on survival, disease-free and overall, and toxicity.[59] In this retrospective study, they compared participants on a clinical trial comparing chemotherapy CMF to ovarian ablation (OA) to non-participants treated similarly. This study demonstrated no difference in adjusted and unadjusted 10-year survival rates, disease-free or overall, between participants and non-participants. Lastly, the authors examined toxicity in a

subgroup of patients whom received CMF and demonstrated significant differences in the frequency of reported toxicity, (nausea and vomiting, conjunctivitis or stomatitis, and alopecia) whereby participants reported toxicity more frequently compared to non-participants.

In 2013, Schwentner published results from the only prospective observational study which enrolled women with breast cancer who participated in a clinical trial and women who did not participate and were treated in the adjuvant setting.[60] All patients who did not enroll in one of 44 adjuvant breast cancer trials, were prospectively enrolled an observational study to compare their outcomes to clinical trials participants. This study demonstrated longer DFS for participants compared to non-participants but not statistically significant difference in OS, after adjusting for confounding variables. While participation did not significantly affect OS (p=0.15), when separated into cohort years of diagnosis (1992-2001 and 2002-2008), the latter cohort (2002-2008) demonstrated clinical trial participation significantly increased OS compared to non-participation (p=0.008).

Most recently, Le Du studied trial participation on survival outcomes of metastatic breast cancer (MBC) patients.[61] In this retrospective analysis of MBC patients enrolled on clinical trials (participants) compared to non-participants they demonstrated, both in the unadjusted and adjusted survival estimates, PFS and OS were similar. Even after sub-group analysis based upon molecular sub-types, survival was not different for trial participants compared to non-participants.

Gastrointestinal

Similarly, in gastrointestinal cancer results regarding participation are vague. Specifically in gastric cancer, both limited and advanced stage disease results have demonstrated limited survival advantages in the unadjusted analysis. Ward, for example, in a retrospective analysis demonstrated patients with stage II or III gastric cancer enrolled on an adjuvant chemotherapy

RCT have an improved survival when compared to gastric patients in a registry with the same stage disease(p=0.0001).[62] Unfortunately, after applying all inclusion and exclusion criteria to the trial and non-trial patients, there was no difference in survival, at any time point (p=0.24). This may demonstrate the impact of inclusion and exclusion criteria on outcomes. Similarly, Tenai examined RCT participation in advanced stage gastric cancer (stage III, IV, and recurrent) patients compared to equivalent patients treated with similar therapies.[44] The study also demonstrated no significant difference (p=0.121) in response rates (RR) for participants (30.5%) compared to non-participants (21.9%). Median follow-up time did not differ nor did median survival time. Risk of death was not significantly different for participants compared to non-participants, both unadjusted and unadjusted. When comparing the different treatment regimens for participants to non-participants, again there was not a significant difference in survival.

These findings were confirmed by Dahlberg, Glimelius and Påhlman whom examined the influence of clinical trial participation in rectal cancer patients who had a surgical resection in a clinical trial compared to patients with the same treatment outside of a clinical trial. [63] This study demonstrated no difference in DFS or 5-year overall all-cause and cancer specific survival rates for participants compared to non-participants. Mol confirmed these findings in patients with colon, rectal, and rectosigmoid cancer in a recent study of advanced stage (IV) colorectal patients who participated on a RCT compared to eligible patients who did not participate, as well as ineligible patients treated similarly.[64] There was no significant difference median OS of participants compared to eligible non-participants. While they showed a significant increase in risk of death of ineligible participants compared to participants, they did not compare participants to eligible non-participants for risk of death.

Genitourinary

In the genitourinary cancer field, again, studies and results regarding the effect of trial participation on cancer related outcomes are varied. In this section, male and female and

gender non-specific malignancies have been incorporated. Only a few studies were able to demonstrate improved responses or survival for trial participants compared to non-participants. They are broken down by the following diseases: prostate, testicular, ovarian, and renal cell cancers.

As with other cancers of high incidence, such as breast and lung, research of the effect of trial participation in prostate cancer has had more consideration, although on a relatively limited basis. Studies of trial participation and outcomes for prostate cancer have been focused on advanced stage disease, either metastatic "hormone refractory" or castration-resistant prostate cancer (mCRPC). In a study by Dowling of patients with refractory prostate cancer treated with mitoxantrone and prednisone both within the context of a clinical trial and then subsequently as standard practice, crude survival estimates demonstrated significantly improved median survival compared to non-participants.[65] However, after adjusting for prognostic variables, a survival difference could not be demonstrated (p=0.42). Further, Dowling was unable to demonstrate a significant difference in prostate specific antigen (PSA) response, a discreet clinical outcome, between the CT participant group compared and the non-participant group. These findings were further corroborated by Templeton in another retrospective study of mCRPC.[66] Again, unadjusted analysis demonstrated a difference in survival; however, after controlling for prognostic variables, no difference showed between the two groups. This is true as well for PSA response in the participants compared to non-participants.

Only the study by Goyal reported an effect of clinical trial participation in the mCRPC population over a similar time period to Templeton, which revealed outcomes favoring trial participation.[67] This retrospective analysis demonstrated a statistically significant improvement in median OS of 4 months (21.3 versus 17.3 months p=0.024) for trial participants compared to non-participants. The study demonstrated, in a univariate analysis, trial participation was significantly associated (p=0.024) with the reduction of risk of death by 27% (hazard ratio: 0.73, 95% CI: 0.551-0.969)

compared to non-participants. Additionally, multivariate analysis demonstrated a 43.3% (hazard ratio: 0.567, 95% CI: 0.343-0.936) reduction in risk of death for trial participants compared to non-participants (p=0.027).

Most likely due to the rarity of testicular cancer, limited research has been done in this histology.[4] A single testicular cancer study was identified which examined trial participation and outcomes compared to population-based testicular cancer patients.[68] Feuer scrutinized the differences in survival of stage IV testicular cancer patients from the Surveillance, Epidemiology, and End Results (SEER) Program dataset to patients enrolled in 3 different clinical trials conducted at a single institution during the same time period. Crude survival patterns demonstrated differences in OS (up to four year) for patients on clinical trials compared to SEER patients (p<0.001). However, this difference is only substantiated when minimal and moderate disease burdens are compared to each other by group, participant versus SEER; however, advanced stage disease did not demonstrate a difference between the two groups. Further, when excluding patients who did not get treatment and comparing those patients within the groups the difference is maintained. (p=0.001).

Although ovarian cancer incidence is not nearly as high as some other cancers, it is the fifth deadliest malignancies for women in the US and in the top ten worldwide.[4, 69] The fatality could explain why this disease has some limited research looking at women with ovarian cancer who participate in clinical trials, compared to other tumor types. This review identified 2 individual trials focused solely on ovarian cancer patients. The earliest study, by Bertelsen, compared ovarian cancer patients of various disease stages (I-IV) from the Danish Ovarian Cancer Group (DACOVA) registry who participated on a clinical trial to those who were treated outside of a clinical trial.[70] OS for the clinical trial participants was similar to the non-participants. When evaluated by stage, a difference in survival for stage III and IV was significantly better for participants compared to non-participants (p=0.0002). However, early stage (Ib, Ic, or II) survival

remained similar for clinical trial participants compared non-participant patients (p=0.45). Unfortunately, this survival advantage for advanced stage disease is not supported when stage III and IV participants, whom received similar treatments of combination chemotherapy, are compared to non-participants (p=0.98). This could speak to the benefits of experimental therapies or combinations available on a clinical trial, rather than the trial alone offering a survival advantage.

Moore recently, Robinson conducted a retrospective analysis which supported the findings from Bertelsen regarding trial participation and outcomes for women with various stages (high-risk stage I, stage II-IV) ovarian cancer. [71] In this single institution analysis they compared women which participated in one of 4 clinical trials compared to non-participants treated in the standard manner (non-participants). While the two populations were similar, they did not control for any prognostic variables affecting survival. In the unadjusted survival analysis, the study demonstrated improved OS for participants compared to non-participants. However, DFS was similar for the two groups.

Most recently, in genitourinary cancers, a retrospective study reported on metastatic renal cell (mRC) patients treated with sunitinib at multiple centers across 2 countries (United States and Israel), either as a participant in a clinical trial or as part of standard of care.[72] This study demonstrated, albeit with a small sample size, no difference in RR, progression of disease, PFS, OS, of participants compared to non-participants.

Primary Central Nervous System (CNS)

Three (3) studies of primary CNS cancers examining study participation and outcomes have been reported. Two were focused on patients with glioblastoma multiforme (GBM), the most common and deadliest of brain cancers.[73] The first, a retrospective analysis by Shahar et al, published in 2012, evaluated the impact of enrollment in a clinical trial on patient survival

comparing patients from 12 different clinical trials to patients included in the brain tumor database of the Tel Aviv Medical Center. [74] They evaluated non-participants to 2 groups of trial participants, those in an experimental treatment arm and those in the control arm. After adjusting for confounding variables, Cox proportional hazard ratios demonstrated a significant survival advantage (p=0.0009, clinical trial experimental group and p=0.0095 clinical trial control group), regardless of which arm patients were enrolled. Even with the introduction of improved therapeutic approaches to primary GBM, the analysis of the subset of patients, treated after 2005, demonstrated similar survival advantages with an increase in median survival for clinical trial participants, regardless of arm, experimental or control.

Subsequently, Field conducted a similar, larger, retrospective study in GBM patients regarding the impact clinical trial participation had on survival and clinical outcomes.[75] This study differed slightly in that it included newly diagnosed patients as well as previously treated patients. Additionally, it did not include any information or analysis of subsequent therapy after surgical intervention nor did it include an analysis based upon year of diagnosis which related to a change in standard therapy in 2005. Although it was missing some of the variables of the smaller, Shahar study, they also demonstrated a significant increase in median survival for clinical trial participants any line of therapy (first, second or third-line therapy); and a reduction in the relative risk of death in the univariate analysis by 54% and a 33% in the multivariate analysis compared to non-participants.

Finally, colleagues in Germany examined primary central nervous system lymphoma (PCNSL), an uncommon type of lymphoma to determine the difference between trial participants and non-participants related to outcomes.[76] They found no differences between the trial participants and non-participants overall response rates (ORR) or disease progression. Median OS, while showing a tendency towards longer for participants compared to non-participants, was not statistically significant. OS at 2 years and 5 years was significantly higher for the trial

participants compared to the non-participants. Lastly, this small trial demonstrated median PFS to be superior in the trial participant group compared to the non-participant group; likewise, PFS was higher for trial participants compared to non-participants at 2 and 5 years.

Hematologic Malignancies

Hematologic malignancies have had a fair amount of research regarding trial participation and outcomes conducted over the past 3 decades. This could be due to the large expanse of cancers covered by hematologic malignancies, or because of the long-standing relationship between hematologic malignancies and clinical research. On an individual basis, there is not extensive or exhaustive research for any particular hematologic cancer. This review identified 9 original studies in the following adult hematologic malignancies: multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, acute non-lymphocytic leukemia, acute lymphocytic leukemia (ALL), chronic myelocytic leukemia (CML), and acute myelocytic leukemia (AML).

One of the earlier trials examining trial participation and outcomes for acute non-lymphocytic leukemia patients was a retrospective analysis conducted by Boros et al.[77] As part of this retrospective study, they analyzed a subset of patients whom received one of 15 different combination chemotherapy regimens and compared them to study participants on one of many clinical trials studying similar combination chemotherapy regimens. There was a wide range of patient ages (15 to greater than 69 years), differences in chemotherapy dosing (high, mixed, and low) and a variety of other clinical features (e.g. leukocyte count, fever, performance status, platelet count). Outcomes, response to therapy, either complete response (CR) or no response (NR), and survival time, demonstrated participants had an increased rate of CR. Moreover, participants had significantly longer median survival than non-participants. In the adjusted analysis of survival and response, trial participation was significantly associated with a CR ($p=0.016$) and improved survival ($p=0.023$), in addition to other well-known predictors of response outcome.

The study early study by Boros was followed by Hjorth and the Myleoma Group of Western Sweden (MGWS) who subsequently published their retrospective outcomes study of stage I-III multiple myeloma (MM) trial participants compared to non-participants who were not eligible and non-participants excluded from trial consideration.[78] The OS of participants compared to non-participants, both ineligible and excluded, demonstrated a significant increase in 4-year survival for the participants compared to ineligible non-participants ($p<0.05$), participants compared to excluded non-participants ($p<0.0010$), and lastly, for ineligible non-participants compared to excluded non-participants ($p<0.05$). After controlling for age and chemotherapy treatment, there was still a significant difference in 4-year survival ($p<0.05$) between participants and non-participants.

Greil and colleagues, studied outcomes of survival and quality of life (QoL) for patients with Hodgkin's disease whom participated in a clinical trial (participants) and compared them to similar patients who received similar therapy outside of a clinical trial (non-participants).[79] There was a significant difference ($p=0.037$) in 5-year relapse-free survival of participants compared to non-participants; however, after adjusting for other prognostic indicators (e.g. stage, age, and treatment modality), clinical trial participation had no effect on survival, 5-year relapse-free ($p=0.064$). Additionally the univariate and multivariate analyses demonstrated no significant difference in OS between the two groups, ($p=0.067$ and $p=0.65$, respectively). Moreover, the authors were not able to show any difference in QoL for participants compared to non-participants. This could be related to the relatively high QoL responses from patients, regardless of group. The global QoL scores for all groups was 82.0 (±17.9, standard deviation), and remained high regardless of time since diagnosis; and QoL scores for participants versus non-participants were not compared.

Additionally, Roy in 2000, utilizing general population-based registry data from EUROCARE and the British National Lymphoma Investigation (BNLI), compared Hodgkin's lymphoma (HL)

patients enrolled from 1970 to 1987on BNLI trials compared to the general population diagnosed with HL from 1978 to 1984.[80] In this retrospective inquiry, the relative risk of OS at 5 and 10 years for trial participants compared to the general population, after adjusting for age, was different only for certain age groups, (45-64 and 65-74 years); however, the statistical significance was not described between the two groups.

Similarly, Chen and colleagues in the same year studied outcomes in elderly (>65 years) patients with non-Hodgkin's lymphoma (NHL), advanced stage IB-IV and patients with B symptoms of any stage.[81] In this study, they compared elderly (>65 years) patients whom participated (participants) in a RCT study of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) examining different doses and administration schedules to patients whom were not enrolled but received similar therapy as standard treatment outside of a trial (non-participants). Age adjusted, survival demonstrated median survival for participants was better than non-participants, (44.9 months versus 8.7 months, $p<0.00001$). Additionally, they demonstrated survival at 5 years was significantly ($p<0.0001$) higher in the participant group than the non-participant group.

In 2011, Pulte et al. attempted to compare outcomes of clinical trials for 29 different chronic lymphocytic leukemia (CML) studies to outcomes of CML patients in a population-based cancer registry, SEER-9, with regards to OS from 1980 to 2005.[82] This study compares the survival outcomes of each study to SEER-9 survival rates for the similar time period. Additionally, if a specific age range was provided, they adjusted the SEER-9 ages for outcomes. There are not any explanatory statistics and the interpretation of the data unclear as only side-by-side survival frequency, without mention of variables, other than age, and treatment modalities, provided.

Recently, Esteban presented original outcomes data from a retrospective review of clinical trial participation in relapsed chronic lymphocytic leukemia (CLL) compare to non-participation of

eligible patients treated at a single institution.[83] In the unadjusted survival analysis, trial participants showed a trend towards higher ORR compared to non-participants (p=0.070); however, it was not significantly different. They were able to show a significant difference in unadjusted complete response rates for participants compared to non-participants (35% compared to 21%, p=0.042), as well as longer DFS for participants compared to non-participants (28 months compared to 17 months, p=0.025); however, in the adjusted analysis, DFS differences were no longer seen. Crude, OS was significantly better for participants compared to non-participants, p=0.004. This was supported in the adjusted analysis which demonstrated trial participation significantly increases overall survival for CLL patients compared to non-participation.

Lastly, researchers from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), an international consortium, examined the outcomes of study participants compared to eligible non-participants with 5 years of follow-up.[84] They examined survival (overall and relapse-free) and transplant associated sequelae, such as graft versus host disease (GVHD), chronic and acute, and transplant-related mortality (TRM). Both the unadjusted and adjusted analysis did not demonstrate a difference in overall risk of death or risk of TRM or GVHD, acute or chronic, for participants compared to non-participants. Yet, there was a higher relapse rate in the non-participant group compared to the participant group. The study demonstrated no differences between OS or DFS; although, DFS tended to be lower in the non-participant group, but not statistically significant. Furthermore, there was not a difference between trial participants and non-participants risk of GVHD, acute or chronic, (p=0.57 and p=0.41, respectively).

Lung Cancer

Perhaps because of the frequency and lethality of lung cancer, this area has received considerable attention regarding participation on in clinical trials and patient outcomes over the decades and continues to draw attention.[4, 85] As previously noted, one of the seminal articles

published on this topic in adult oncology, by Davis et al, in 1985 examined survival of patients with stage I or II non-small cell lung cancer (NSCLC) who participated in clinical trials compared to NSCLC patients in the institutional cancer registry database who did not participate.[54] This retrospective study demonstrated patients who participated in an adjuvant RCT, after adequate surgical resection of their NSCLC, had significantly better OS at 1, 2, and 3 years than those who did not ($p<0.001$). Further, participation in a RCT reduced the risk of death by 36% when compared to non-participation. The authors explored many factors which may have influenced survival outcomes in this analysis including, age, sex, nodal status, tumor size and radiation therapy. After adjusting for these variables, the participation status was the most important prognostic indicator of survival. This study was one of the first to explore advantages of clinical trial participation for oncology patients and recapitulated in NSCLC, as well as small cell lung cancer (SCLC) over the years.

Several more studies followed the Davis study in the NSCLC population. Researchers in Taiwan attempted to demonstrate similar results, among others, for patients with NSCLC, stage IIIB and IV either enrolled on a clinical trial or treated outside of a trial and recorded in a tumor registry.[86] In this analysis, they could not demonstrate a difference in RR, although trial participants tended to have a higher response rate than non-participants, 43.4% to 40.3%, respectively ($p=0.053$). OS and PFS, at 1 year and 2 years, after controlling for performance status and brain metastases, were the same for both participant and non-participant groups ($p=0.454$ and $p=0.456$, respectively). These findings were further supported by Tanai and colleagues in a similar prospective observational study of advanced stage (IIIB and IV) NSCLC patients whom either participated on a trial or were eligible but refused enrollment.[43] Interestingly, there was no difference in OS for trial participants compared to non-participants ($p=0.987$). After controlling for other prognostic variables, the risk of death was the same for participants compared to non-participants. Median survival and response rates were similar trial participants and non-participants. These findings were further corroborated by Abu-Hejleh and colleagues, whereby

they examined the effect of trial participation in advanced stage (IIIB and IV) NSCLC patients compared to similar patients in a population-based cancer outcomes database (CanCORS).[87] Notwithstanding a relatively small study of clinical trial participants compared to non-participants, crude survival analysis demonstrated no significant difference in survival for clinical trial participants compared to non-participants. Moreover, after controlling for prognostic variables, clinical trial participation did not alter risk of death compared to non-participants significantly.

While results subsequent to the Davis study have not demonstrated differences in survival for NSCLC patients who participate in clinical trials compared to those who do not, it is important to note the large gap in time between the Davis trial and the Kuo study, almost 30 years. Even more critical, the studies subsequent to the Davis study were focused on advanced stage NSCLC patients and not early stage as in the David study. Although in the advanced stage NSCLC setting, trial participation did not support improved outcomes, different findings were presented for patients with SCLC, specifically, early stage disease.

Schea demonstrated survival advantages for trial participants in a small study of early stage SCLC patients.[88] The unadjusted survival estimates demonstrate a significant improvement in OS ($p=0.0023$) for participants on clinical trials compared to non-participants treated similarly. Moreover, median disease-specific survival was also significantly longer ($p=0.0176$) for participants compared to non-participants. Schea, however, did not demonstrate a statistically significant difference in DFS, only a trend towards longer DFS. However, researchers looking at both early and late stage SCLC patients could not demonstrate the same findings. Burgers in a single institution study in an unadjusted analysis, reported no differences in any outcomes, including RR or OS for the trial participants compared to non-participants.[89]

Sarcoma

Unsurprisingly, only a single study was identified in adults with sarcoma. Antman and colleagues sought to understand the effect of clinical trial participation in adult patients with intermediate or high-grade sarcoma across three different institutions in the United States.[90] Patients were included in the analysis if they met all criteria for clinical trial participation and either participated in a trial (participants) or declined participation after it was offered or not offered participation by their physician (non-participants). OS favored the participant group compared to the non-participant group but was not statistically significant (p=0.15). Although, survival worsened for the group whom refused participation compared to those not offered or participants, it was still not statistically significant.

Multiple Histologies

Researchers at the Karmanos Cancer Institute retrospectively examined the effect of clinical trial participation on survival for elderly patients (65 years or older) who were evaluated, considered, and treated on phase I clinical trials over a ten year period across over 10 different histologies, most frequently colorectal and lung cancer, and unknown stages of disease.[91] Interestingly, the distribution of comorbidities (cardiovascular, renal, hepatic, hematologic and endocrine diseases) between the trial participants and non-participants was similar across groups. Survival estimates demonstrated improvement in median survival of 4.5 months of participants versus non-participants. Unadjusted OS showed trial participants had improved survival compared to non-participants ($p<0.0001$). After adjusting for performance status, there continued to be improved survival for participants over non-participants, ($p=0.0003$).

