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Survival following adjuvant trastuzumab-based treatment among older patients with HER2-positive early invasive breast cancer: A national population-based cohort study using routine data

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ABSTRACT

Background: Randomised controlled trials (RCTs) reported adjuvant trastuzumab-based treatment improved overall survival (OS) among patients with HER2-positive early invasive breast cancer (EIBC). Few RCTs included older patients or those with comorbidity/frailty. This study aimed to determine whether the effect of adjuvant trastuzumab-based treatment on survival outcomes varies by patient age and fitness, using national data from routine care.

Methods: Women (50+ years) newly-diagnosed with HER2-positive EIBC between 2014 and 2019 were identified from England Cancer Registry data. Registration records were linked to Systemic Anti-Cancer Therapy data for treatment details and ONS death register for mortality details. A propensity score analysis employing the inverse probability of treatment weighting method was used to balance the patient variables across treatment groups. Cox models were used to evaluate whether the effect of treatment on OS was associated with patient age and fitness; competing risks regression models were used for breast cancer-specific survival (BCSS).

Results: 5238 women initiated adjuvant trastuzumab-based treatment. Median follow-up was 56.7 months. Comparison with 3421 women who did not receive adjuvant trastuzumab highlighted differences at diagnosis in relation to age, fitness, grade, nodal involvement, surgery type and use of radiotherapy. Weighted survival analysis found trastuzumab was associated with improved OS (hazard ratio HR 0.56, 95 %CI: 0.45–0.70) and improved BCSS (subHR 0.62, 95 %CI: 0.47–0.82). We found no evidence of a difference in effect by age or patient fitness for either outcome.

Conclusion: In this national dataset, adjuvant trastuzumab was associated with improvements in survival, with an OS effect size similar to RCT evidence. The effect size was not found to vary by patient age or fitness. Chronological age and fitness alone should not be barriers to receipt of effective adjuvant targeted treatment.

1. Introduction

Trastuzumab was approved for use within English NHS services for patients with HER2-positive early invasive breast cancer (EIBC) in 2006, following evidence of efficacy from several randomised controlled trials (RCTs), most notably the HERA trial [1]. A subsequent meta-analysis, which included 11,991 patients across eight RCTs with a median follow-up of 36 months, reported a hazard ratio (HR) of 0.66 (95 % confidence interval [CI]: 0.57–0.77) for overall survival (OS) [2]. National and international guidelines, including those published by the European Society of Medical Oncology (ESMO), NICE and the American Society of Clinical Oncology (ASCO), recommend treatment with chemotherapy and trastuzumab [3–5]. Additionally the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) make comparable recommendations for the management of older patients with breast cancer [6,7].

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Women aged 70 years and older account for more than one-third of breast cancers diagnosed annually in England. However, the evidence base for trastuzumab in this population is narrow due to the limited number of older women participating in trials; an estimated 2.5 % of all patients in RCTs evaluating adjuvant trastuzumab were aged 70 + years. An individual patient data meta-analysis found no evidence that the benefit of trastuzumab, compared with chemotherapy alone, differed by patient age but this result was based on trials that included few older women [8]. The resulting lack of outcome evidence in older patients can result in considerable variation of management in routine care according to age [9,10]. In the context of trastuzumab, we have previously reported increasing age was associated with a reduced used of adjuvant trastuzumab, even after accounting for tumour characteristics and comorbidities [11].

Among patient populations where evidence is limited, observational studies can provide information to support treatment decision-making. Within a UK setting, a handful of small studies have described survival among women treated with adjuvant trastuzumab, but none looked at differences in treatment effect across age groups. For example, a study that included patients with HER2-positive EIBC treated with trastuzumab at a single London NHS trust from 2006 to 2008 reported an association between trastuzumab use and improved disease-free survival at 3-years, but had insufficient deaths to look at OS and did not examine if effect size was associated with patient factors [12]. A study conducted in South-East Wales reported improved 3-year OS among women treated with trastuzumab, but did not report a formal estimate of possible treatment effect [13]. In the absence of trials to provide the evidence, an observational study can be designed to mimic a randomised trial and provide estimates of treatment effect from the hypothetical "target trial", an approach that is advocated to reduce the risk of bias from limitations of the study design [14].

The aim of this study was to evaluate whether the effect of adjuvant trastuzumab-based treatment on survival varies by patient age and fitness, among women aged 50 + years diagnosed with HER2-positive EIBC using a national, population-based dataset. We hypothesised that there would be no difference in treatment effect by age or fitness. The study also aimed to investigate factors associated with differences in survival following treatment with trastuzumab, to understand which patients had better/worse survival.

The study is reported according to the RECORD extension to STROBE guidelines for observational studies using routinely collected data [15].

2. Patients and methods

2.1. Study design

This non-randomised, retrospective population-based cohort study was designed using the methodological framework of a target trial emulation approach [14]. Within this approach, the observational study is designed to emulate the set-up of a hypothetical RCT, i.e. the 'Target Trial' by applying analogous criteria relating to patient eligibility, treatment assignment, definition of the follow-up period and analysis plan [14,16,17]. Supplementary Table S1 summarises the steps followed to guide selection of the study cohort and the conduct of the statistical analysis. We adopt this method primarily to reduce the risk of bias in the estimated hazard ratio of initiating trastuzumab-based treatment versus not. The study results are not interpreted as estimating the causal effects of treatment.