Additionally, Chow's retrospective cohort study with patients from a population-based registry, the California Cancer registry (CCR), who participated in "study protocols" compared to those who did not demonstrated improvements for trial participants.[92] The study included 553,688 patients with various histologies (most frequently breast, melanoma, colon, and lung) and disease stages (I to IV). The researchers examined trial participation on disease-specific and

all-cause mortality; and after adjusting for known prognostic variables, (e.g. age, sex, race, organ site, tumor stage, treatment modality) demonstrated a 26% reduction in risk of both cancer-related death (hazard ratio: 0.74; 95% CI: 0.66-0.83) and all-cause mortality (hazard ratio: 0.74; 95% CI: 0.67-0.81). The authors additionally examined histological specific outcomes based upon trial participation. They identified colon cancer patients who participated in treatment protocols compared to those who did not have the greatest reduction in risk of death, disease specific (43%) and all-cause (41%). Disease specific relative risk was also reduced for trial participants compared to non-participants for breast (hazard ratio: 0.69), lung (hazard ratio: 0.73), and upper GI (hazard ratio: 0.77) cancers. Interestingly, there was no effect of trial participation in patients with the most aggressive kinds of cancer: melanoma, hepatocellular, biliary or pancreatic cancers. This study demonstrated a relative risk death for trial participants compared to non-participants after controlling for multiple prognostic variables. There was considerable variation in relative risk of death reduction across histologies (41% to 14%); however, there were limited sample sizes for certain histologies. Colon cancer patient participants demonstrated the highest reduction of risk; however, they had a small sample size.

Finally, Unger in 2014 published a retrospective analysis of more than 5000 patients who enrolled in 21 different South Western Oncology Group (SWOG) phase III trials and compared them to patients from a population-based cancer registry, SEER.[55] The findings from this study were interesting in that they provide evidence which stipulates trial participation has an effect on outcomes, although it is limited by time. The trial enrollment period spanned more than 25 years, 14 different histologies and various stages of disease. Studies were categorized as "good" or "poor" prognosis based upon the observed results using average 2-year Kaplan-Meier survival estimates which noted ≥ 50% of patients alive at 2 years compared to <50% of patients alive at 2 years. In this study, RCT-participants on "good" prognosis did not see a significant improvement of survival compared to the general population in SEER. However, in the poor prognosis RCT-participants, there was a significantly lower risk of death ($p<0.001$) compared to

SEER patients, across all histologies in the adjusted and unadjusted analysis. Furthermore, when the researchers examined the effect of RCT-participation on survival beyond the first year, the impact of RCT-participation did not continue to be statistically significant. This also held true when examining cancer-specific deaths. This study demonstrated the effect of RCT-participation on cancer-related deaths was limited to the first few years after diagnosis and did not continue beyond the second year.

Discussion:

Davis conducted one of the earlier studies which demonstrated a survival advantage, independent of other prognostic factors, for NSCLC patients whom participated in a clinical trial.[54] Subsequently researchers have attempted to examine the relationship between clinical trial participation and outcomes or benefits for adults with cancer. While these studies and others have clearly demonstrated and confirmed, across multiple histologies and medical disciplines, clinical trial participation generally is not harmful to adult participants, they have not indisputably demonstrated improved cancer-related outcomes based upon trial participation alone.[52, 46, 93, 47] This review of findings from many trials, across multiple histologies and various stages, studying improved outcomes of clinical trial participation compared to controls (non-participants or population based registry patients) are equivocal. This review of 38 original, peer-reviewed articles, of those 12 studies demonstrated the same outcomes for participants compared to controls; and 11 studies demonstrated better outcomes for clinical trial participants compared to controls. Additionally, there were 15 studies with varied results. These 15 studies, either demonstrated in one of the analyses an improvement of outcomes, and another no difference in outcomes; or the improved outcomes were only for a sub-group of the study population or were not sustained over time, as with the Unger trial.[55]

For those studies were there were varied results or improved clinical outcomes for participants in clinical trials compared to non-participants, there have been multiple rationale provided for

these differences. Some studies note the differences in outcomes of clinical trial participation might relate to a “trial effect” for participants. The elements of a “trial effect” are multi-faceted. They have been described as a “Hawthorne effect,” ”therapeutic effect”. “protocol effect,” and “cluster effect”. [52, 74]

Hawthorne Effect

The Hawthorne effect is the outcome of changed behavior or either by the patient and/or clinicians who are participating in clinical trials. It was first described by in the 1920’s related to industrial workers which specified any change would improve productivity. Subsequently, it has been studied extensively in the social sciences.[94,95] Over the years, it took hold in clinical research, basically the observer (clinician) and the observed (patient) who participate in clinical trials will change their behavior as they are observing someone or being observed. The behavior change could be caused by more vigilant monitoring, more frequent reporting of symptoms or health changes, and more compliance with treatments. This change may be intentional based upon the requirements of the clinical trial protocol or unintentional, due to the nature of being observed. This change in behavior may affect outcomes.

Many of the studies in this review noted the improvements in outcomes may be related to the changed behavior of the patients and clinicians; however, there were more studies which demonstrated similar or varied outcome results of the participants compared to the control group. This may speak to the validity of Hawthorne effect in clinical research or the extensive confounding variables associated with clinical research; and there are more than changed behaviors associated with the outcomes.

Therapeutic Effect

Additionally and most frequently, researchers have cited the cause of improved outcomes for clinical trial participants is strictly related to the access to novel, more efficacious medical

interventions, drugs or procedures, the therapeutic effect. A conclusion of therapeutic effect is challenging to make as many of the studies did not control for confounding variables, including type of treatment, if different from the control group. In the Shahar trial, they not only compared patients in the clinical trial whom received experimental treatment, but patients in the control arm (best supportive care) as well, to non-participants whom also received best supportive care. They did an analysis of the entire clinical trial participant population (both arms) compared to non-participants; and they did a sub-set analysis of the control patient population compared to the non-participant population and still demonstrated a survival advantage, dispelling the notion there may only be a trial effect which improves outcomes.[74] For those few other studies which did control for treatment, often the outcomes were the same for both groups. The conclusions one is able to draw from the data reviewed her regarding therapeutic effect are ambiguous at best.

Protocol Effect

The "protocol effect" has been described as outcomes based upon the strict and clear adherence to a treatment protocol and on-going follow-up, and intervention at follow-up. Interestingly, one study examined the clinical management of GBM patients inside and outside of a clinical trial to determine if the follow-up visits contributed to improved survival. While there was a trend towards more follow-up care in the clinical trial participants, the trend was not statistically significant. There were statistically significant differences in additional non-surgical cancer therapies and surgical resections ($p=0.019$ and $p=0.039$, respectively) for clinical trial participants compared to BSC patients.[74] These additional second and third-line non-surgical therapies and additional resections could explain the improved survival for the clinical trial participants. Zeremski also regarded to the improved follow-up in the PCNSL patient population may contribute to improved outcomes, although the follow-up differences and direct effect were not provided.[76] Why this happens is not necessarily well understood and a compelling area of future research. Even if this is true, there are clearly advantages to participating on a trial.

Cluster Effect

Many of the studies in this review were conducted a single institutions or across a couple of similar institutions where clinical research is being conducted. Consideration has been given to the improvement of patients based upon the facility where they are being treated and by whom, a “cluster effect”. Some hypothesized, those centers or medical institutions which participate in clinical research, tend to be superior health centers in general and will provide better care to their patients; moreover, clinicians whom participate in clinical research may be superior healthcare providers. This has been noted in some of the studies were population-based registries have been used and clinical trial participants had better outcomes.[60, 68, 80, 84, 54, 92]

There has been research looking at patient outcomes based upon treatment centers and participation in clinical trials as an institution. Once original study by, Du Bois examined ovarian cancer patients and outcomes regarding survival based upon whether or not the patient was treated in a hospital which participated in cooperative clinical trials.[96] The primary outcome of this study was to determine the impact institutional participation in clinical trials on individual patient survival and risk of death. The study included 165 different German hospital gynecology departments, 80 of which participated in cooperative clinical trials and 85 which did not. In the multivariate analysis looking at the prognostic factors determine to be significant in survival, risk of death was significantly elevated by 82% (p=0.001) for patients treated in hospitals which did not participate in cooperative clinical trials. While significant, this study was examining many different aspects of care provided at the different participating facilities. The outcomes of this study may be directly related to the care provided at the different facilities with regards to guidelines and adherence to guidelines.

This concept was also studied in patients with MM. Karjalainen looked at similar outcomes of patients who lived in geographic locations where three (3) different clinical trials enrolled (trial area) and compared them to patients who lived in regions of Finland where these trials were not

conducted (reference area).[97] This study demonstrated MM patients living in the trial area had a 10% (37.8% versus 27.5%) higher cumulative relative survival rate than MM patients living in the reference area. This study demonstrated an association between trial participation and survival compared to non-participation based upon the region where they were treated. Although, the comparison of the two groups was challenging based upon the retrospective nature of the study, it does suggest "cluster effect" may contribute to the improved outcomes of trial participants compared to controls.

Additionally, in a study included in this review, patients treated at the same centers were asked to retrospectively review their quality of life and quality of care.[87] There were no differences in the symptoms or symptom management outcomes between clinical trial participants and non-participants. The only significant finding was the response to the perception of the quality of care received by the patient (completed by patient or respondent of deceased). Clinical trial participants 30% of the time were more likely to respond their care was "better than other patients" compared to only 14% of non-participants ($p<0.01$). This last outcome regarding quality of care may begin to explain the "trial effect" so frequently discussed in research, although not well documented. As the authors note, the reasons for this perception are not clear, as the survival and symptom management outcomes were not different. It may be the perception of having better care based upon the size of the team; although, the authors do not describe the type of care received by participants compared to non-participants. They may also be inherently optimistic patients who chose to go on clinical trials, enhancing their perception of the type of care they are receiving. Lastly, they have little which with to compare, only their own experience. Lastly, there may be a form of agency at work here, whereby patients are making the choice to go on a clinical trial, and putting some of their important care decisions in their own hands.

Limitations of Studies Reviewed

This comprehensive review has provided substantial insight to the research conducted regarding the effect of clinical trial participation on clinical outcomes in adults with cancer. There are challenges and limitations of interpreting the results based upon some of the limitations of the studies. It is important to note the heterogeneity of the studies included in this exhaustive review. While this review focused on adult oncology trials, across the 38 studies, very few studies were conducted in similar populations or recapitulated over time to confirm results. For example, the Davis study, conducted in 1985 in stage I and II NSCLC, has since not been repeated to determine the accuracy and generalizability of the results and germane to current research and patients. In a few circumstances similar populations (histology and disease stage) have more recently been investigated again to confirm findings and applicability; however, this effort has not revealed consistent findings outside of advanced stage NSCLC. Equally important is the inconsistencies between the studies which included or provided information about the type of clinical trials (e.g. RCT, open-label, unblinded) in which patients did participate.

Moreover, the duration of clinical trial participation effect is difficult to evaluate and is not consistently reported. This may be due to studies including patients with a variety of different disease stages, including late or advanced stage or highly aggressive cancers in multi-histology studies which are unlikely to provide “long-term” effect data. Effect is relevant only to the type of cancer and stage. It is challenging to conclude benefit of improved survival or relative risk of death for such varied disease states. Only a few studies were able to examine outcomes over long periods of time; and in those studies the variety of cancers and stages of disease, make the results challenging to understand or apply.

All of the trials reviewed were retrospective analyses. There were only 2 were studies in which data was prospectively collected for research purposes; however, the primary objective of the research was not based upon trial participation outcomes. Working with retrospective data has

inherent problems, in that the data may be captured inconsistently, not detailed enough, or missing. Some studies, such as Chow could not report on the trials their patients participated on because the data was not available.[92] Additionally, reasons patients did not participate is not always available. It can be concluded from retrospective chart review that patients may have not met medical inclusion criteria; however, it is not always possible to know if they were not offered a trial for some reason not documented or if they refused. This goes to the limitation of patient selection bias.

Selection bias of patients enrolled in clinical trials favors patients with better performance status, fewer or no comorbidities, younger age and higher socioeconomic status. Some studies demonstrated, and authors noted, patients with better prognostic indicators, such as younger or higher performance status, are enrolled on study.[90, 77] While age and health are important prognostic indicators, it should be noted, older people (≥65 years) develop cancer more frequently, have more comorbidities and die more often. The idea of including upper age limits, better performance statuses, or fewer health conditions for patients on clinical trials needs to be carefully reviewed and considered. If it is part of the clinical trial selection, all studies looking at outcomes should have taken into account the selection criteria in the analyses. Again, many studies did not perform adjusted or controlled analyses, making their results unconvincing, at best.

Patients on trial may “self-select” to participate, as they are more likely to be compliant and follow a strict regimen of therapies, interventions, exams and follow-up appointments. By adhering to this type of care, inherently the clinical trial participants may have other co-morbid conditions detected and managed early, cancer specific care provided more robustly, including disease recurrence or relapse and early intervention. Interestingly, no studies in early cancers, demonstrated a higher frequency of relapse or disease recurrence in the trial population which

one might expect if early intervention was part of trial participation. This type of selection criteria may also alter the ability to generalize to the broader population.

Sample sizes for many of the studies were very small. While there were some large population based studies, most of the trials were limited to less than 1000 patients, total. Again, this may limit the generalizability of the findings, as well as affect the interpretation of the statistical significance based upon a small sample size. Additionally, most of the studies were single-center or limited to less than 5 treatment centers. If there were more than 1 treatment center involved, they were usually similar, such as an academic medical center or cancer center. There were very few studies which included community practices or multiple centers' research participants or non-participant controls. The only circumstances where they included non-participant controls were when they were using population based registries; however, even then, the participant population was generally from a limited sample of institutions.

These trials span several decades. Individually, many of the trials were conducted over several decades as well. For many trials, the standard of care changed during the course of the retrospective review period. Not all trials accounted for year of diagnosis or treatment as a prognostic indicator or confounding variable, where there may be a period effect.

Future Opportunities

While clinical trials are essential for moving the medical field forward, we have poor patient and clinician engagement. It is valuable to understand any effect (benefits or improved outcomes) trial participation offers beyond access to experimental therapy, which itself is very important. This review highlights several opportunities for study and research. There needs to be more research examining the effect of clinical trial participation on outcomes, not just survival but clinical endpoints as well. Only a few studies have attempted to examine clinical outcomes beyond survival such as PSA, toxicity, and quality of life and quality of care measures.[79,66, 67, 59]

This is an area of research where not only survival outcomes, but clear measureable, clinical outcomes could be used to evaluate trial participation effect. This is especially important as we look at the generalizability of clinical trial results and move them forward as evidenced based clinical practice.

While some of the studies have demonstrated the same outcomes for participants compared to non-participants or a population-based group, there were many where the results were different or mixed. This brings into question the generalizability of trial results to certain patient populations, especially those groups which are under-represented or not addressed (e.g. different races, ethnicities, socio-economic statuses, geographic regions), where outcomes may directly be affected. Additionally, many of the authors hypothesize regarding the cause of improved outcomes; however, to date, there are not studies which explicitly examine reasons why patients on clinical trials may see improved outcomes compared to non-participants or the general population. This is a field of research where a considerable amount of research could be done, both with clinical trial participants and non-participants. Moreover, there needs to be more studies conducted looking at trial participation and effect in the different adult histologies to report and confirm any findings regarding differences in outcomes, whether positive or negative. In conjunction with these studies, there needs to be prospective research examining the differences between patient participants compared to similar non-participants; and if the outcomes are different, the reasons for the difference.

Many have suggested a prospective RCT of participation on a clinical trial may be the cleanest way of extracting the differences in outcomes and control for many confounding variables. While this would be ideal, it is not a feasible option in North America where trial participation, specifically RCT participation is extremely low and ethically it poses many problems. Short of that, there may be other ways to identify trial participation effect and underlying cause. One approach would be to prospectively study all participants considered for clinical trial participation

and then planned clinical outcomes of patients enrolled, were eligible but refused, and were ineligible but receive similar treatment outside of a clinical trial. While this does not eliminate all confounding variables, or control for patient self-selection bias, it does provide a cleaner study environment. Tanai and colleagues included these populations (ineligible, refused, or not-considered for trial) in their studies for both their advanced gastric and NSCLC studies and had interesting results.[44, 43]

Additionally, there is a group of researchers in Japan, who are attempting to examine in a prospective fashion, the effect of trail participation in women with advanced (metastatic or recurrent) breast cancer whom are eligible to participate on one of 2 large RCT phase III trials.[98] The treatments being compared in the 2 RCT are standard therapies available in the community which eliminates a placebo or untreated control group. Moreover, the patients randomized to not participating will receive one of the 2 therapies outside of the trial. Although this does not eliminate the possibility of a Hawthorne effect entirely, it may provide some insight regarding whether patients on trials do better than those not on trials and if so, some reasons to account for this difference.

Furthermore, as previously noted physician engagement is critical to trial participation and ensuring patients whom are eligible are considered and subsequently enrolled on trials. Some have suggested those physicians enroll and participate in clinical trials may be better physicians. This “cluster effect” may be the reason outcomes of their patients will be superior to other physicians at different centers or those that do not participate in clinical trials. Working with physicians regarding their experience, clinical trial interest, enrollment strategies and patient messaging may provide insight on ways to improve clinical engagement as well as increase enrollment.

Tanai provided compelling data point, from analyses done in both the advanced NSCLC and gastric studies, that the most significant predictor of enrollment was the treating physician ($p<0.001$). Physicians with less experience had much higher rates of declination than the more experienced clinicians.[44, 43] Additionally, Ejlertsen, noted of a large population of women with MBC, the majority did not participate, and the reasons were lack of offer by the health care provider or it was not recommended. Of the patients whom chose to participate, clinical engagement and "encouragement" were critical to their accepting participation.[59] This further exposes the necessity to understand the messaging processes of health care providers with regards to research and patient acceptance.

Lastly, patient reported outcomes regarding clinical trial participation are focused on why they do not participate or if they do participate, quality of life measures and symptom management. There is a large opportunity to engage patients who decline participation or are not eligible to participate in clinical trials, as well as participants, to evaluate different psychosocial measures which may have a role in outcomes, such as agency, advocacy, compliance, and messaging. There has been a great deal of speculation regarding the reasons for improved outcomes with regards to patient self-selection; however, there is little research in this field which supports the concepts associated with "trial effect".

Conclusion

While, data has proven participating in a clinical trial does not have a negative impact on outcomes for cancer patients, there remains a significant amount of fear and reluctance to engage in the clinical research process, both from patients and clinicians. If there was more data and a better understanding regarding the advantages of trial participation, patients and clinicians alike, may be more eager to take part in clinical oncology research. However, attempting to provide undisputable data regarding survival advantages for participation is difficult. There are confounding variables which are extraordinarily challenging to overcome in a

retrospective analysis. Moreover, based upon this review and others like it, there has not been robust enough evidence, in most cancers, which proves clinical trial participation alone is beneficial compared to not participating.[93, 46, 52, 47]

Although there is not strong and clear data demonstrating participation benefits for adults with cancer, it should still be highly recommended and considered both by patients and clinicians, alike. Clinical trials offer new and innovative treatments which may prolong life, prevent recurrence or reduce side effects for patients well before they are commercially available. This allows clinicians to offer more therapeutic options to patients faster and earlier. Clinical trials tends to attract cancer patients to the clinical practices seeking different, new or alternative treatment options; as well as having the element of prestige to being involved in important science to move the oncology field forward. Additionally, patients do not need to be treated in large, academic medical centers in order to get access to clinical trials. Many of the new therapies or studies of standard therapies are available in the community practices and centers. In addition to access to novel therapies, for early cancer patients, benefits of trial participation may be less invasive management of their cancer, reduced risk of recurrence, and improve survival. There is a great deal of future research opportunities in this area as the oncology community continues to explore novel approaches to cancer management. The field needs to continue to research clinical trial participation in order to stimulate commitment, enrollment, and results.

Figure 1: Diagram of Exclusion and Inclusion of Articles for Review

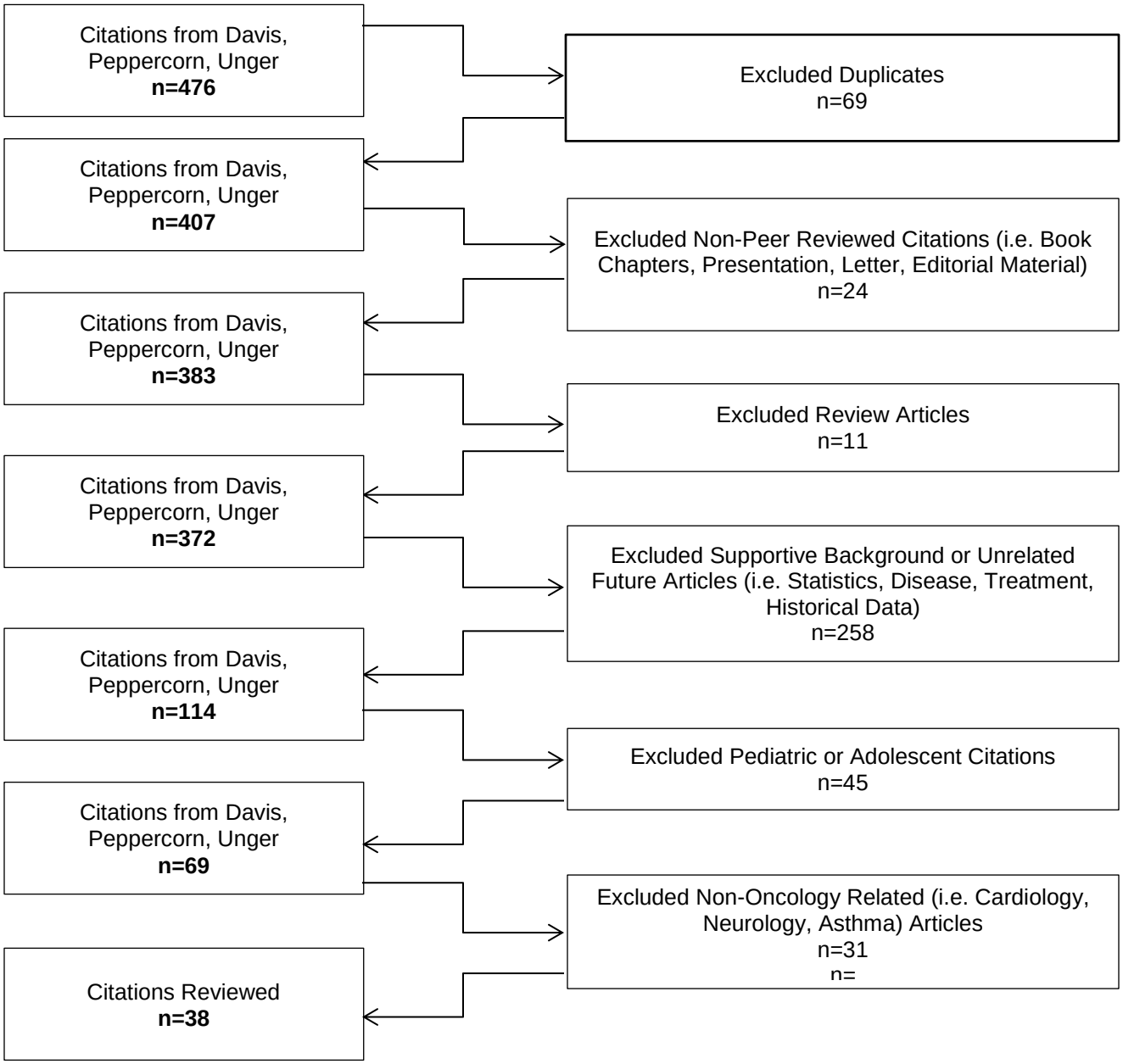

Table 1. Articles in Review

Author	Year	Cancer Type	Extent of Disease	Type of Study	Study Dates	Randomized (RCT) or Non-Randomized (NRCT)	Clinical Trial Participants n=	Controls (Non-Participants) n=	Trial Participation Results
Marubini[56]	1996	Breast	Early Stage: T1-3, LN -/+, M 0	RCS	1973-1980 (participants) 1980-1984 (controls)	RCT	352	1408	**VARIED:** Unadjusted OS and DFS of participants vs. control was better; adjusted DFS of participants vs. controls was better; [HR: 0.610 (95% CI: 0.369-1.007, p=0.0423). Adjusted OS of participants vs. control was the same.
Mayers[57]	2001	Breast	Early Stage: T*1-3, LN** -/+, M‡ 0	RCS	1980-1990	Unknown	160 (only LN +)	519 (LN +/-)	**VARIED:** Unadjusted OS of participants vs. controls was better (p=0.02). Adjusted OS of participants vs. control was the same.
Hébert-Croteau[58]	2005	Breast	In site, stage I and II, LN**-	RCS	1988-1994	Unknown	207	1520	**BETTER**: Unadjusted and adjusted OS of participants vs. controls were better (p<0.00005, unadjusted); adjusted analysis of participants vs. controls not treated according to guidelines was better [HR: 0.45 (95% CI: 0.27-0.74), p=0.0001].
Ejlertsen[59]	2008	Breast	Early Stage: T*0-x (unknown); LN** +/-, M‡ 0	RCS	1990-1998	RCT	525	970	**SAME**: Unadjusted and adjusted OS and DFS of participants vs. controls were the same. Toxicity frequency was different between the two groups, with participants reporting more frequently (p<0.01).
Schwentner[60]	2013	Breast	Localized: T*1-4: LN +/-; M‡ 0	POS	1992-2008	Unknown 44 Trials	1255	8178	**VARIED**: Adjusted DFS of participants vs. controls was better [HR: 0.80 (95% CI: 0.69-0.94); p=0.006]. Adjusted OS of participants vs. controls was the same. Subgroup analysis of OS based on year of

									diagnosis (1992-2001 and 2002-2008), cohort of 2002-2008 participants vs. controls was better [HR: 0.807(95% CI: 0.72-1.05); p=0.008].
Le Du[61]	2016	Breast	Metastatic	RCS	2000-2010	Unknown	285	367	**SAME**: Unadjusted and adjusted PFS and OS of participants vs. controls were the same.
Ward[62]	1992	GI: Gastric	Stage II/ III	RCS	1976-1980	RCT	249	960	**VARIED:** Unadjusted OS of participants vs. controls was the same. Excluding stage I (non-participants), unadjusted OS for participants vs. controls was better (p=0.0001). Matching on inclusion criteria, unadjusted OS was the same.
Tanai[44]	2011	GI: Gastric	Advanced (Stage III, IV, recurrent)	RCS	2000-2006	RCT	190	96	**SAME**: Unadjusted and adjusted OS of participants vs. controls were the same.
Dahlberg[63]	1999	GI: Rectum	Early stage (Dukes A, B, C)	RCS	1987-1990	RCT	557	242	**SAME**: Unadjusted and adjusted 5-Year OS of participants vs. controls were the same.
Mol[64]	2013	GI: Colon and Rectum	Stage IV	RCS	2003-2004	RCT	394	Total 309 224 (eligible) 85 (ineligible)	**SAME:** Unadjusted and adjusted OS of participants vs. controls (eligible) were the same. Unadjusted OS of participants vs. controls (whom were not eligible) was better [HR: 1.70 (95% CI: 1.33-2.17); p<0.01]. Adjusted OS not done of participants vs controls (eligible).
Feuer[68]	1994	GU: Testicular	Minimal, Moderate, & Advanced	RCS	1978-1984	Unknown	133	172	**VARIED**: Unadjusted OS of participants vs. controls was better (p<0.001). Adjusting for disease, OS of participants with minimal/moderate disease vs. controls was better (p<0.001); OS for advanced disease of participants vs. controls was the same.

Dowling[65]	2000	GU: Prostate	Metastatic	RCS	1992-1995 (participants) 1994-1998 (controls)	RCT	80	133	**VARIED:** Unadjusted OS of participants vs. controls was better (p=0.003). Adjusted OS of participants vs. controls was the same. PSA response of participants vs. controls was the same.
Templeton[66]	2013	GU: Prostate	Metastatic	RCS	2001-2011	Unknown	43	314	**VARIED:** Unadjusted 1 & 2 years OS of participants vs. controls was better (p=0.032 and 0.025, respectively). Adjusted OS of participants vs. controls was the same [HR: 0.82 (95% CI: 0.51-1.31); p=0.40]. PSA response of participants vs. controls was the same.
Goyal[67]	2012	GU: Prostate	Metastatic	RCS	1998-2010	11 Trials, 6 RCT, 3 Open Label, 2 Unknown	142	105	**BETTER:** Unadjusted OS of participants vs. controls was better (p=0.024). Adjusted OS for participants vs. controls was better [HR: 0.57 (95% CI: 0.343-0.936); p=0.027].
Keizman[72]	2016	GU: Renal	Metastatic	RCS	2004-2013	3 Trials: 1 RCT, 2 NRCT	49	49	**SAME:** Unadjusted OS of participants vs. controls was the same. Adjusted OS and PFS of participants vs. controls was the same.
Bertelsen[70]	1991	GU: Ovarian	Stage I-IV	RCS	1981-1984	RCT	337	144	**VARIED:** Unadjusted OS of participants vs. controls was the same. Unadjusted OS of early stage participants vs. controls was the same. Unadjusted OS of advanced stage participants vs. controls was better (p=0.0002). Unadjusted OS of advanced stage participants vs. controls treated similarly was the same.
Robinson[71]	2009	GU: Ovarian	Stage II-IV, High-Risk Stage I	RCS	2002-2007	RCT	53	105	**VARIED:** Unadjusted OS of participants vs. controls was better (p=0.0343). Unadjusted DFS of participants vs. controls was the same.

Shahar[74]	2012	GBM	Primary or de novo, Grade IV	RCS	1995-2008	Unknown 10 Trials	124 Experimental Group n=81; Non-Experimental Group n=43	137	**BETTER:** Adjusted OS of participants vs. controls was better; Experimental Arm vs. Control [HR: 0.599 (95% CI: 0.406-0.882); p=0.0095] and Non-experimental Arm vs. Control [HR: 0.596 (95% CI: 0.438-0.809); p=0.0009].
Field[75]	2013	GBM	Grade IV	RCS	1998-2010	Unknown	61	481	**BETTER**: Unadjusted OS of participants vs. controls was better, [HR: 0.46 (95% CI: 0.34-0.61); p<0.001]. Adjusted OS of participants vs. controls was better, [HR: 0.67 (95% CI: 0.46-0.99); p=0.042].
Zeremeski[76]	2016	Primary CNS Lymphoma (PCNSL)	Newly diagnosed	RCS	2000-2015	RCT	20	66	**VARIED:** Unadjusted response rates, median OS of participants vs. controls was the same. Unadjusted 2 & 5 year OS of participants vs. controls was better (p=0.006 & p=0.006, respectively). Unadjusted median, 2 & 5 year PFS of participants vs. controls was better (p=0.004 & p=0.005, respectively).
Boros[77]	1985	Acute non-Lymphocytic Leukemia	Secondary malignancy and/or pre-leukemia and de novo	RCS	1975-1982	Unknown	46	84	**BETTER:** Unadjusted RR and OS of participants vs. controls was better (OS: p<0.0025). Adjusted RR and OS of participation vs. control was better (p=0.023 and p=0.016, respectively).
Hjorth[78]	1992	MM	Stage I-III	RCS	1984-1986	RCT	180	Total 120 71 (ineligible) 49 (not-reported to study)	**BETTER**: Unadjusted OS of participants vs. controls (ineligible & not-reported to study) was better. Age adjusted OS of participants vs. controls (ineligible and not-reported to study) was better.
Greil[79]	1999	Hodgkin's Disease	Stage I-IV	RCS	1969-1994	RCT	62	163	**VARIED**: Unadjusted and adjusted OS of participants vs. controls were the same. Unadjusted, 5-year relapse-free

									survival of participants vs. controls was better (p=0.037). Adjusted, 5-year relapse-free survival of participants vs. controls was the same (p=0.064).
Roy[80]	2000	Hodgkin's Disease	Stage I-IV	RCS	1970-1987 (participants) 1978-1984 (controls)	Unknown	1106	4807	**BETTER**: Adjusted for age, 5 year OS for 2 different age groups (45-64 & 65-74) of participant vs. controls was better (0.70 versus 0.54 and 0.62 versus 0.33, respectively). 10 year relative risk of survival for 2 different age groups (45-64 & 65-74) was better of participants vs. controls (0.54 versus 0.44 and 0.39 versus 0.27, respectively). No CI or p-value provided.
Chen[81]	2000	NHL	Stage IB-IV, any B symptoms	RCS	1990-1992	RCT	38	30	**SAME**: Adjusted for age only, OS of participants vs. controls was better (p<0.0001).
Pulte[82]	2011	CML	Unknown	RCS	1980-2005	Unknown	9481	Unknown	**VARIED**: Unadjusted and adjusted, for age (for certain studies), OS of participants vs. controls were better for most of the trial participants presented.
Esteban[83]	2015	CLL	Relapsed/ Refractory	RCS	2000-2014	Unknown	68	184	**VARIED**: Unadjusted and adjusted OS of participants vs. controls were better [HR: 2.6, (95% CI: 1.1-5.7), p=0.022]. Unadjusted DFS of participants vs. controls was better (p=0.025). Adjusted DFS of participants vs. controls was same.
Khera[84]	2015	Varied: CML, CLL, AML, other	Varied	RCS	2004-2009	RCT	494	1353	**VARIED**: Unadjusted and adjusted risk of death, TRM, and GVHD of participants vs. controls were the same. Adjusted risk of relapse of participants vs. controls was better [HR: 1.22, (95% CI: 1.02-1.46), p=0.028].

Davis[54]	1985	NSCLC	Stage I & II	RCS	1977-1979	RCT	78	Total 471 152 (matched) 319 (other)	**BETTER**: Unadjusted OS of participants vs. controls was better (p<0.001). Adjusted OS of participant vs. controls was better, [HR: 0.39, (95% CI: 0.18-0.83), p=0.015, regardless if using all controls, n=471 or matched, n=152].
Kuo[86]	2005	NSCLC	IIIB/IV	RCS	1996-2001 (participants) 1997-1999 (controls)	Unknown	129	100	**SAME**: Adjusted, for PS and brain metastases, OS and DFS of participants vs. controls was the same.
Tanai[43]	2009	NSCLC	IIIB/IV	POS	2000-2005	RCT	196	73	**SAME**: Unadjusted OS of participants vs. controls was the same (p=0.987). Adjusted OS of participants vs. controls was the same [HR: 0.96, (95% CI: .73-1.28), p=0.805].
Abu-Hejleh[87]	2016	NSCLC	IIIB/IV	POS	2003-2005	Unknown	56	759	**SAME**: Unadjusted OS of participants vs. controls was the same (p=0.21). Adjusted OS of participants vs. controls was the same [HR: 1.05, (95% CI: .71-1.55), p=0.81].
Schea[88]	1995	SCLC	"Limited" stage	RCS	1987-1992	Unknown	41	40	**BETTER**: Unadjusted OS and DFS of participants vs. controls were better (p=0.023 and p=0.0176, respectively).
Burgers[89]	2002	SCLC	"Limited" & "Extensive" stages	RCS	1994-1998	RCT	60	46	**SAME**: Unadjusted OS and RR of participants vs. controls were the same.
Antman[90]	1985	Sarcoma	IIb-IV	RCS	1978-1982	RCT	42	48	**SAME**: Unadjusted OS of participants vs. controls were the same.
Multiple Histology Studies									
Author	**Year**	**Cancer**	**Extent of Disease**	**Type of Study**	**Study Dates**	**Randomized (RCT) or Non-Randomized (NRCT)**	**Clinical Trial Participants n=**	**Controls (Non-Participants) n=**	**Trial Participation Results**
Zafar[91]	2011	Head & Neck; Thyroid; Breast;	Various	RCS	1995-2005	Unknown	95	114	**BETTER**: All patients were ≥ 65 years old. Unadjusted OS of participants vs. controls was better (p<0.0001). Adjusted for

		Lung; Esophagus; Stomach; Pancreas; Other GI; Prostate; Bladder; Renal; Other GU; NHL; Melanoma; Hodgkin's Disease; Other Cancers							PS, OS of participants vs. controls was better (p=0.0003).
Chow[92]	2012	Breast; Colon; Lung; Gastric/ Esophagus; Liver/Biliary / Pancreas;	I-IV & Unknown	RCS	2002-2008	Unknown	1846	553,688	**BETTER**: Adjusted OS, cancer specific and all-cause, of participants vs. controls were better [HR: 0.74; (95% CI: 0.66-0.83) and HR: 0.74; (95% CI: 0.67-0.81), respectively].
Unger[55]	2014	Breast; NSCLC, Bladder; MM; Melanoma; Cervical; Brain; Gastric; SCLC, Pancreas; Prostate; AML, NSCLC; Renal	Various	RCS	1987-2011	RCT	5190	69187	**VARIED**: Adjusted and unadjusted OS of poor prognosis participants vs. non-participants were better for all included histologies. Adjusted and unadjusted OS of good prognosis participants vs. non-participants were the same.

CI=Confidence Interval; **CLL**=chronic lymphocytic leukemia; **CML**= chronic myelocytic leukemia; **CR**= complete response;

DFS=disease free survival; **DSS**=disease specific survival; **GBM**=glioblastoma multiforme **GI**=Gastrointestinal;

GU=Genitourinary; **GVHD**=graft versus host disease; **HR**=Hazard Ratio; **LN=**Lymph node involvement "-" **=** to negative and "+"**=**to positive; **M** =to metastatic disease (M0=no metastatic disease, MI=metastatic disease, and Mx=metastatic spread not studied or unknown; **MM**= multiple myeloma; **NHL**= non-Hodgkin's lymphoma; **NSCLC**=non-small cell lung cancer; **PCNSL**=primary central nervous system lymphoma; **PFS**=progression free survival; **POS**=prospective observational study; **PS**=performance status; **PSA**=prostate specific antigen; **OR**=odds ratio; **OS**=overall survival; **RCS**=retrospective cohort study; **RR**=response rate; **SCLC**=small cell lung cancer; **T**=tumor size; **TRM**=transplant related mortality;

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SPECIFIC AIM 1: MANUSCRIPT

The effect of participation in neoadjuvant clinical trials on outcomes in patients with early breast cancer

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Abstract

Background: Clinical trials can offer novel and more advanced treatments to cancer patients in advance of them being approved and available for all patients. While several studies have examined the effect of clinical trial participation on prognosis, there has been no clear conclusion from these studies. This might be the consequence of biases, such as selection and detection, linked to the nature of these comparisons. Therefore we chose pathological complete response (pCR) as the primary outcome and mastectomy rate as the secondary outcome measure to compare patients treated neoadjuvantly with chemotherapy.

Methods: In this retrospective study, all patients treated with neoadjuvant chemotherapy between 2001 and 2015 were selected. A total of 1038 patients with complete treatment, patient and tumor characteristics data were included in this study. Of those patients 260 were treated in clinical trials. Study participation status, in addition to commonly known predictors for pCR, was tested to determine if it improves the prediction of pCR. Similar analyses were conducted for the outcome measure mastectomy rate. Survival analyses were conducted as part of an exploratory study aim.

Results: Study participation was an independent predictor of pCR in addition to commonly known predictors. Adjusted analysis showed study participants had 53% higher odds of pCR than non-trial participants; and mastectomy odds among participants decreased by 61% (OR:1.53; CI: 1.03 to 2.28 and OR: 0.62; CI: 0.42, 0.90, respectively). Subgroup specific differences concerning the impact of study participation could not be shown for both pCR and mastectomy rate. Although survival comparisons could not be conducted, pCR was a predictor of prognosis in both groups, trial participants and non-participants.

Conclusion: Patients taking part in neoadjuvant chemotherapy clinical trials have a higher pCR rate and a lower mastectomy risk than patients not taking part in clinical trials. This finding is another supporting factor for trial participation in neoadjuvant chemotherapy trials.

Key Words: breast cancer; neoadjuvant therapy; clinical trial participation; pCR; mastectomy; trial participation outcomes

Introduction and Background

Worldwide, breast cancer is the leading cause of cancer and cancer related deaths in women. Annually, more than 1.6 million women were diagnosed with breast cancer in 2012, worldwide [1, 2]. By 2030, the World Health Organization (WHO) estimates the global incidence of cancer to almost double (21.4 million) [3, 4]. Although mortality associated with early breast cancer is low in developed countries, the social, physical and financial burdens of surgeries, treatments, and cancer recurrence are high [5-13]. Low mortality rates may be attributed to earlier detection and improved therapy options in developed countries. Additionally, the negative impact of extensive treatment and management of early breast cancer can be mitigated by improved therapy options, such as neoadjuvant therapy.

Neoadjuvant treatment, which is administered prior to definitive surgical management, with systemic therapy, chemotherapy, hormonal therapy, or both, for women with early breast cancer has been extensively studied and an established standard of care since the 1990's [14-18]. Data show neoadjuvant systemic management of breast cancer may lead to better outcomes such as minimized surgical management and improved disease free survival (DFS) [19-25]. The intent of neoadjuvant therapy is to achieve a pathological response of the tumor in the breast and lymph nodes, if involved. Based upon the clinical and radiological response to treatment, less invasive surgery options, such as breast conserving surgery, become feasible. Survival outcomes are based upon the pathologic response of the tumor to neoadjuvant therapy. More specifically, pathological complete response (pCR) is equivalent to the eradication of all invasive tumor in the breast and lymph nodes. Patients with a pCR are the most likely to see improved survival, overall and DFS [26, 27]. Furthermore, for patients with incomplete, limited, or no tumor response to systemic treatment, neoadjuvant therapy provides in vivo evidence which could be beneficial for future cancer management and treatment decision.

Although neoadjuvant management of early breast cancer with chemotherapy is a well-established pattern of care, there continues to be extensive clinical trials research in this setting. Many of these clinical trials are to improve treatment-related morbidity and outcomes, as well as identify potentially successful new systemic agents and biomarkers to be used in this setting [18, 28]. Data suggest participation in clinical trials (CT), independently, may improve cancer outcomes, such as reduced morbidity and improved survival, in cancer patients over standard management outside of the CT setting [29-31]. Unfortunately, minimal analyses have involved breast cancer patients, and those which do, include breast cancer of different stages with other histologies and associated stages [32-35]. Moreover the few studies concentrated on studying breast cancer only, at any stage, have been focused solely on survival, DFS and overall survival (OS) [36, 37]. These few studies examining CT participation on survival outcomes may be inherently biased due to the extent of follow-up inside and outside of a CT. No studies to date, in breast cancer, have examined CT participation in the neoadjuvant setting or with regards to pCR or surgical outcomes. Therefore it seems appropriate to investigate an endpoint well-documented and accessible in the health record for all patients regardless of clinical trial participation, such as pCR after neoadjuvant chemotherapy.

Thus, to study the association between CT participation and pCR and mastectomy, we evaluated 1038 women treated at a regional cancer center in Germany. The primary aim of this retrospective cohort study is to determine whether participation status in CT is associated with pCR after neoadjuvant therapy for breast cancer, taking into account commonly established predictors of pCR. Further research aims are whether participation status in clinical trials is associated with mastectomy rates after neoadjuvant therapy for breast cancer taking into account established predictors of mastectomy. Exploratory study aims are the influence of trial participation on the prognosis with regard to DFS and OS.

Material and Methods

Patient selection

Patients for this retrospective study were from the Erlangen-Nuremberg tumor registry, which includes all patients with invasive breast cancer diagnosed between 1995 and January 2015 (n=8614). From those patients, we selected women who were diagnosed with unilateral, invasive breast cancer who received standard of care treatment in the neoadjuvant setting and showed no distant metastases at the time of diagnosis. Cases were excluded in the following hierarchical order: patients treated before 2001, as clinical trials were systematically implemented in 2001 (n=1813); patients not treated with neoadjuvant chemotherapy (n=5226); patients with bilateral breast cancer at the time of diagnosis (n=94); and patients with primary distant metastases at initial diagnosis (n=92). Additionally, patients from studies not yet published, presented, and/or ongoing at the time of this analysis were excluded (n=6). Of those, 345 were excluded because of missing information of pCR or at least one covariate, resulting in a final study population of 1038 patients (see **Figure 1**). All patients registered in the tumor registry consented to have their data collected and analyzed anonymously. The ethics committee of the medical faculty approved this study as well as the institutional ethics committee, IRB #14-000634.

Data Collection

All patients entered in the tumor registry are documented in larger detail for quality control purposes at the University Breast Center. Data is collected prospectively, as required by the certification process of the German Cancer Society and by the German Society for the Study of Breast Diseases (Deutsche Gesellschaft für Senologie) [38]. Accordingly, each breast cancer case is prospectively documented, including patient and tumor characteristics, detailed treatment data, and epidemiological data. Treatments are independently abstracted for all patients; and are administered in accordance with approved trial protocols and national guidelines for breast cancer to ensure objectively homogeneous treatment of breast cancer

patients across several institutions. Follow-up treatment and disease characteristics are collected for up to 10 years after the primary diagnosis. All histological tumor data are documented, such as tumor size, axillary lymph-node status, grading, estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (HER2/neu) status. Comorbid conditions relevant to survival are routinely collected. For example, the center routinely records renal function, cardiac disease and diabetes mellitus characteristics. As part of the continuous certification process, the quality of the data is audited annually. Data obtained from the above described collection and audit processes were used in the analysis presented here.

Definition of pCR and molecular subtypes

Pathological complete response (pCR) is defined as the complete disappearance of invasive tumor cells from the breast and the lymph nodes (ypT0/is ypN0) after the chemotherapy at the time of the surgery.[26]. Molecular subtype of the tumor is defined by hormone receptor (HR) status, HER2 status and cellular proliferation rate (Ki-67). Luminal A-like tumors were ER and/or PR positive, HER2 negative, and low Ki67; luminal B-like tumors were ER and/or PR positive, HER2 negative with high Ki-67; triple-negative (TN) breast cancers were required to be ER, PR, and HER2 negative. Finally, all HER2 positive tumors were considered to be included in a HER2 positive group, regardless of hormone receptor status or Ki-67.

ER and PR were assessed by immunohistochemistry (IHC) by the breast centers' pathologists and determined positive or negative according to the guidelines of the respective year. This was the same assessment used to determine hormone receptor status for the inclusion into clinical trials. HER2 was deemed positive when IHC staining indicated a 3+ result or the tumor was positive for fluorescence in situ hybridization (FISH) staining. FISH was performed systematically for all patients with IHC 2+ results for HER2.

Studies conducted at the Breast Center

During the observation time (2001-2015) a total of 11 clinical trials in the neoadjuvant setting were conducted; and 10 studies enrolled and completed follow-up for study procedures. These are listed below:

- A Randomized Phase III Trial Comparing Preoperative, Dose-Dense, Dose-Intensified Chemotherapy with Epirubicin, Paclitaxel, and CMF Versus Standard-Dose Epirubicin-Cyclophosphamide Followed by Paclitaxel With or Without Darbepoetin Alfa in Primary Breast Cancer (*Prepare* [*AGO-B/GBG*]) [20, 21];
- Preoperative Therapy with Epirubicin/Cyclophosphamide Followed by Paclitaxel/Trastuzumab and Postoperative Therapy with Trastuzumab in Patients with HER2-Over Expressed Breast Cancer (*Techno*[*AGO-B/GBG*]) [22];
- A Randomized Phase III Study Exploring the Efficacy or Capecitabine Given Concomitantly or in Sequence to EC-Doc with or without Trastuzumab as Neoadjuvant Treatment of Primary Breast Cancer (*GeparQuattro, GBG/AGO-B*) [39-41];
- A Randomized Phase II Biomarker Neoadjuvant Study of Sequential Doxorubicin Plus Cyclophosphamide (AC) Followed by Ixabelpilone Compared to Sequential AC Followed by Paclitaxel in Women with Early Stage Breast Cancer (*Epothilon CA 163-100*) [42, 43];
- A Phase III Trials Program Exploring the Integration of Bevacizumab, Everolimus (RAD001) and Lapatinib into Current Neoadjuvant Chemotherapy Regimens For Primary Breast Cancer (*GeparQuinto[GBG/AGO-B]*) [44-49];
- A Randomized, Open-label, Multi-Center Study of Larotaxel at 90mg/m2 or Docetaxel Every 3 Weeks, Alone or in Combination with Trastuzumab According to Her2Neu Status, Administered After a Combination of Anthracycline and Cyclophosphamide as Pre-operative Therapy in Patients with High Risk Localized breast Cancer (*Satin*) [50];
- A Randomized Phase II Trial Investigating the Addition of Carboplatin to Neoadjuvant Therapy for Triple-Negative and Her2-Positive Early Breast Cancer (*GeparSixto [GBG/AGO-B]*) [51];

- Dual Blockage with Afatinib and Trastuzumab as Neoadjuvant Treatment for Patients with Locally Advanced or Operable Breast Cancer Receiving Taxane-Anthracycline Containing Chemotherapy (*DAFNE [GBG/AGO-B]*) [52];
- Pi3k Inhibition in Her2 Over-Expressing Breast Cancer: A Phase II, Randomized, Parallel Cohort, Two Stage, Double-Blind, Placebo-Controlled Study of Neoadjuvant Trastuzumab Versus Trastuzumab+ BKM120 in Combination with Weekly Paclitaxel in HER2-Positive, PIK3CA Wild-Type and PIK3CA Mutant Primary Breast Cancer (*NeoPHOEBE [GBG/AGO-B]*) [53];
- A Randomized, Multi-Center, Open-Label, Two-Arm, Phase III Neoadjuvant Study Evaluating Trastuzumab Emtansine Plus Pertuzumab Compared With Chemotherapy Plus Trastuzumab And Pertuzumab For Patients With Her2-Positive Breast Cancer (*KRISTINE* [*Roche BO28408*]) [54].

See **Table 1** for the details of the CT, participation and therapy.

Statistical Analysis

Patient and tumor characteristics of CT participants and non-participants are presented as means and standard deviations or frequencies and percentages.

The primary objective was to evaluate the association between CT participation and pCR, adjusting for the effects of age at diagnosis (continuous), tumor size before chemotherapy (ordinal, cT1 to cT4), lymph node status before chemotherapy (categorical; negative versus positive), ER, PR, HER2 (each categorical; negative versus positive), grading (ordinal; G1 to G3) and year of diagnosis (continuous). To control for treatment variation over time, year of diagnosis was evaluated as a covariate. Neoadjuvant treatment changed over the course of time for patients with early breast cancer, we assumed there would be a strong association between year of diagnosis and the outcome, pCR.

For this purpose, a logistic regression model with pCR (yes versus no) as the outcome and the above mentioned predictors was fitted (*the basic model*). Subsequently, an additional logistic regression model was fitted containing trial participation (categorical, yes versus no), the predictors of the previous basic model and the interactions between trial participation and the other predictors (*the interaction model*). Both models were compared using the likelihood ratio test. A significant test result means trial participation influenced pCR in addition to the well-known predictors, either across all patients or at least within one of the subgroups defined by considered predictors. In case of a nonsignificant result, no further analyses were carried out to avoid false-positive results. If, however, the p-value was significant, the interaction model was compared with a reduced logistic regression model, the basic model with trial participation added, but without the interaction terms (*the reduced model*), using the likelihood ratio test again. In case of significance, subgroup-specific odds ratios (ORs) for trial participation adjusted for the other predictors were calculated, using the interaction model. In the case of a nonsignificant result, an adjusted overall OR for trial participation was calculated, using the reduced model.

Patients with missing outcome or missing predictor values were excluded from analyses. Continuous varaibles were used as natural cubic spline functions to describe non-linear effect [55]. The number of degrees of freedom (1 to 3) of each predictor was determined as done recently in Salmen et al. [56].

The performance of the logistic regression models, with regard to discrimination and calibration ("goodness of fit"), was assessed using the area under the receiver operating characteristic curve (AUC) and the Hosmer-Lemeshow statistic. The AUC ranges from 0.5 (no discrimination between patients with pCR and patients without pCR) to 1 (perfect discrimination). In accordance with Hosmer and Lemeshow, patients were ranked with respect to the predicted probability of pCR and categorized into equal-sized groups based on percentiles. Frequencies

of predicted events in each group were compared with frequencies of observed events in each group using a scatter plot and the Hosmer–Lemeshow χ^2 test. A large p-value indicates satisfactory calibration.

Model building was evaluated by 10-fold cross-validation with 20 repetitions to address overfitting. For this purpose, the complete model-building process, including determination of cubic spline functions and estimation of regression coefficients, was carried out on each training set, resulting in several logistic regression models (one model per set), which were then used to calculate the AUC on the corresponding validation data sets. The average of all these AUC was taken as an evaluation measure. The smaller the difference between the cross-validated AUC and the original AUC means the lower the amount of overfitting.

To explore the association between trial participation and surgical management, mastectomy versus breast conserving therapy, similar analysis was performed as with pCR. Survival analysis was performed. Follow-up duration for trial participants and non-participants were compared and where follow-up differed, violating statistical modeling assumptions, we estimated survival functions for patents with pCR and patients without pCR were estimated and compared separately for trial participants and non-participants, using the Kaplan-Meier product limit method and the log-rank test. All of the tests were two-sided, and a p value of < 0.05 was regarded as statistically significant. Calculations were carried out using the R system for statistical computing (version 3.0.1; R Development Core Team, Vienna, Austria, 2013).

Results

Patient and Tumor Characteristics

Complete data for 1038 patients, 260 who participated in CT and 778 that did not, showed some demographic and disease-related differences (**Table 2**). Specifically, CT subjects were slightly younger, showed large, histologically more advanced tumor characteristics than non-participants. However, CT participants and non-participants were similar relative to hormone and HER2 status, co-morbidities, and body mass index seemed to be similar.

There was a clear difference in tumor size between patients treated within and outside clinical trials. While less than 10% of CT patients had T1 tumors, outside CT it was more than 20%; additionally, the CT patients with T2 tumors comprised more than 70% of the CT group versus <60% of the non-participant group ($p<0.01$)/ Other tumor characteristics such as grading, ER status, PR status, HER2 status and molecular subtype were similar within both patient groups (**Table 2**). In total, 296 patients (29%) had a pCR. The association of pCR with year of diagnosis is shown in **Figure 2**. Patients treated within a CT were treated with a mastectomy in 24% of the cases, while patients outside CT underwent mastectomy in 35% of all cases (**Table 2**).

Prediction of pCR and the role of study participation

Comparing a prediction model with and without CT participation showed trial participation significantly influenced pCR additional to the considered predictors ($p= 0.03$, first likelihood ratio test). The interactions between trial participation and the other predictors, however, were not significant ($p = 0.06$, second likelihood ratio test). Thus, we could not show the effect of participation differed between patient subgroups. The adjusted OR for trial participants versus non-participants was 1.53 (95% CI, 1.03 to 2.28).

The reduced logistic regression model used to predict risks was well calibrated. The difference between actual and predicted events was quite low ($p = 0.58$, Hosmer–Lemeshow test). The

discrimination ability of the final regression model was also good, at AUC = 0.829. The cross-validated AUC was 0.813, indicating minimal overfitting. The cross-validated AUC values of the basic and the interaction model were lower (0.810 and 0.809, respectively), confirming the main result that trial participation is predictive without differences between subgroups.

Prediction of Mastectomy

Trial participation significantly influenced surgical management (p= 0.01, first likelihood ratio test). The adjusted OR for trial participants versus non-participants was 0.62 (95% CI 0.42 to 0.90). Again, subgroup-specific differences could not be shown (p = 0.054 second likelihood ratio test).

Trial Participation and Prognosis

Trial participants and non-participants differed with regard to follow-up time. The median follow up time of CT participants without disease progression or recurrence during observation time of this study was 8.3 years, whereas the median follow-up time of non-participants without progression or recurrence was 3.2 years. The distribution of the follow-up time is shown in **Figure 3**. Therefore survival analyses according to CT participation status were not performed. However, we did examine disease free survival based upon pCR within each group of patients (trial participants and non-participants) which demonstrated pCR was a predictor of disease free survival in both groups of patients (**Figures 4a and 4b**).

Discussion

Overall findings

This is the first analysis of CT participation and outcomes in early breast cancer in the neoadjuvant setting. Moreover, it is also one of the only trials examining the potential impact of CT participation on discreet outcomes, such as pCR and surgical management. This study demonstrated in addition to known factors associated with pCR, (i.e. clinical tumor size and/or

lymph node involvement, age at diagnosis, molecular subtypes and year of diagnosis) CT participation significantly increases the chance of pCR in women with early breast cancer. There was a more than 50% higher pCR rate in patients taking part in neoadjuvant CT than patients who were treated according to standard of care. Additionally, we examined predictive models for surgical outcomes which included CT participation and were able to demonstrate, CT participation is significantly associated with an increased chance of breast conserving therapy when compared to non-participants.

pCR it is less likely to be influenced by a detection bias than prognosis. Several publications regarding prognosis of breast cancer patients whom take part in CT compared to patients treated outside clinical trials. [32-35, 37, 57] However, none of these studies could show a clear benefit from patients taking part in CT. Most of the studies reported on a large difference between patients treated within and outside CT, indicating selection bias with regard to the compared patient populations. Like our study, these studies reported CT participants to be younger and to have a more advanced stage[34, 35, 57]. In our study there was a nominal and clinically not relevant difference of 2.1 years between patients inside and outside CTs. In this analysis, three of the trials had both lower and upper age limits; which accounted for more than 40% of the patients in the treatment group.

In addition to this selection bias, several more biases could have influenced the ascertainment of the follow-up information. A detection bias with regard to breast recurrences and metastases, as well as death seems to be probable when comparing the prognosis of patients treated within and outside CT. In CT there is significant effort put into the ascertainment of follow-up information. Outside CT, many patients do not return to their primary institutions and are not attending regular follow-up programs. Within the first 2 years of diagnosis, more than two-thirds of all patients appear to not return for their surveillance mammograms [58]. In our study, median

follow-up time of patients without events (recurrence or death) for non-participants was more than 5 years shorter compared to CT participants.

Additionally, in observational studies the Hawthorne effect has been described. [59]. It showed patients who take part in observational studies could start to show a different behavioral pattern. Similarly patients treated within CT could start to show different behaviors influencing prognosis differently than patients who did not take part in clinical trials. Since we studied the effect of participation compared to non-participation on a biological outcome, such as pCR, we demonstrated beyond patient behavior, “Hawthorne effect”, the benefit of trial participation, because it is unlikely, that the percentage of patients who get a final surgery is different in study patients vs. non-study patients.

Nonetheless, this study shows significant benefits related to CT participation. We showed CT participation results in higher pCR rates for patients of all examined subgroups. Also, the risk for mastectomies was lower in patients taking part in CT, which could be a subsequent effect of a better response of the tumors to the therapies. While we do not believe there is a detection bias in both subgroups and all patients had a similar likelihood to receive a final surgery, the clinical relevance with regard to prognosis remains unclear. There have been efforts to link an increase of pCR rates with a corresponding increase of prognosis [27]. However, this analysis by Cortazar et al, did not show, pCR is a surrogate of event-free survival or overall survival in the examined study population of more than 12,000 breast cancer patients treated with neoadjuvant chemotherapy. The only subgroup, confirmed as well in another study, which demonstrated a trend in association between an increase of pCR rate and increased survival was the HER2 positive subgroup [27, 60]. Independent from the question whether the increase of pCR is a surrogate for a better prognosis, in our study, pCR was associated with a better survival for both CT participants and non-participants. Further analyses need to be conducted to explore the association between pCR and increased survival.

While this study focused at an outcome, most likely not compromised by a detection bias, it has some limitations. First, it is a retrospective analysis and therefore, we had to manage missing data and variables. Further, we had to control for confounding variables in the analysis as these were not managed prospectively. Indeed, there may have been some sample bias with regards to those patients whom entered into clinical trials compared to those who did not. Some patients declined participation, some were not eligible, and for some there were not trials available for them during the time frame when they were diagnosed. Because we have included patients which were not eligible for participation, there may be other unknown predictors for pCR which were not accounted or controlled for in the analysis.

Conclusion

Regardless of the demonstrated association between better outcomes for women with early breast cancer who participated on clinical trials, albeit with some limitations, it is critical to recall the importance of clinical trial participation regardless of outcomes. Interventional clinical studies provide the necessary evidence based back-bone to develop new standards of care and ensure forward progress with respect to cancer patient management and care.

Table 1: List of clinical trials conducted in the observation period (*all studies but Techno and Dafne were randomized trials, **patients included into the Prepare study were mainly HER2 negative because of the competing Techno trial at that time, (cT_{clin}: palpable tumor size, ct_{rad}: radiological tumor size).

RCT Trial Name n=260	n	Enrollment Dates	cT_{clin} (cm)	cT_{rad} (cm)	Molecular Subtype	Age	Treatment	Reference
Prepare (AGO)	78	2002-2005	≥2	≥2	All**	≥18-≤65	Dose-Dense, Dose-Intensified Epirubicin, Paclitaxel, And CM Vs Standard Dose Epirubicin/Cyclophosphamide Followed By Paclitaxel +/- Darbepoetin Alfa	20, 21
Techno (AGO)*	20	2002-2008	≥2	≥2	HER2+	≥18-≤65	Epirubicin + Cyclphosphamide Followed By Paclitaxel + Trastuzumab	22
GeparQuattro	52	2005	≥2	≥1	All	≥18	Epirubicin/Cyclophosphamide Followed By Docetaxel With Or Without Capecitabine (HER2+ patients got Trastuzumab)	39-41
Epothilon CA 163-100	9	2007-2009	≥2	≥2	All	≥18	AC Followed By Ixabepilone Or Paclitaxel	42, 43
SATIN	13	2007-2010	≥3	≥3	All	≥18-≤75	AC Followed by Larotaxel +/- Trastuzumab versus AC Followed by Docetaxel +/- Trastuzumab	50
GeparQuinto	54	2007-2010	≥2	≥1	All	≥18	Epirubicin + Cyclphosphamide Followed By Docetaxel Vs Epirubicin + Cyclphosphamide Followed By Docetaxel + Bevacizumab Vs Paclitaxel Vs Paclitaxel + Everolimus Vs Epirubicin + Cyclphosphamide Followed By Docetaxel + Trastuzumab Vs Epirubicin + Cyclphosphamide Followed By Docetaxel + Lapatinib	44-49
GeparSixto	16	2011-2013	≥2	≥2	TNBC HER2+	≥18	TNB: Non-Pegylated Liposomal Doxorubicin + Paclitaxel + Bevacizumab +/- Carboplatin HER2+: TNB: Non-Pegylated Liposomal Doxorubicin + Paclitaxel + Trastuzumab + Lapatinib +/- Carboplatin	51

DAFNE*	3	2012-2013	≥2	≥2	HER2+	≥18	Afatinib (Stopped 2 weeks prior to EC)+ Trastuzumab (Continued post 1 year) Followed by Paclitaxel Followed by Epirubicin + Cyclophosphamide	[52]
NeoPHOEBE	6	2013-2015	≥2	≥1.5	HER2+	≥18	Trastuzumab +/- BKM120 Followed by Paclitaxel + Trastuzumab +/- BKM120	[53]
KRI5TINE	9	2014-2015	>2	>2	HER2+	≥18	Trastuzumab + Pertuzumab + Docetaxel + Carboplatin (continuation post-operatively) Trastuzumab + Pertuzumab Versus Trastuzumab Emtansine + Pertuzumab (continuation post-operatively) Trastuzumab Emtansine + Pertuzumab	[54]

Figure 1: Patient Selection

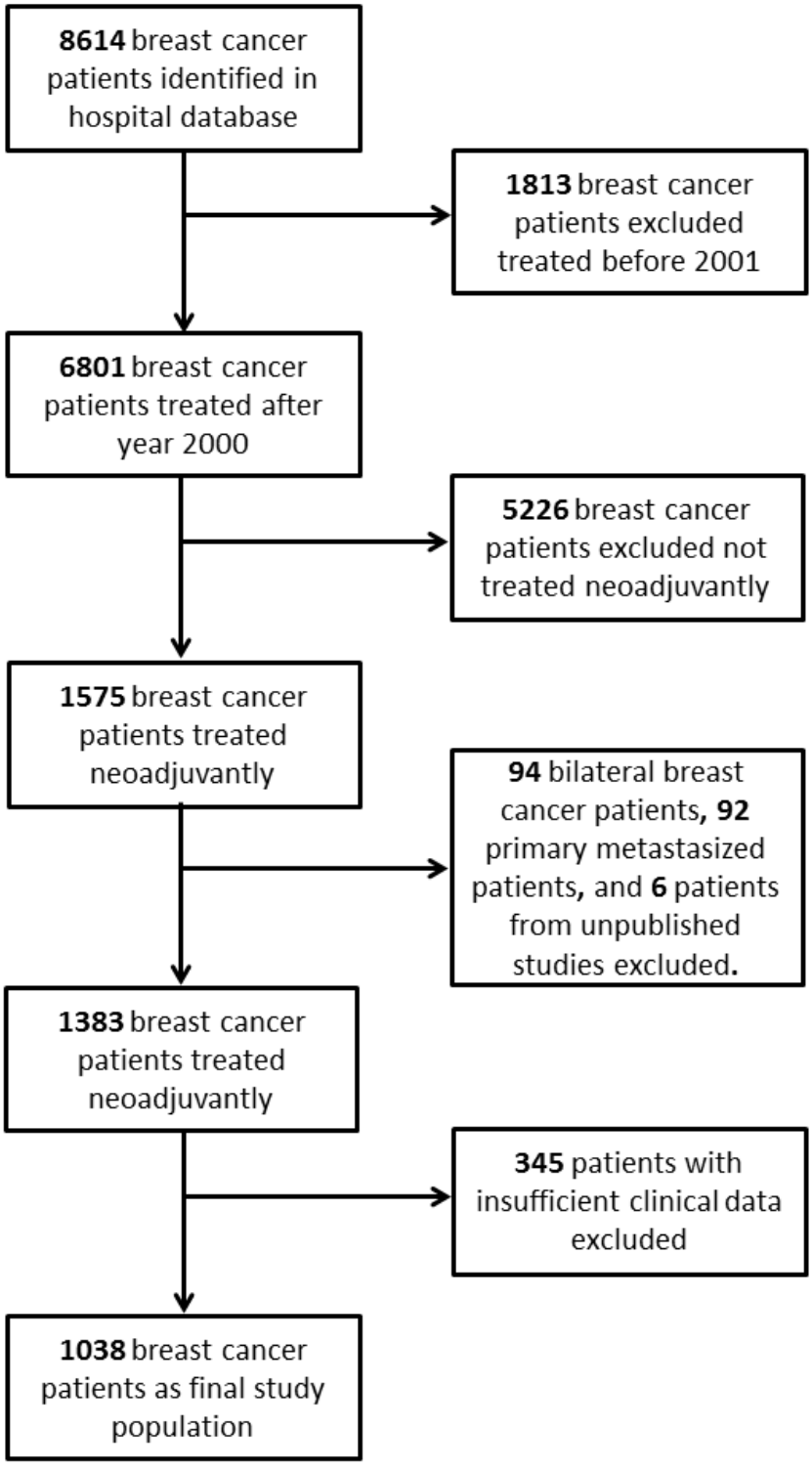


Table 2: Patient characteristics according to trial participation

Patient or Tumor Characteristic	Treatment within study (n=260) n or mean	% or SD	Treatment outside study (n=778) n or mean	% or SD
Age	51.3	10.9	53.4	13.0
BMI	25.8	5.2	25.9	5.0
Year of Diagnosis				
<2006	111	42.7	137	17.6
2006-2010	114	43.8	232	29.8
>2011	35	13.5	409	52.6
Tumor size before chemo				
cT1	20	7.7	192	24.7
cT2	201	77.3	462	59.4
cT3	11	4.2	43	5.5
cT4	28	10.8	81	10.4
Grading				
1	11	4.2	30	3.9
2	131	50.4	310	39.8
3	118	45.4	438	56.3
ER Status				
negative	85	32.7	271	34.8
positive	175	67.3	507	65.2
PR Status				
negative	103	39.6	351	45.1
positive	157	60.4	427	54.9
HER2 status				
negative	191	73.5	614	78.9
positive	69	26.5	164	21.1
Molecular subtype				
HER2 positive	69	26.5	164	21.1
Luminal A like	50	19.2	122	15.7
Luminal B like	79	30.4	303	38.9
TNBC	62	23.8	189	24.3
Known heart Disease				
no	239	91.9	719	92.4
yes	21	8.1	59	7.6
Known renal disease				
no	257	98.8	768	98.7
yes	3	1.2	10	1.3
Known Diabetes				
no	246	94.6	732	94.1
yes	14	5.4	46	5.9
Known Neuropathy				
no	256	98.5	762	97.9
yes	4	1.5	16	2.1

Mastectomy				
No	197	75.8	504	64.9
Yes	63	24.2	272	35.1

Figure 2: Pathological complete response (pCR) rates relative to the year of treatment/diagnosis (solid curve) with 95% confidence intervals (dashed curves). Estimations are based on a simple logistic regression model with year of diagnosis as cubic spline function.

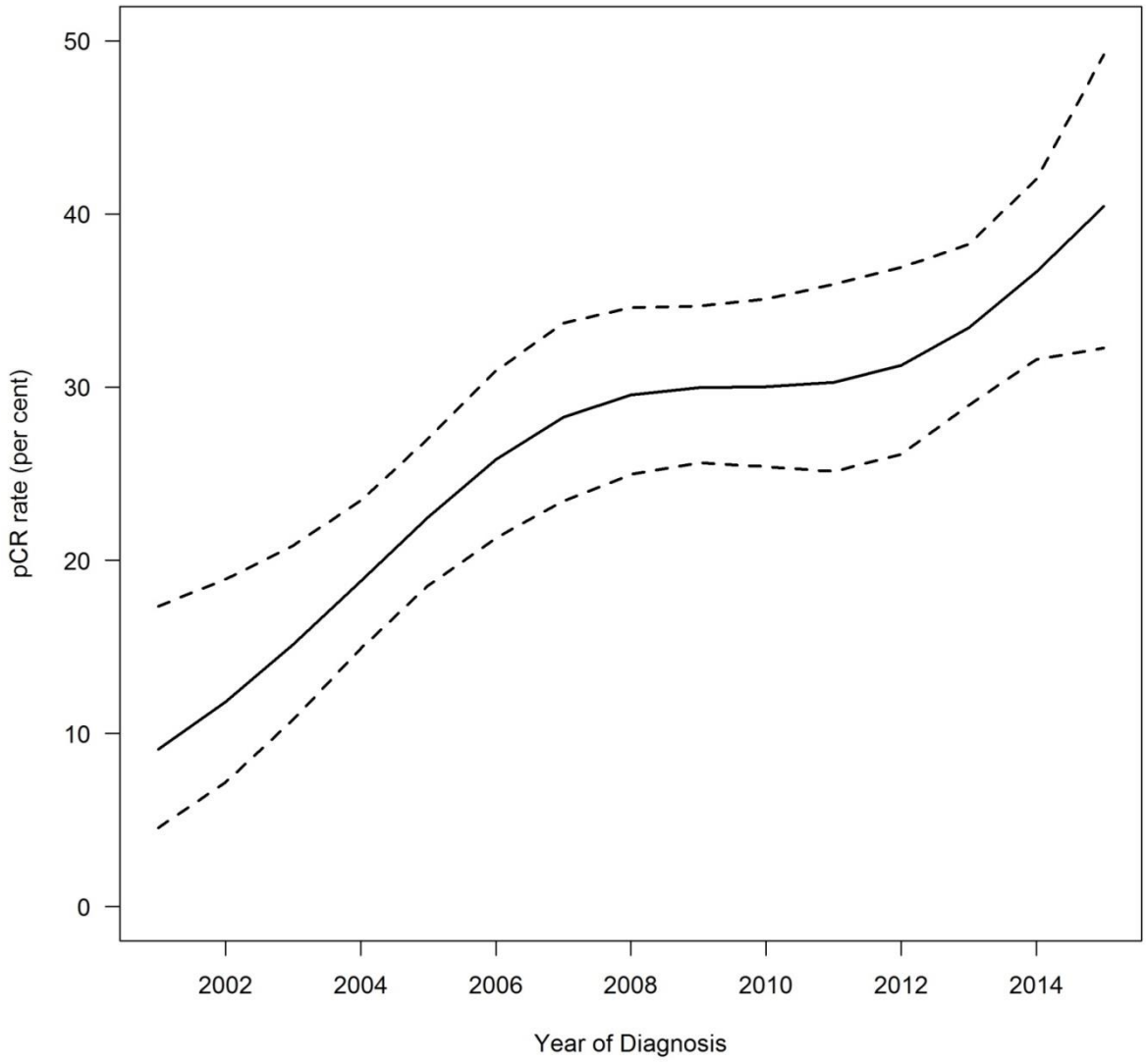


Figure 3: Boxplots for the follow up time in the groups of patients with and without trial participation

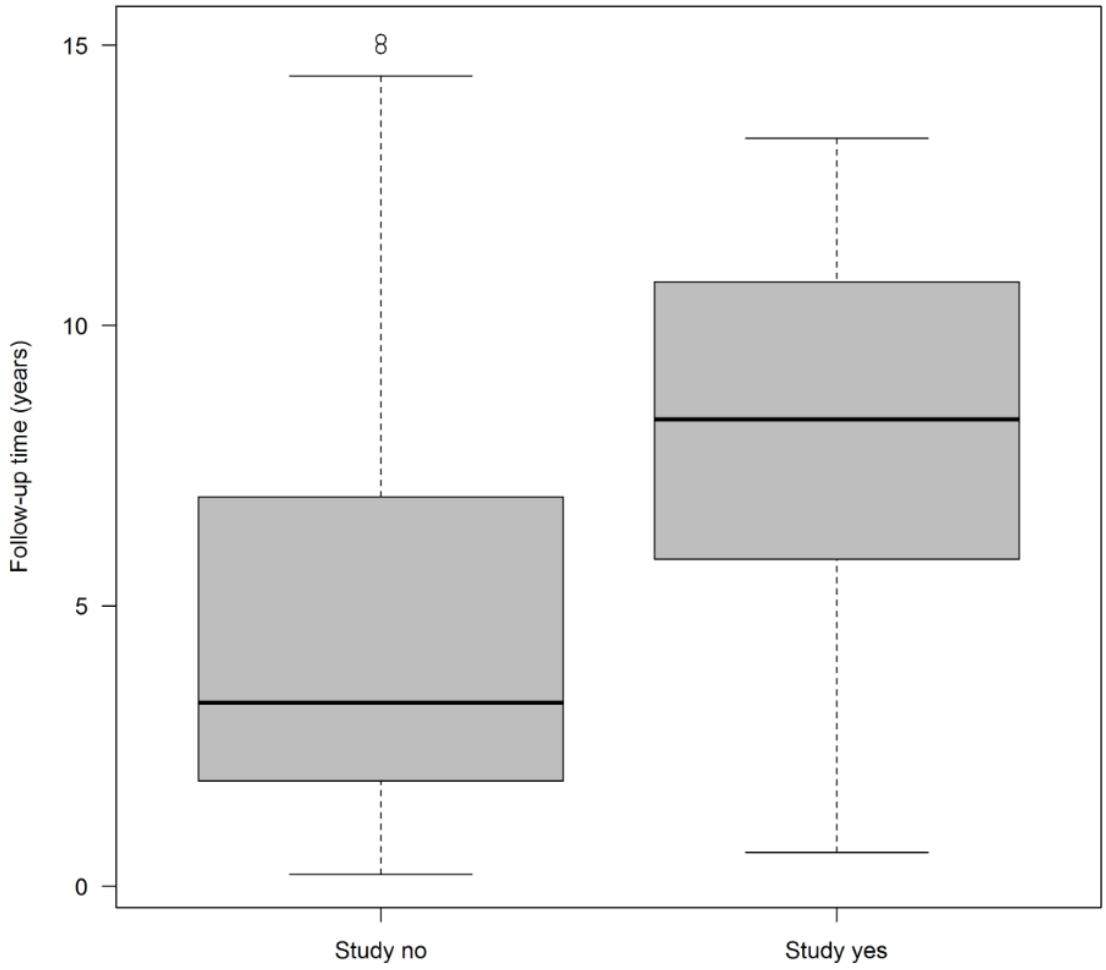


Figure 4a: Disease free survival according to pCR in patients, who did not take part in clinical trials (p-value for the log-rank test <0.001)

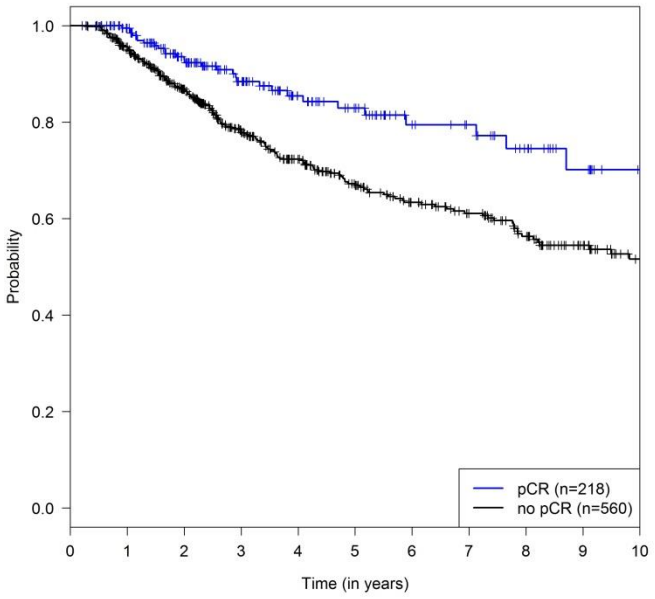
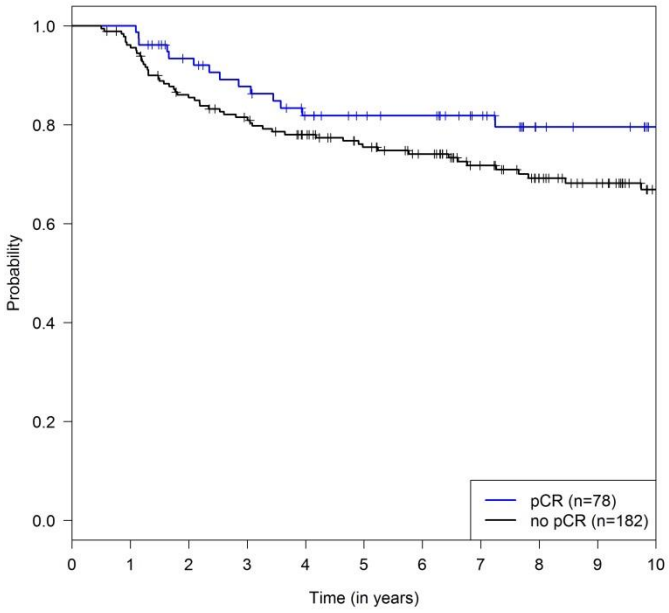


Figure 4b: Disease free survival according to pCR in patients, who did take part in clinical trials (p-value for the log-rank test = 0.09).



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SPECIFIC AIM 2: MANUSCRIPT

The effect of participation in RCT on outcomes in patients with early breast cancer compared to the general breast cancer population

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Abstract

Background: Invasive breast cancer is the leading malignancy and the second most common cause of malignancy-related death for women in Canada and the United States (North America). Over the last 30 years, there has been a dramatic increase in 5-year survival of breast cancer patients related to advances in technology and treatment. Most of these technological advances are from scientific efforts translated into clinical trials. While advances such as, prevention, treatment, and management, and possible cure, may be improved by findings from clinical trials, participation of adult cancer patients is low. Breast cancer trial enrollment, while slightly higher than some other oncologic disciplines, still remains significantly low at less than 4%. Research suggests lack of participation in clinical trials is due to poor patient and clinician (physicians and nurses) commitment and interest. Increasing incentive for trial participation may enhance engagement of patients and healthcare providers leading to increased patient enrollment. One incentive would be to understand the benefits of trial participation with regards to better survival and outcomes.

The purpose of this study is to determine differences in survival, overall and breast cancer specific, and surgical management, for North American women who participate in early breast cancer randomized clinical trials (RCT) compared to the general breast cancer population who received similar standard therapy outside of a RCT.

Methods: Patients in this retrospective analysis were from one of three (3) international, RCT adjuvant breast cancer trials (RCT-participants) and women with similar stage breast cancer from the general U.S. population, from *Surveillance Epidemiology and End Results Program* (SEER-13), the controls. Kaplan-Meier curves were generated to display differences in survival patterns between the RCT-participants and the SEER-13 controls . Propensity score analysis (PSA) was calculated for each patient and applied to a Cox proportional hazards model to determine hazard ratios (HR) of trial participation on survival. Similarly, propensity score analysis was also calculated and utilized when performing multivariable logistic regression to

calculate the odds ratios of surgical management (mastectomy or BCS) for RCT participation compared to the SEER-13.

Results: Women diagnosed between 1997-2004 with invasive breast cancer, tumor (T) size 1-3, lymph node (LN) positive (LN1/2), hormone receptor positive or negative, HER2 positive or negative, treated with surgery and adjuvant chemotherapy were included in the analysis. The total sample size was 9255 patients, 1795 RCT-participants and 7460 SEER-13 controls. Crude 10-year survival estimates demonstrate RCT-participation was associated with a significantly better breast cancer survival ($p<0.001$) compared to controls. Overall survival at 10 years was not different. Multivariate analysis demonstrated reduction in risk of death by 17% [HR: 0.83 (95% CI: 0.72-0.95;) $p<0.001$] for patients at 5-years and 21% reduction in risk for 10 years [HR:0.79 (95% CI: 0.71-0.87;) $p<0.001$]. RCT-participants were significantly less likely to undergo mastectomy compared to SEER-13 controls [OR: 0.78 (95% CI: 0.66-0.92;) $p=0.03$].

Conclusion: RCT-participants have a reduction of risk of death at 5 years and 10 years compared to the general breast cancer population. Additionally, they are less likely to undergo mastectomy than the SEER-13 controls.

Key Words: clinical trial participation; breast cancer; SEER; general population; oncology; outcomes

Introduction and Background

Invasive breast cancer is the leading malignancy and the second most common cause of malignancy-related death for women in North America (Canada and the United States, excluding Mexico).[1, 2] In 2016, more than 250,000 women in the United States and Canada will be diagnosed with breast cancer. In this same year, about 45,000 North American women will succumb to breast cancer. While breast cancer incidence and deaths in North America have remained relatively stable for a number of years, they continue to rise globally with the global population increase.[3, 4, 5] There are enormous physical, psychosocial and financial burdens associated with cancer diagnosis and management. Support and treatment costs for cancer-affected adults are significant, with breast cancer is one of the most costly.[6, 7, 8]

Much of that cost is related to the improvements in breast cancer diagnosis and treatment. Over the last 30 years, there has been a dramatic increase in 5-year survival of breast cancer patients related to advances in technology and treatment.[9] Globally, breast cancer survival at 5-years now is quite high (60-89%), depending on the country. [10] Currently, there are more than 3.7 million North American women living with a history of invasive breast cancer. [11, 12] While new technologies, primary treatments and supportive care have increased treatment costs exponentially since 1991, they have been justified based upon an increase in years of life, as well as quality-adjusted life-years (QALY).[8], [13, 14, 15]

Most of these technological advances are from scientific efforts translated into clinical trials. While advances such as, prevention, treatment, and management, and possible cure, may be improved by findings from clinical trials, participation of adult cancer patients is low. Data indicate less than 18% of adults with cancer in the United States and Canada (7%) participate in randomized clinical trials, with even less participation (between 1-5%) in adjuvant studies.[16, 17,

[18, 19, 20, 21] More specifically, breast cancer trial enrollment, while slightly higher than some other oncologic disciplines, still remains significantly low at less than 4%.[22, 23]

Research suggests lack of participation in clinical trials is due to poor patient and clinician (physicians and nurses) understanding, limited access, mistrust, fear, lack of engagement and commitment, importance of research, and poor communication.[16, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32] Increasing the non-monetary motivation for trial participation may enhance clinical trial engagement by patients and healthcare providers and lead to increased patient enrollment. One way to increase motivation and engagement would be to determine positive effects of trial participation, independent of the experimental agent, which may incentivize participation, leading to quicker development of supportive and curative therapies. Specifically, trial participation, regardless of experimental treatments, may improve early detection of recurrent disease, prevention or early detection of comorbidities, thereby improving survival. Participation alone may also minimize side-effects of standard-of-care therapies, improve access to effective primary and secondary prevention interventions, and potentially, improve quality of life for women diagnosed with early breast cancer.

Some research has been conducted examining the effect of clinical trial participation across multiple health disciplines, including oncology.[33, 34] These studies suggested randomized clinical trial (RCT) participation can improve outcomes in the oncology setting.[35, 36, 37] Although studies have explored clinical RCT in breast cancer, often they are included in an analysis of other histologies or stage disease.[38, 39, 40] There are limited studies which exclusively explored trial participation in the early breast cancer setting.[41, 42, 43, 44, 45] These studies tended to be small samples, often at single centers, and none compared the patients to general breast cancer population patients.

The purpose of this retrospective, secondary data analysis was to compare the outcomes, overall survival and surgical management, of early breast cancer RCT participants in North America to the general breast cancer population who received similar standard therapy outside of a RCT. Additionally, this study explored predictors of trial participation compared to the general breast cancer population.

Material and Methods

Patient Selection

Patients included in this retrospective analysis were from one of three (3) international, RCT adjuvant breast cancer trials (RCT-participants) and women with breast cancer from the general U.S. population, (controls). RCT-participant cases were enrolled in 1 of the following Phase III adjuvant trials studying available standard of care treatment regimens for superiority:

- A Multicenter Phase III Randomized Trial Comparing Docetaxel in Combination With Doxorubicin and Cyclophosphamide (TAC) Versus 5-fluorouracil in Combination With Doxorubicin and Cyclophosphamide (FAC) as Adjuvant Treatment of Operable Breast Cancer Patients With Positive Axillary Lymph Nodes (*BCIRG-001*)[46]
- A Multicenter Phase III Randomized Trial Comparing Docetaxel in Combination With Doxorubicin and Cyclophosphamide Versus Doxorubicin and Cyclophosphamide Followed by Docetaxel as Adjuvant Treatment of Operable Breast Cancer HER2neu Negative Patients With Positive Axillary Lymph Nodes (*BCIRG-005*)[47]
- Multicenter Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed By Docetaxel (AC-T) With Doxorubicin and Cyclophosphamide Followed By Docetaxel and Trastuzumab (Herceptin®)(AC-TH) and With Docetaxel, Carboplatin and Trastuzumab (TCH) in the Adjuvant Treatment Of Node Positive and High Risk Node Negative Patients With Operable Breast Cancer Containing the HER2 Alteration (*BCIRG-006*)[48]

These studies were conducted over multiple years (1997-1999 and 2000-2004). Data for these studies (BCIRG-001, BCRIG-005, and BCIRG-006) were collected prospectively during the course of the study. It was monitored and reviewed for accuracy and a formal data management plan adhered to during the conduct of the studies. Utilization of the trial data for this unplanned analysis was granted in May of 2014 by the scientific advisory board (SAB) responsible for the conduct and oversight of the studies and data. Subsequently, the IRB at the University of

California approved the retrospective analysis. Outcome data, overall survival, (all cause and cause specific) and surgical management (breast conserving surgery or mastectomy) were available for up to ten (10) years subsequent to the completion of study treatment for the majority of the RCT participants.

Controls were women included in the U.S. population-based cancer surveillance program for thirteen (13) major sentinel sites, *Surveillance Epidemiology and End Results Program* (SEER).[49] SEER collects and publishes cancer incidence and survival data from population-based cancer registries from diverse areas of the United States, covering about 30% of the population. SEER data are commonly used by researchers and clinicians; and the details regarding data collection and control are available on their website: http://seer.cancer.gov. The SEER-13 registries are Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia and the Alaska Native Tumor Registry. Data were made available from all cases diagnosed from 1992 to 2013 for these registries.[50] After IRB approval, a formal request to SEER for utilization of the data was requested and granted in August 2015. Upon approval by SEER, anonymized data was also transferred from the secure web-based server.[51]

RCT-Participant Selection

The full population of RCT-participant cases included 8,014 women enrolled in either BCIRG-001 (n=1492), BCIRG-005 (n=3300), or BCIRG-006 (n=3222). The population of 8,014 RCT-participant cases was refined to include only women enrolled in North America (U.S. and Canada), n=5,642. Additionally, women (n=755) in two arms of the BCIRG-006 study who received HER2 antibody therapy, trastuzumab, were excluded as well. Because trastuzumab was not commercially available as standard of care to the general population for early breast cancer until approved by the United States, Food and Drug Administration in 2006, patients whom received experimental therapy were excluded from the RCT-participant group. Women

without lymph node involvement whom were considered “high-risk” for recurrence and included in the study, were also excluded from the analysis, as the nature of their “high-risk” status was subjective and variable, making it unlikely to find an equivalent comparator population from the control group. (See **Figure 1**). The refined total RCT-participant cases for analysis was n=1795 (BCIRG-001 trial: 647, BCIRG-005 trial: 898, BCIRG-006: 250). These 1795 women had invasive breast cancer, with lymph node involvement treated with or without radiation therapy after surgery and adjuvant chemotherapy.

Control Selection

To start, the SEER-13 dataset included 4,285,310 cancer patients diagnosed between the years 1992 and 2013. SEER-13 control patients were excluded if the record was incomplete for certain diagnostic criteria or lacked follow-up or patients died before a single month (30-days) had elapsed. Controls from the SEER-13 database were included in the analysis based upon a hierarchical order. SEER-13 controls were selected based on the criteria of inclusion for the RCT-participant group. This included the same date of diagnosis as the RCT-participants, June, 1997 through July, 1999 and August, 2000 through February, 2004. From this group patients were further excluded who did not have invasive breast cancer at initial diagnosis, presented with distant metastases at diagnosis, or did not receive primary cancer management similar to the RCT-participants, including primary surgical approach and/or radiation and/or systemic therapy. **Figure 2** delineates the hierarchical inclusion criteria and process. The SEE-13 controls were fully refined to a total of n=7460 invasive breast cancer patients with lymph node involvement, treated with chemotherapy and surgery with possible radiation therapy as well, depending on the surgical management.

Statistical Analysis

This is an independent study of RCT-participants and the SEER-13 general breast cancer population. Descriptive, (frequencies, means, standard deviations, and ranges), tabular, and inferential statistics were used to describe the two patient populations. For continuous variables, student t-test was used to compare the mean values. All categorical variables were compared using the chi-square (χ^2) or Fisher's exact test. Statistical significance was established with an alpha of 0.05.

Kaplan-Meier curves were generated to display survival (breast cancer specific, other cause and all-cause) patterns between the RCT-participants and the SEER-13 controls, using log-rank to test for OS functions equally across time. Statistical significance of survival data was established by using an alpha of 0.05.

As noted previously, patients with some missing data were excluded from analysis. However, key predictive variables where the majority of the data was missing for either the RCT-participant group or SEER-13 control group was reviewed and considered. There were two important variables, race and HER2 status where either the majority of the data was missing or no data was available for the selected group. For these two variables, missing data was imputed using a multiple imputations procedure.

The SEER-13 control group did not have validated HER2 status available for the cohort of patients included in this analysis; however, it was available for SEER-13 patients diagnosed after 2010. Based on this data, multiple imputations procedure was used to assign missing HER2 status to all the patients in the SEER-13, including patients in the control cohort. [52] Using the following variables: race, ethnicity, histological type, grade, method of diagnosis, surgical type, ER status, PR status, tumor size and age at diagnosis, multiple imputations procedure

assigned HER2 status for the SEER-13 patients, as positive, negative or borderline. Subsequently, the 7460 patients in the SEER-13 control cohort were evaluated to ensure complete data.

The RCT-participant group only collected race information on patients in the first trial, BCIRG 001, based upon this data, we imputed race for the remaining RCT-participants (BCIRG 005 and BCIRG 006), using a multiple imputation procedure. Race was imputed using the following variables: treatment city and county, age at diagnosis, histological type, HER2 status, ER status, and PR status.

Survival outcomes were calculated for breast cancer specific, other cause and all-cause mortality. In this study, propensity score analysis (PSA) was done to provide weight to each data point for each variable in order to more closely represent similar populations. PSA is considered superior to a standard Cox multivariate analysis because it attempts to reduce the bias due to confounding and correlated predictive variables. Propensity score is calculated by modeling the probability of RCT-participant group or SEER-13 control group, using multiple logistic regression including the following variables: histological type (categorical), tumor size and grade (both categorical), age (continuous), stage (II or III), estrogen receptor (ER) status, progesterone (PR) status, ER/PR status combined (categorical), nodal status (categorical <4 or ≥ 4), HER2 status (categorical) and race (categorical). [53] This results in an inverse probability weight for each data point, the propensity score. Subsequently, the propensity score was applied to a Cox proportional hazards model to determine hazard ratios (HR), with a Wald 95% confidence interval (CI), of trial participation on survival. The regression model included several variables from a step-wise selection, histological type (categorical), tumor size and grade (both categorical), age (continuous), stage (II or III), estrogen receptor (ER) status, progesterone (PR) status, nodal status (categorical <4 or ≥ 4), HER2 status (categorical) and race (categorical),

and any interaction variables. In the step-wise selection, the variable “Group” (RCT-participant or SEER-13 control) was not selected for inclusion in the model, and was therefore, manually included or forced, in the model for the purposes of this inquiry.

The same process was utilized to generate a propensity score using logistic regression and the same variables; however we added an additional variable, treatment region (rural urban code), to generate the propensity score. Step-wise selection was performed to determine the appropriate variables to be included in the model. Again, in this model the treatment group (SEER-13 control versus RCT-participant) was forced. Using the propensity score, multivariate logistic regression was done to calculate the odds ratios, with a Wald 95% CI, to determine if RCT participation compared to the SEER-13 control had an impact on surgical outcomes, mastectomy versus breast conserving surgery (BCS). Analyses were performed using SAS software, Version 9.4 of the SAS System for Windows. (Copyright © 2013 SAS Institute Inc., Cary, NC, USA).

Results

Patient and Tumor Characteristics

Patient characteristics are presented for both the RCT-participants and SEER-13 controls in **Table 1**. To summarize the control group had slightly older women, patients with smaller tumors, more low to moderate grade (1-2) tumors, and patients with fewer positive lymph nodes. Both groups were similar with regards to surgical management and radiation therapy after surgery. All patients in both groups received chemotherapy in the adjuvant setting. The type of chemotherapy for SEER-13 was not available. RCT-participants received either combination docetaxel, doxorubicin, and cyclophosphamide or combination 5-fluorouracil, doxorubicin, and cyclophosphamide.

We performed the multiple imputations procedure for HER2 in the SEER-13 data set to provide data for the missing HER2 status variable. As noted previously, we utilized several variables to perform the multiple imputations procedure including race, ethnicity, histological type, grade, method of diagnosis, surgical type, ER status, PR status, tumor size and age at diagnosis. As expected with multiple imputations procedure, this changed the frequency of some of the data for variables included in the multiple imputations procedure for SEER-13. For the total SEER-13 sample, race was recoded for 2805 patients; ER status was recoded for 84131 patients, PR status was recoded for 95749 patients, and age at diagnosis for 14 patients was recoded. After applying the selection criteria to the new SEER-13 data set, with HER2 imputed, only 9 patients had data change with the imputation. There were no longer any patients with race missing (n=9; 0.12%), 8 patients recorded were now reported as white (n=5390 to 5398) and 1 patient as black (n=865 to 868), changing the frequency for the groups but not the percentage represented for each group. No other data was assigned during the multiple imputations procedure for any other variables (age, ER or PR status) for the selected SEER-13 patient population in this analysis. The final frequency for HER2 status for SEER-13 after imputation, was 1371 (18.4%) positive, 5930 (79.5%0) negative and 159 (2.1%) borderline.

Additionally, after performing the multiple imputations procedure for race for the RCT-participant group, several variables were included in the procedure although only 2 variables other than race were imputed, HER2 status and age. A single patient had age imputed which assigned the data from less than 40 years to between 61-70 years and 77 patients had HER2 status imputed. This altered the HER2 frequency across all categories. All patients with borderline HER2 status (n=77) were converted to either positive (n=735; was 685) or negative (n=1060; was 1033). This minimally altered the percentage of positive HER2 patients from 60.1% to 59.1% and the negative patients from 39.8% to 41.0%. The final frequency for race after multiple imputations, was 1702 (94.8%) white, 16 (0.9%) black, and 77 (4.3%) other.

In this analysis, administrative censoring was done at 120 months (10-years) for the entire data set. Because this was a long-term survival study, we gave careful attention to the follow-up time for all patients. There were considerations regarding informative censoring, as it was thought patients on clinical trials are more likely to be followed long-term regardless of event status (recurrence or death). The follow-up data was evaluated to determine those patients lost to follow-up (LTF) prior to the 120-months point, as well as those which experienced an event (death prior to 120 months). Of the entire patient population, RCT-participants and SEER-13 controls, 6672 (72.1%) of the living patients continued to be followed and data recorded on their status up to at least 120 months. More than 1900 patients died during the follow-up period, of breast cancer or other causes. The remaining 672 (7.3%) were LTF at some point during the 120 months. Interestingly, the majority of alive SEER-13 controls n=5762 (97%) were still being followed at 10 years, whereas only 64.8% (n=910) of the alive RCT-participants were still being followed at 10-years. The median follow-up time for LTF patients for the RCT-participant group was 72.5 months and for the SEER-13 control group was 77.0 months (see **Figure 3**). While we cannot prove there was not informative censoring, evidence regarding LTF patients demonstrates censoring was non-informative. Median overall survival for RCT-participants was 49.0 months compared to 61.0 months for SEER-13 controls. Breast cancer specific median survival was 48.5 months for the RCT-participant group and 57.0 months for SEER-13 control group. Additionally, median survival time for women who died of other causes was 54.0 months for the RCT-participant group and 115.0 months for SEER-13 control group (see **Table 2**).

Using the imputed data sets, we performed crude survival analysis and demonstrated while breast cancer specific was significantly better for RCT-participants compared to SEER-13 controls ($p<0.001$), overall survival was the same ($p=0.48$) for both groups (see **Figure 4** and **5**). Cox proportional hazard ratio analysis for up to 5-years and 10-years survival for all-cause mortality, breast cancer specific, and other cause was done. This crude analysis demonstrated

patients whom participated in the RCT had a significantly worse breast cancer specific 10-year and 5-year survival. Additionally, all-cause mortality at 5-years was significantly worse (HR: 1.41; CI: 1.22-1.64) for the RCT-participant group compared to SEER-13 controls, (see **Table 3**). This is most likely, related to the more aggressive clinical features of the RCT-participants cancers: larger tumors, more lymph node involvement, higher grade tumors, more HER2 positive patients, and more ER/PR negative hormonal statuses.

Subsequently, multivariate logistic regression was completed in order to calculate a propensity weight for each data point. This propensity weight was applied in a Cox proportional hazard ratio (HR) model to determine risk of death (all cause, breast cancer specific and other cause) for patients in the RCT-participant group compared to the SEER-13 control group. After controlling for all other significant predictors of survival, trial participation significantly reduced risk of breast cancer related death at 5-years by more than 25% and 18% at 10 years [HR: 0.75 (95% CI: 0.64-0.87); p=0.00020; and HR: 0.83 (95% CI: 0.74-0.93); p=0.00165, respectively]. Additionally, we demonstrated a significant reduction in risk of all-cause mortality for RCT-participants, at both 5-years and 10-years [HR: 0.83 (95% CI: 0.72--0.95); p=0.009; and HR: 0.79 (95% CI: 0.71-0.87); p<0.00001, respectively]. Refer to **Table 4** for details regarding the multivariate survival outcomes.

Additionally, we explored survival for a subset of patients. In this analysis, we excluded SEER-13 controls from 16 counties which were represented in our RCT-participant group. This resulted in a total dataset of 5799 patients, 4004 from SEER-13 control and 1795 from RCT-participant groups. The frequency data for this subset is available in **Table 5**. Subsequently, we performed a multivariate cox proportional hazard ratio analyses for 5 and 10 year survival using the previously generated propensity score for the smaller subset of patients (see **Table 6**). In these analyses, we found RCT-participation to have a significant impact on survival. Both 5

and 10-year breast cancer mortality risk was reduced by 20-40%, ($p<0.001$ and $p=0.008$, respectively), as well as 5 and 10-year all-cause mortality risk ($p<0.001$ and $p<0.001$) for RCT-participants compared to controls.

Surgical Outcomes

In this study, we hypothesized trial participation is associated with less morbidity associated with breast cancer. With regards to morbidity, we examined surgical management of breast cancer for patients in the RCT-participant group compared to the SEER-13 control group. It has been noted breast conserving surgery (BCS) is associated with less morbidity than mastectomy. Therefore, we examined the association of RCT participation on surgical outcome, in this case mastectomy compared to BCS. Again, the rates of BCS (57.0% for SEER-13 control group and 59.2% for RCT-participant group) and mastectomy (43.0% for SEER-13 control group and 40.8% for RCT-participant group) were similar for both groups. In this analysis, several variables were considered for inclusion in the model, such as tumor size, histological type, grade, hormonal status, race HER2 status, lymph node involvement and age at diagnosis. Additionally, region where patients received treatment was considered, due to post-operative care and radiation requirements after surgery. Therefore, an additional variable, which described the region in which the patient was care for as either rural or urban, based upon population and location near a metropolitan area. Because this code was only available for patients treated in the United States, approximately 800 patients from the RCT-participant group and 111 from the SEER-13 control group (total 912 patients excluded from analysis). In the univariate logistic regression, using this subset of patients, participation was associated with less risk of mastectomy (OR: 0.91; CI: 0.82-1.02); although, it was not statistically significant (see **Table 7**).

Next, step-wise selection was completed to determine the appropriate variables to be included in the multivariate logistic regression model. Again, in this model the treatment group (SEER-13 control versus RCT-participant) was forced. The propensity score was used to perform multivariate logistic regression for odds ratios with mastectomy compared to BCS as the outcome for RCT-participants compared to SEER-13 controls. In this multivariate analysis, RCT-participation was significantly (p=0.026) associated with a reduction in risk of mastectomy by more than 20%, (OR: 0.78; CI: 0.66-0.92) when compared to SEER-13 controls (see **Table 8**).

Discussion

This study demonstrated, after controlling for confounding variables, compared to the general breast cancer population RCT participants with stage II and III, treated with chemotherapy, experienced significantly reduced risk of death, breast cancer specific and all-cause, both in the short and long-term. Moreover in a subset of patients this reduction in risk of death increases from approximately 20% to as high as 40%. Additionally, we demonstrated RCT-participants are less likely to undergo mastectomy compared to the general breast cancer population with similar prognostic factors. The findings are consistent with other studies which demonstrated survival benefits for adults who participated in oncology clinical trials. [37, 36, 38, 40, 45, 54, 55, 56, 57, 58, 59,] However, this study did provide evidence for long-term improvements beyond 5 years in the breast cancer patient population which has not been consistently demonstrated in this population. [39, 44]

This is the first study to date which evaluated RCT-participants to the general cancer population, SEER-13, in a study focused entirely on early breast cancer patients treated at multiple institutions across North America. Patients in both groups were treated in different regions (urban and rural) and different types of treatment centers, academic medical centers (AMC),

community hospitals, and private medical oncology practices, both in the United States and Canada.

This reduced risk of death or mastectomy may be related to patient selection or the “trial effect” (treatment, Hawthorne, protocol and cluster effects). Patient selection for this analysis was done through access to RCT dataset and access to the general population. There is potential for selection bias for patients of this study as it was a retrospective analysis. Data regarding co-morbid conditions was not available for either of the patient groups; and therefore, could not be controlled or considered in the analysis. It is likely, based upon other studies and the eligibility criteria, the RCT-participant group had fewer comorbidities and better performance statuses (an eligibility criteria) compared to the general breast cancer population in this study which may account for their improved outcomes.

It could be also argued patients on the RCT had better outcomes because of the “treatment effect”. It should be noted, however, while the type, strength, and duration of chemotherapy patients in the SEER-13 group received was unknown, only those patients that received chemotherapy were included in the analysis. Furthermore patients in the RCT-participant group all received chemotherapy which was available as standard therapy in the community. The patients on BCIRG006 which received HER2 based therapy, an experimental therapy, were not part of this study. While this does not eliminate the “treatment effect” entirely, no patients received experimental or novel therapy on the RCT which could account for the reduced risk of mortality. Additionally, it is not known if patients in the SEER-13 group received any experimental therapy. So while there is a moderate reduction in risk of death and more invasive surgery, it may be even greater if it was possible to account for any experimental treatment patients in the general population control group received.

Consideration is also given to the Hawthorne effect which provides patients and healthcare providers who are being observed or studied, will change their behavior. This is often a requirement of the protocol. Health care providers may be more diligent in their care of patients on trials, either as part of the trial or just based on the nature of caring for patients on a trial. Similarly, patients on trial may behave differently because they are being studied. They may be more compliant or diligent about following a treatment plan and seeking care when a health condition arises. In this study, OS was better for RCT-participants; however non-breast cancer specific death was higher in the RCT-participant group compared to the control group, which contradicts the idea more diligent follow-up care for RCT-participants has a positive effect on survival.

There are several strengths of this study. In order to control for a variety of confounding variables, strict eligibility criteria were used for inclusion of the SEER-13 controls. Only patients whom received surgical management and chemotherapy treatment were included in the analysis. We utilized a robust statistical approach for controlling for confounders with the propensity score analysis. Additionally, this was a large data set with extensive long-term follow-up information on all the patients, both SEER-13 and RCT-participants.

There were some limitations to this study. First, it is a retrospective analysis, and therefore several variables and data points were beyond control of the researcher. The two patient populations, while matched on several variables and then controlled for additional variables affecting outcome, were not a randomized sample. Only patients who participated in an RCT were included and used the general breast cancer population as the control. Moreover, data was not available regarding whether SEER-13 patients participated in a clinical trial or not. Therefore some of the SEER-13 patients may have participated on a clinical trial, although the incidence of participation as anticipated to be low based on historical data of participation.

Additionally, because there was overlap of 16 counties which included 3456 patients, it is conceivable some of the RCT-participants were part of SEER-13 control group of patients. In order to better understand this and explore the differences of the effect of RCT-participation, a subset analysis of survival was done, after excluding the 16 counties of SEER-13 patients. This subset analysis demonstrated an even greater effect of RCT-participation on survival outcomes than for the total group. Another limitation of the study was the missing data for key predictive variables.

As stipulated, in this analysis it was necessary to impute for HER2 status for the SEER-13 controls as the data prior to 2013 regarding HER2 was unreliable and not available. Although, in this analysis patients treated with trastuzumab were excluded, there were a significant number of HER2 positive patients in the RCT-participant group, which does have an impact on survival. While not perfect, the multiple imputations procedure resulted in reliable statistics and made it possible to control for the effect of HER2 status on survival outcomes.

Additionally, only one of RCT studies collected race information and then the subsequent two trials did not. While, it may have seemed reasonable to the researchers conducting the global trial, race may be an important prognostic factor in the United States. The data is conflicting on this particular issue. Some studies have stipulated race maybe a proxy for socioeconomic status and the impact of race, or SES, on outcomes is related to access to care and ability to continue long-term care.[60] Based upon this, women diagnosed with the same stage disease and treated similarly, regardless of race, have the same survival outcomes.[61,] Other studies stipulate there are some biological differences between races and ethnicities for women breast cancer which directly affect outcomes. For example, there is a higher incidence of triple negative breast cancer in African American women; and African American women with hormone receptor positive breast cancer have worse outcomes than white hormone receptor positive breast

cancer, after controlling for stage and treatment. [62, 63, 64, 65, 66, 64] Based upon this information, either race or socioeconomic status, or both need to be carefully considered when examining outcomes and generalizability of trial results.

In this study, the researchers attempted to evaluate different variables which may be associated with socioeconomic status (SES), in addition to race. However, there were not variables available in both groups of patients to evaluation SES. Further, it was necessary to impute race for the RCT-population; and after the multiple imputations procedure, only white or "other" race was assigned to patients due to the very small percentage (<3%) of African American women represented in the first trial. There are several concerns with the lack of data and representation. First, collecting data regarding race and ethnicities in clinical trials is critical to evaluate outcomes for populations and determine if there are differences. Additionally, it further supports the lack of engagement of minorities in clinical trials, specifically oncology. While we imputed and controlled for race in the analysis, it does still bring into question the generalizability of results to minority populations and under-represented groups in clinical trials.

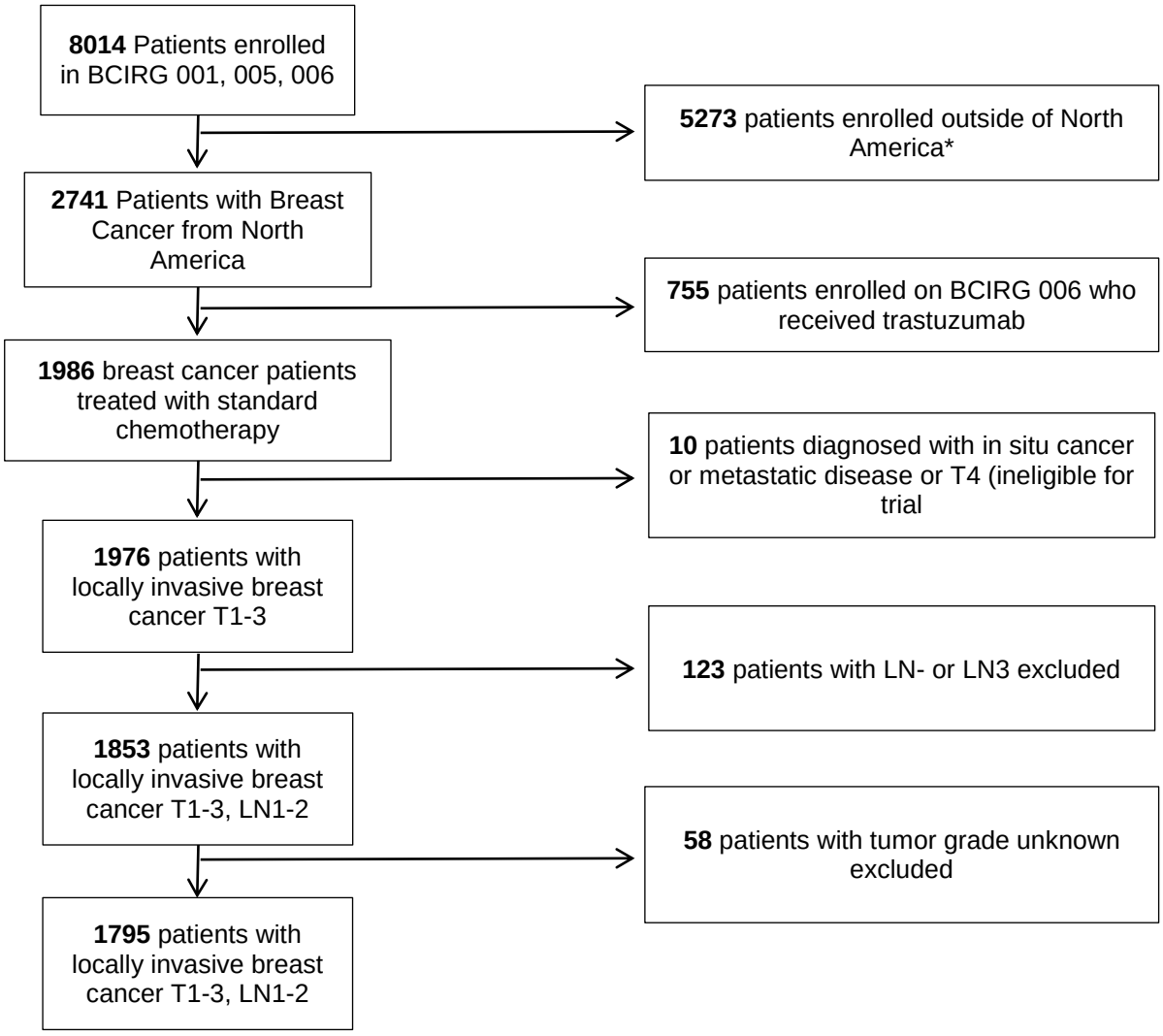
As noted by other researchers, patient self-selection may have an impact on the outcomes for RCT-participants compared to the general population. This study only included participants and the general population. As earlier stated, data about trail participation for SEER-13 patients was not available. Therefore, whether patients in the SEER-13 group participated on a clinical trial or not was unknown. Some have suggested patients whom enroll on clinical trials are more willing to follow stricter guidelines and patterns of care which would not otherwise be available as standard of care.[35, 67, 39] This may be the case in this inquiry, as only participants were included in the analysis and not those whom were offered trials but declined or who were eligible but not offered a trial. This is an opportunity for further research in the future, examining the differences between eligible patients whom enroll, decline or are not offered trial

participation. This has been studied in a very limited fashion in advanced gastric and lung cancer.[68, 69] Currently, a researcher in Japan is studying patient enrollment and outcomes for enrolled versus those whom refused in women with metastatic breast cancer.[70]

Conclusion

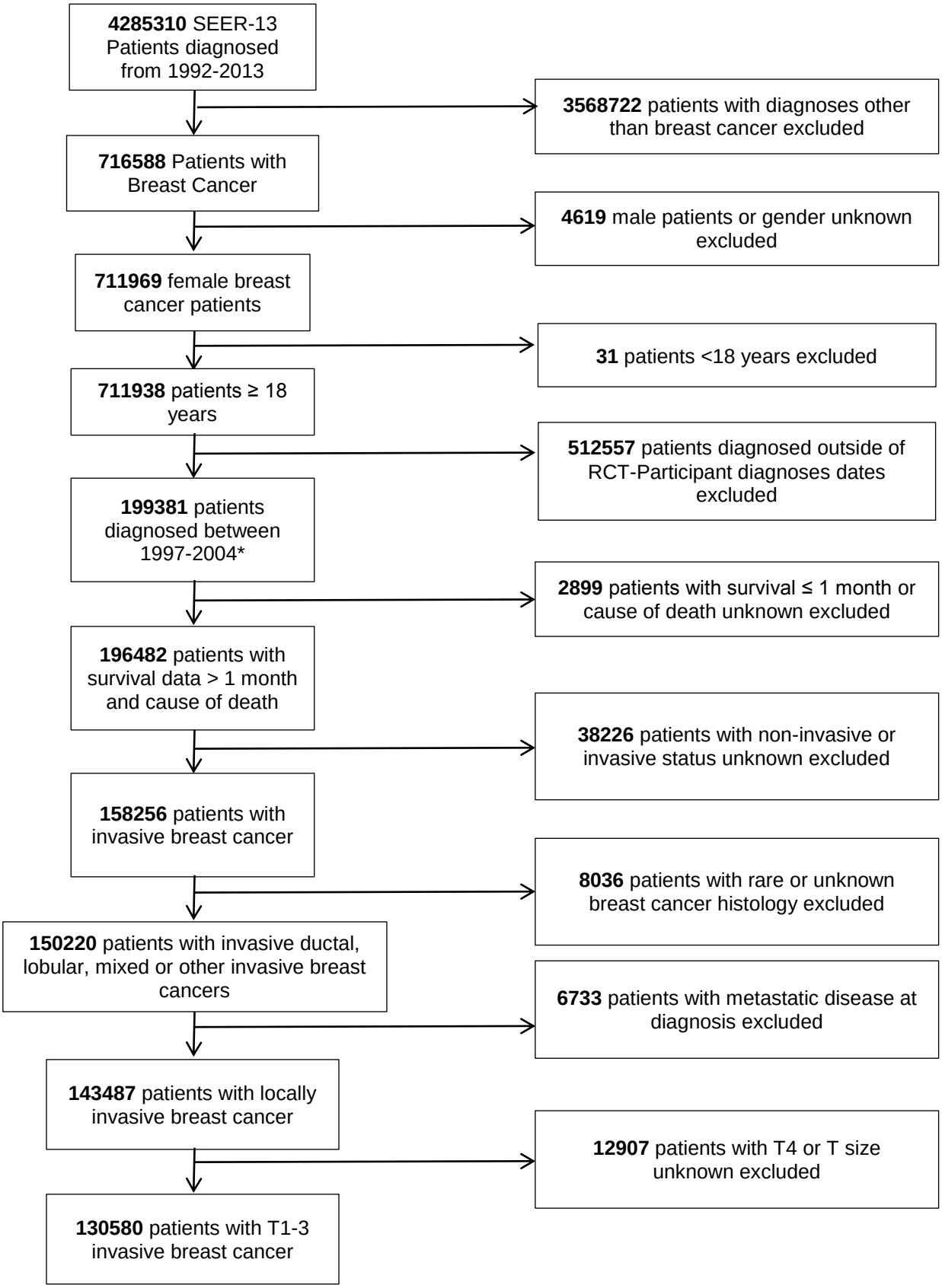
This study demonstrates a positive impact of trial participation for women with early stage breast cancer independent of treatment or other prognostic indicators. That being stipulated, caution should be used when using this information when discussing trial participation with patients, as the generalizability of this information may be considered limited. There continues to be a lack of representation for minority women with breast cancer which could have an impact on outcomes. Clinical trial participation should be promoted for patients with cancer and strongly considered by clinicians when offering therapy options to patients. Research needs to be continued examining messaging of clinical trial participation to patients and families members, engagement of healthcare providers and inclusion of minority populations.

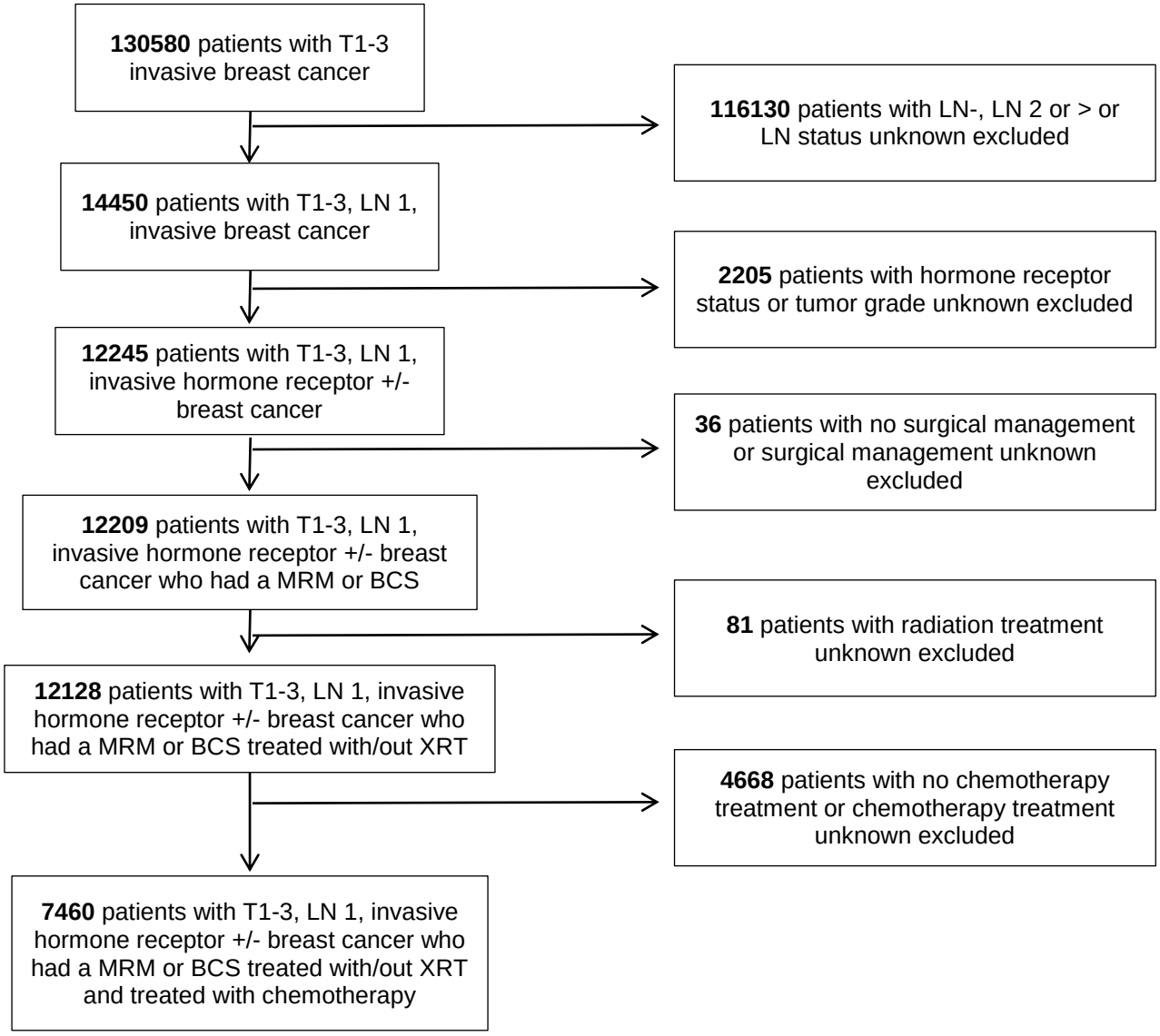
Figure 1. CONSORT Diagram of RCT-Participants Data for Analysis



*North America defined as United States and Canada, not including Mexico

Figure 2. CONSORT Diagram of SEER-13 Data for Analysis





*Dates of diagnosis June 1997-July 1999 and August 2000-February 2004.

BCS=breast conserving therapy; MRM=mastectomy (simple, modified radical or radical); T=tumor; LN=lymph nodes; XRT=radiation therapy

Table 1. Patient Characteristics (prior to imputation of missing data)

Characteristics		SEER-13 Patients n=7460 (%)	RCT-Participants n=1795 (%)	p-value
Age (yr)	Median (range) Mean ± SD	52 (22-94) 52.7 ±10.9	50 (23-74) 50.1 ± 9.4	p<0.001*
Age (category)	≤ 40 41-50 51-60 61-70 >70	949 (12.7) 2387 (32.0) 2352 (31.5) 1291 (17.3) 481 (6.5)	286 (15.9) 639 (35.6) 608 (33.9) 256 (14.3) 6 (0.3)	p<0.001
Year of Diagnosis	1997 1998 1999 2000 2001 2002 2003 2004	559 (7.5) 947 (12.7) 467 (6.3) 932 (12.5) 1409 (18.9) 1552 (20.8) 1594 (21.4) 0 (0)	163 (9.1) 366 (20.4) 118 (6.6) 61 (3.4) 407 (22.7) 557 (31.0) 112 (6.2) 11 (0.6)	p<0.001
Race	Black White Other Missing	685 (9.2) 5930 (79.5) 836 (11.2) 9 (0.1)	16 (0.9) 584 (32.5) 24 (1.3) 1171 (65.2)	**
Histology	Invasive Ductal Invasive Lobular Mixed Invasive Ductal/Lobular Other	6028 (80.8) 442 (5.9) 197 (2.6) 793 (10.6)	1572 (87.6) 132 (7.4) 28 (1.6) 63 (3.5)	p<0.001
Grade	1 2 3 4	961 (12.9) 3183 (42.7) 3189 (42.8) 127 (1.7)	172 (9.6) 737 (41.1) 882 (49.1) 4 (0.2)	p<0.001
Estrogen Receptor (ER) Status	Positive Negative Borderline	5661 (75.9) 1786 (23.9) 13 (0.2)	1241 (69.1) 549 (30.6) 5 (0.3)	p<0.001
Progesterone Receptor (PR) Status	Positive Negative Borderline	5026 (67.4) 2399 (32.2) 35 (0.5)	1068 (59.5) 702 (39.1) 25 (1.4)	p<0.001
ER/PR Status Combined	ER+/PR+ ER+/PR- or ER-/PR+ ER-/PR- Borderline	4840 (64.9) 978 (13.1) 1597 (21.4) 45 (0.6)	1011 (56.3) 269 (15.0) 485 (27.0) 30 (1.7)	p<0.001
Her 2 Neu	Positive Negative Unknown	0 (0) 0 (0) 7460 (100.0)	685 (39.8) 1033 (60.1) 77 (4.3)	**
Tumor Size*	T1 (≤0.1 cm-≤2.0 cm) T2 (>2.0-≤5.0 cm) T3 (>5.0 cm)	3857 (51.7) 3187 (42.7) 416 (5.6)	756 (42.1) 900 (50.1) 139 (7.7)	p<0.001
Lymph Nodes	Median (range) Mean ± SD	1 (1-23) 1.6 (1.1)	2 (1-36) 3.9 (4.2)	p<0.001*
AJCCC Stage	IIa/IIb IIIa	7044 (94.9) 416 (5.1)	1656 (92.3) 139 (7.7)	p<0.001
Treatment Region (Rural-Urban Coding)	1 (metro) 2 3 4 (rural) Missing	6720 (90.1) 310 (4.2) 274 (3.7) 45 (0.6) 111 (1.5)	940 (52.4) 3 (0.2) 49 (2.7) 2 (0.1) 801 (44.6)	p<0.001ǂ
Surgical	BCS	4254 (57.0)	1063 (59.2)	p=0.09

Management	Mastectomy (simple, modified radical, or radical)	3206 (43.0)	732 (40.8)	
XRT Therapy	None Yes Unknown	2439 (33.4) 4662 (62.5) 305 (4.1)	401 (22.3) 1350 (75.2) 44 (2.5)	p<0.001
XRT Therapy by Surgery Type: BCS	None Yes Unknown	544 (12.8) 3511 (82.5) 199 (4.7)	119 (11.2) 928 (87.3) 16 (1.5)	p<0.001
XRT Therapy by Surgery Type: MRM <4 LN +	None Yes Unknown	1928 (61.5) 1106 (35.3) 102 (3.3)	233 (56.6) 165 (40.0) 14 (3.4)	p=0.145
XRT Therapy by Surgery Type: MRM ≥4 LN +	None Yes Unknown	21 (30.0) 45 (64.3) 4 (5.7)	49 (77.8) 257 (22.2) 14 (4.6)	p=0.01

*Statistical significance calculated using student's t-test; ǂ Statistical significance calculated using Fisher's exact test; MRM= modified radical mastectomy; XRT=radiation therapy

** Statistical difference not calculated due to missing data

Figure 3. Box Plot of Distribution of Follow-Up for Patients Lost to Follow-Up (LTF)

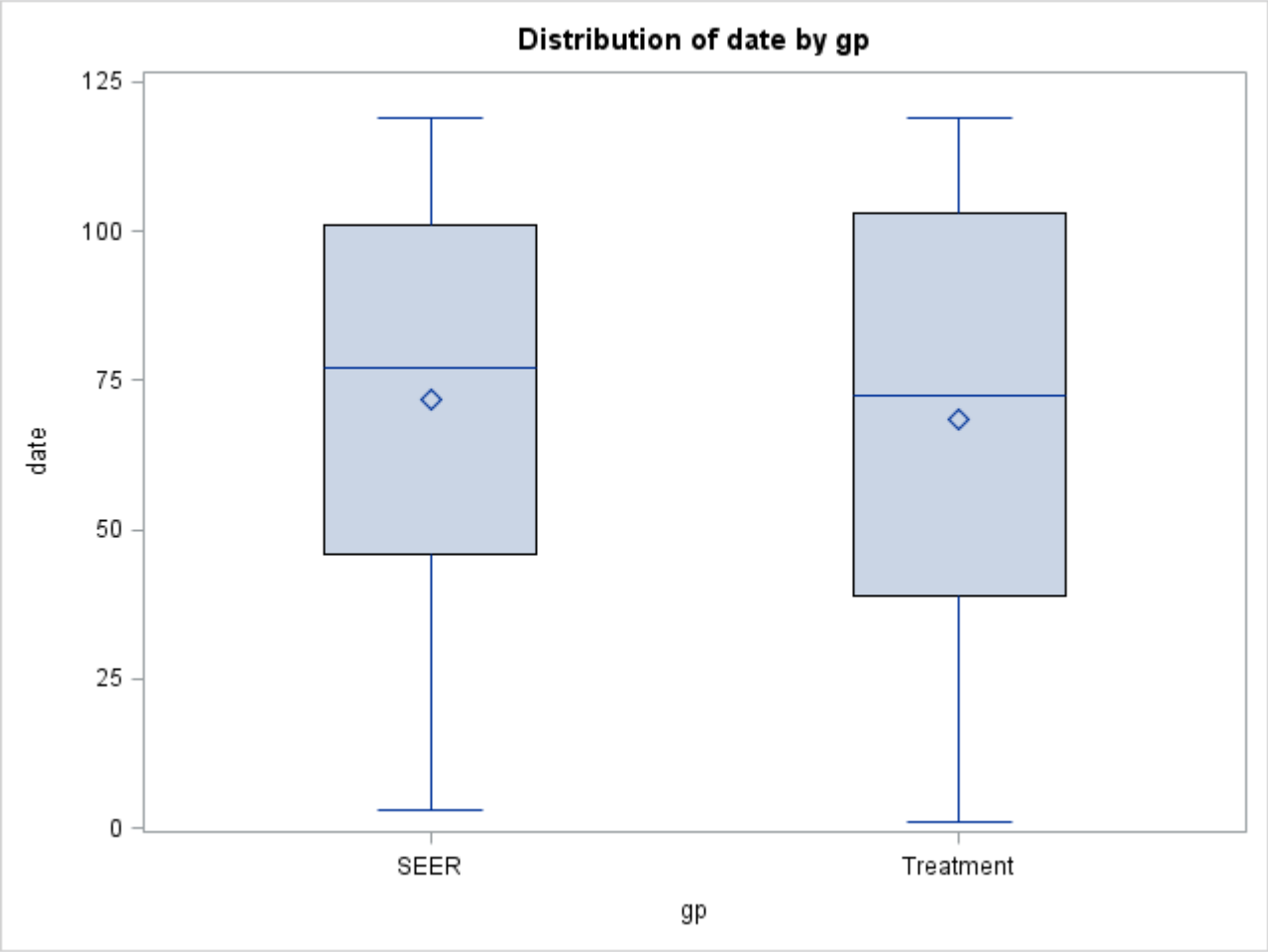
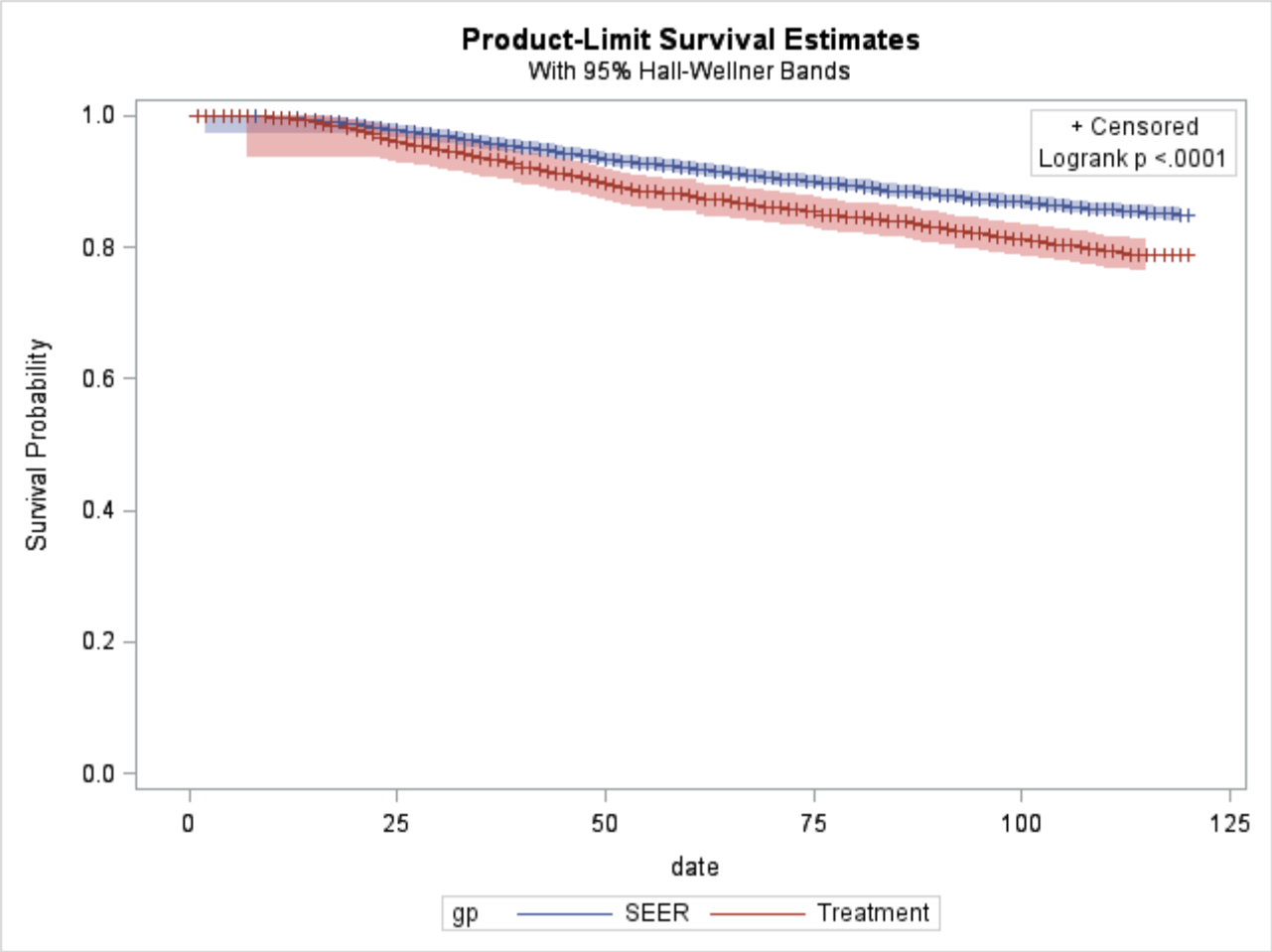


Table 2. Median Survival

Status	SEER-13 Control Group n (%)	RCT-Participant Group n (%)	Total
Alive	5762 (77.2)	910 (50.7)	6672 (72.1)
Dead	**1520 (20.4)**	**391 (21.8)**	**1911(20.6)**
Breast Cancer Related Death	1083 (71.3)	328 (83.9)	1411
Other Cause of Death	437 (28.7)	63 (16.1)	500
Lost to Follow-Up	178 (2.4)	494 (27.5)	672 (7.3)
Total	7460	1795	9255

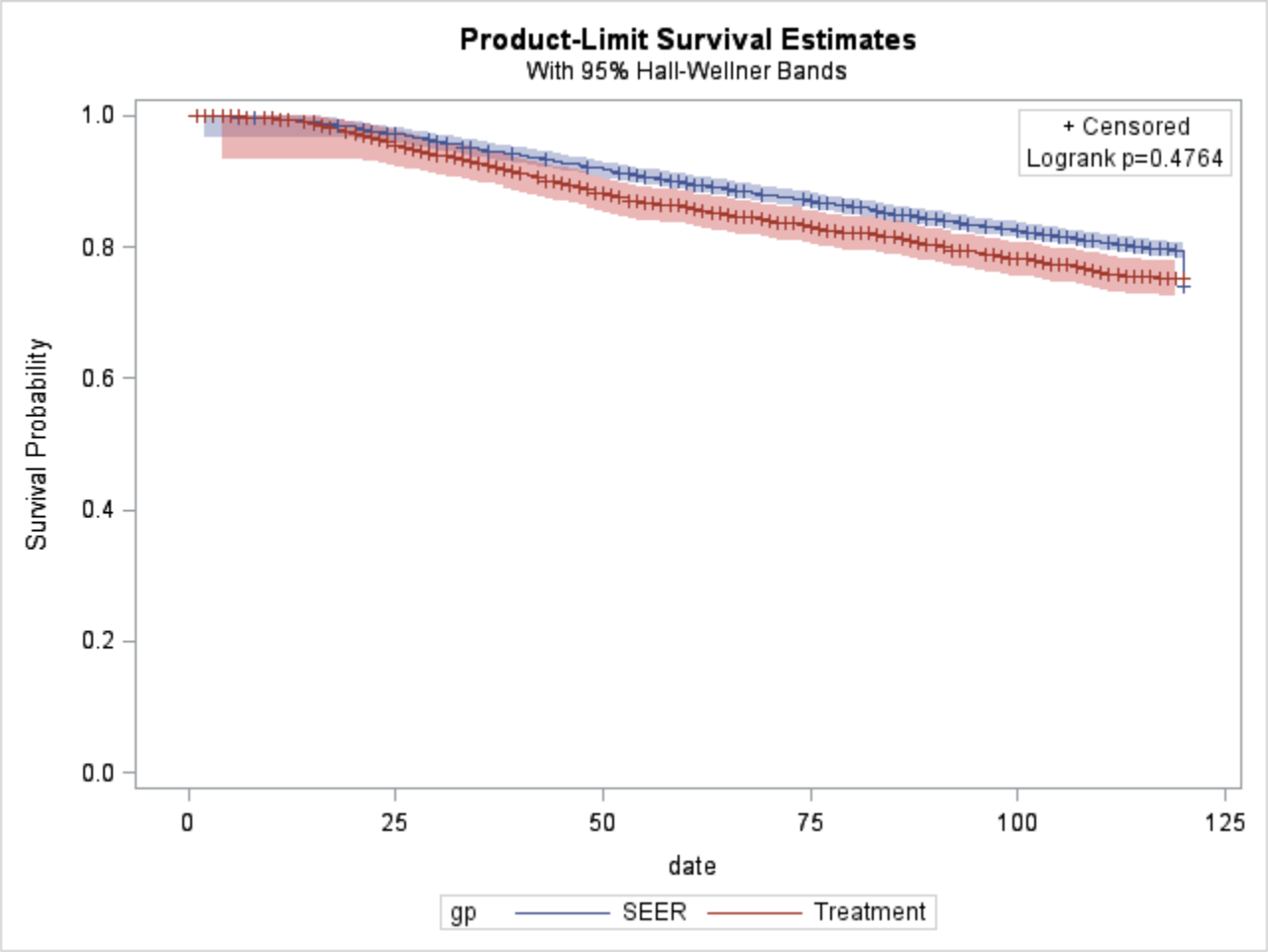
**Full Data Set with HER2 and Race Imputed

Figure 4. Breast Cancer Specific Survival (10 Years)*



***Full Data Set with HER2 and Race Imputed

Figure 5. Overall Survival (10 Years)*



*Full Data Set with HER2 and Race Imputed

Table 3. Crude Analysis of Survival for RCT-Participants compared to SEER-13 Controls**

Outcome	Hazard Ratio	95% Confidence Interval	p-value
All-Cause Mortality-at 5 years	1.41	1.22-1.64	**<0.01**
Breast Cancer Mortality	1.57	1.33-1.84	**<0.01**
Other Cause Mortality	0.89	0.61-1.29	**0.54**
All-Cause Mortality-at 10 years	1.04	0.93-1.16	0.47
Breast Cancer Mortality	1.47	1.30-1.67	**<0.01**
Other Cause Mortality	0.42	0.32-0.54	**<0.01**

**Full Data Set with HER2 and Race Imputed

Table 4. Propensity Score Multivariate Survival Analysis of RCT-Participants Compared to SEER-13 Controls**

Outcome	Hazard Ratio	95% Confidence Interval	p-value
All-Cause Mortality-at 5 Years	0.83	0.72-0.95	**<0.01**
Breast Cancer Mortality	0.75	0.64-0.87	**<0.01**
Other Cause Mortality	1.58	1.25-2.00	**<0.01**
All-Cause Mortality-at 10 Years	0.79	0.71-0.87	**<0.01**
Breast Cancer Mortality	0.83	0.74-0.93	**<0.01**
Other Cause Mortality	0.59	0.51-0.69	**<0.01**

**Full Data Set with HER2 and Race Imputed

Table 5. Patient Characteristics after imputation of HER2 (SEER-13 Controls) and Race (RCT-Participants) and Deletion of 16 counties from SEER-13

Characteristics		SEER-13 Patients n=4004 (%)	RCT-Participants n=1795 (%)	p-value
Age (yr)	Median (range) Mean ± SD	52 (23-87) 52.7 ±10.9	50 (23-74) 50.1 ± 9.4	p<0.01*
Age (category)	≤ 40 41-50 51-60 61-70 >70	495 (12.4) 1294 (32.3) 1262 (31.5) 692 (17.3) 261 (6.5)	285 (15.9) 639 (35.6) 608 (33.9) 257 (14.3) 6 (0.3)	p<0.01
Year of Diagnosis	1997 1998 1999 2000 2001 2002 2003 2004	306 (7.6) 497 (12.4) 251 (6.3) 509 (12.7) 758 (18.9) 813 (20.3) 870 (21.7) 0 (0)	163 (9.1) 366 (20.4) 118 (6.6) 61 (3.4) 407 (22.7) 557 (31.0) 112 (6.2) 11 (0.6)	p<0.01
Race	Black White Other	253 (6.3) 3203 (80.0) 548 (13.7)	16 (0.9) 1702 (94.8) 77 (4.3)	p<0.01
Histology	Invasive Ductal Invasive Lobular Mixed Invasive Ductal/Lobular Other	3300 (82.4) 260 (6.5) 94 (2.4) 350 (8.7)	1572 (87.6) 132 (7.4) 28 (1.6) 63 (3.5)	p<0.01
Grade	1 2 3 4	564 (14.1) 1720 (43.0) 1658 (41.4) 62 (1.6)	172 (9.6) 737 (41.1) 882 (49.1) 4 (0.2)	p<0.01
Estrogen Receptor (ER) Status	Positive Negative Borderline	3052 (76.2) 946 (23.6) 6 (0.2)	1241 (69.1) 549 (30.6) 5 (0.3)	p<0.01
Progesterone Receptor (PR) Status	Positive Negative Borderline	2760 (68.9) 1227 (30.6) 17 (0.4)	1068 (59.5) 702 (39.1) 25 (1.4)	p<0.01
ER/PR Status Combined	ER+/PR+ ER+/PR- or ER-/PR+ ER-/PR- Borderline	2659 (66.4) 479 (12.0) 844 (21.1) 22 (0.6)	1011 (56.3) 269 (15.0) 485 (27.0) 30 (1.7)	p<0.01
Her 2 Neu	Positive Negative Borderline	705 (17.6) 3221 (80.4) 78 (2.0)	685 (39.8) 1033 (60.1) 0	p<0.01
Tumor Size*	T1 (≤0.1 cm-≤2.0 cm) T2 (>2.0-≤5.0 cm) T3 (>5.0 cm)	2135 (53.3) 1665 (41.6) 204 (5.1)	756 (42.1) 900 (50.1) 139 (7.7)	p<0.01
Lymph Nodes	Median (range) Mean ± SD	1 (1-23) 1.6 (1.1)	2 (1-36) 3.9 (4.2)	p<0.01*
AJCCC Stage	IIa/IIb IIIa	3800 (94.9) 204 (5.1)	1656 (92.3) 139 (7.7)	p<0.01
Treatment Region (Rural-Urban Coding)	1 (metro) 2 3 4 (rural) Missing	6720 (90.1) 310 (4.2) 274 (3.7) 45 (0.6) 111 (1.5)	940 (52.4) 3 (0.2) 49 (2.7) 2 (0.1) 801 (44.6)	p<0.01

Surgical Management	BCS Mastectomy (MRM, Rad Mtx, Simple Mtx)	2225 (55.6) 1779 (44.4)	1063 (59.2) 732 (40.8)	p=0.01
XRT Therapy	None Yes Unknown	1230 (30.7) 2635 (65.8) 139 (3.5)	401 (22.3) 1350 (75.2) 44 (2.5)	p<0.01
XRT Therapy by Surgery Type: BCS	None Yes Unknown	200 (9.0) 1934 (86.9) 91 (4.1)	119 (11.2) 928 (87.3) 16 (1.5)	p<0.01
XRT Therapy by Surgery Type: MRM <4 LN +	None Yes Unknown	1019 (58.6) 673 (38.7) 46 (2.7)	233 (56.6) 165 (40.0) 14 (3.4)	p=0.59
XRT Therapy by Surgery Type: MRM ≥4 LN +	None Yes Unknown	11 (26.8) 28 (68.3) 2 (4.9)	49 (77.8) 257 (22.2) 14 (4.6)	p=0.17

*Statistical significance calculated using student's t-test;

Table 6. Propensity Score Multivariate Survival Analysis of RCT-Participants Compared to SEER-13 Controls in Limited Counties[ł]

Outcome	Hazard Ratio	95% Confidence Interval	p-value
All-Cause Mortality-at 5 Years	0.68	0.59-0.78	**<0.01**
Breast Cancer Mortality	0.61	0.53-0.71	**<0.01**
Other Cause Mortality	1.60	1.23-2.07	**<0.01**
All-Cause Mortality-at 10 Years	0.49	0.68-0.83	**<0.01**
Breast Cancer Mortality	0.79	0.70-0.89	**<0.01**
Other Cause Mortality	0.57	0.49-0.67	**<0.01**

[ł]Data Set with HER2 and Race Imputed and overlapping counties (n=16) of treatment excluded from analysis.

Table 7. Univariate Odds Ratio of Mastectomy[Ŧ]

Variable		Odds Ratio	95% Confidence Interval		p-value
Group	SEER-13 Control	1.00			
	RCT-Participant Group	0.91	0.82	1.02	0.09
Year of Diagnosis (continuous)		0.99	0.96	1.01	0.17
Age (continuous)		0.99	0.99	1.00	0.16
Race	White	1.00			
	Black	0.87	0.74	1.02	0.08
	Other	1.22	1.07	1.41	**<0.01**
Treatment Region	Metro (1)	1.00			
	2	1.14	0.91	1.43	0.25
	3	1.55	1.24	1.93	**<0.01**
	Rural (4)	0.99	0.56	1.77	0.98
Histological Type	Ductal	1.00			
	Lobular	1.99	1.67	2.36	**<0.01**
	Mixed Ductal/Lobular	0.85	0.64	1.12	0.24
	Other	1.40	1.21	1.61	**<0.01**
Tumor Size	T1	1.00			
	T2	2.06	1.89	2.24	**<0.01**
	T3	9.33	7.46	11.65	**<0.01**
Grade	Grade 1	1.00			
	Grade 2	1.28	1.11	1.47	**<0.01**
	Grade 3	1.46	1.27	1.67	**<0.01**
	Grade 4	1.81	1.26	2.61	**<0.01**
Lymph Node Status	<4 +	1.00			
	≥4 +	1.52	1.31	1.76	**<0.01**
Hormonal Status	PR -	1.00			
	PR +	0.85	0.78	0.93	**<0.01**
	PR Borderline	0.81	0.48	1.36	0.42
	ER -	1.00			
	ER +	0.87	0.80	0.96	**<0.01**
	ER Borderline	0.98	0.38	2.49	0.96
HER2 Status	HER2 +	1.00			
	HER2 -	0.79	0.71	0.87	**<0.01**
	HER2 Borderline	0.98	0.71	1.36	0.91

[Ŧ]Surgical outcomes calculated with only RCT-Participants living in the United States and SEER-13 Controls

Table 8. Propensity Score Multivariate Analysis of Odds Ratio of Mastectomy[Ŧ]

Variable		Odds Ratio	95% Confidence Interval		p-value
Group	SEER-13 Control	1.00			
	RCT-Participant Group	0.78	0.66	0.92	**0.03**
Year of Diagnosis (continuous)		0.97	0.95	0.99	**0.02**
Race	White	1.00			
	Black	0.79	0.67	0.94	**<0.01**
	Other	1.22	1.04	1.42	**0.01**
Treatment Region	Metro (1)	1.00			
	2	1.21	0.95	1.53	0.12
	3	1.03	0.56	1.87	**<0.01**
	Rural (4)	0.99	0.56	1.77	0.93
Histological Type	Ductal	1.00			
	Lobular	1.70	1.40	2.07	**<0.01**
	Mixed Ductal/Lobular	0.81	0.60	1.09	0.17
	Other	1.41	1.21	1.64	**<0.01**
Tumor Size	T1	1.00			
	T2	2.09	1.90	2.29	**<0.01**
	T3	8.44	6.65	10.72	**<0.01**
Lymph Node Status	<4 +	1.00			
	≥4 +	1.98	1.57	2.49	**<0.01**
HER2 Status	HER2 +	1.00			
	HER2 -	0.77	0.69	0.86	**<0.01**
	HER2 Borderline	1.00	0.72	1.41	0.99

[Ŧ]Surgical outcomes calculated with only RCT-Participants living in the United States and SEER-13 Controls

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