2.2. Data Source

This study was undertaken as part of the National Audit of Breast Cancer in Older Patients (NABCOP; see www.nabcop.org.uk for full details). The NABCOP received pseudonymised patient-level Cancer Registry data for all women aged 50 + years, diagnosed with breast cancer (BC) from 1 January 2014 to 31 December 2019 within NHS trusts in England [18]. Records were linked at tumour-level to data from the Cancer Outcomes and Services Dataset (COSD); Hospital Episode Statistics Admitted Patient Care (HES-APC) [19]; Systemic Anti-Cancer Therapy (SACT) dataset [20]; national Radiotherapy Dataset (RTDS)); and at patient-level to the Primary Care Prescription Database (PCPD) [21].

2.3. Study cohort

The study cohort was defined to include women aged 50 + years (being the lower age of women included within the NABCOP) diagnosed with HER2-positive EIBC (stage 1–3A; ICD-10 C50) who received surgery within six months of diagnosis. BC was classified as HER2-positive where HER2 status was reported as either positive or borderline but with a positive HER2-FISH (fluorescence in situ hybridization) or equivalent test result. Primary surgery was defined as either breast-conserving surgery (BCS) or mastectomy, identified from Office of Population Censuses and Surveys (OPCS) procedure codes entered within HES-APC.

In line with the emulated trial design, the following exclusion criteria were applied. First, the records of women were excluded if they had: (i) neoadjuvant chemotherapy or trastuzumab recorded, (ii) adjuvant chemotherapy or trastuzumab started more than 4 months after surgery, or (iii) adjuvant treatment included other HER2-targeting agents. Additionally records with missing information on patient fitness, tumour stage, nodal stage and invasive grade, or where the date of death or censoring was before the landmark point were excluded (see Statistical analysis section).

2.4. Treatment assignment

A clinically relevant defined grace period of 4 months to treatment assignment (initiated trastuzumab-based treatment or not) was applied, to reflect the time required for decision-making in routine clinical practice. Patients were defined as initiating adjuvant trastuzumab-based treatment if their SACT data records contained any of trastuzumab, Herceptin or trastuzumab biosimilar in the drug name field, within four months after surgery or after chemotherapy that started within four months of surgery. Records of trastuzumab-emtansine or other HER2-targeting therapy such as pertuzumab were categorised separately as "other HER2-targeting therapy".

Adjuvant chemotherapy, as part of trastuzumab-based treatment, was identified from SACT data where the first recorded cycle was within four months after surgery. It was categorised as: "sequential" where cycles were administered prior to the first trastuzumab date, with no cycles delivered during the trastuzumab cycles; and "concurrent" where any cycles were administered either on the same day as trastuzumab or between trastuzumab cycles (including when chemotherapy started prior to and continued during trastuzumab).

HES-APC was used to supplement data on trastuzumab and chemotherapy from SACT [22]. This provided additional cycle-level information for use of adjuvant trastuzumab and/or chemotherapy and associated treatment initiation date.

2.5. Outcome and follow-up period

Overall survival was defined as death from any cause. BC-specific survival (BCSS) was defined where the cause of death was recorded as BC. Death details from linked Civil Registration (death) records, including date and cause, were provided within Cancer Registry data.

Time zero (start of follow-up) was defined, based on the grace period, as 4 months after date of surgery. Each patient was followed up to date of death or administrative censoring (October 2021). Mortality data were available up to October 2021.

2.6. Study variables

Patient and tumour characteristics were taken from Cancer Registry/COSD. These were: age at diagnosis (years), deprivation, tumour stage (T1–3), nodal stage (N0, N +), hormone receptor status (positive, negative/unknown), tumour grade (G1–3). BC was classified as hormone receptor-positive where either of estrogen or progesterone receptor status were recorded as positive. Deprivation was measured using the Index of Multiple Deprivation 2019 rank, based on the patient's postcode at diagnosis, and assigned to national quintiles of deprivation (most [1] to least [5] deprived).

Patient fitness was measured based on comorbidity and frailty. Comorbidity burden (0, 1, 2 +; defined using the Royal College of Surgeons of England Charlson Comorbidity Index - CCI) and frailty (fit, mild frailty, moderate-severe frailty; defined using the Secondary Care Administrative Records Frailty index – SCARF index) were determined using ICD-10 codes recorded in HES-APC within two years prior to diagnosis [23].

Other treatment characteristics were: type of surgery (BCS, mastectomy), receipt of radiotherapy and receipt of endocrine therapy (ET). Use of radiotherapy was identified based on records within the RTDS dated during the initial treatment episode following diagnosis, defined by sequential use of treatments with no more than an eight month gap. ET use was identified from the PCPD [21].

2.7. Statistical analysis

All analyses were performed in Stata Version 17.

Median follow-up was determined through reverse-censoring on death, in which survival is treated as the event and death as censoring.

Initial analysis investigated whether patient factors were associated with differences in OS following treatment with trastuzumab and was carried out only among patients initiating adjuvant trastuzumab-based treatment for HER2-positive EIBC. Standard survival analysis methods were used to analyse time-to-event data, with OS/BCSS calculated as time from starting treatment to death/death from BC. Kaplan-Meier survival curves were used to visually inspect OS across patient groups. Cox proportional hazards models were used to analyse the association between OS and the study variables, and Fine and Gray regression models for BCSS.

The main analysis estimated the association between use of adjuvant trastuzumab-based treatment and survival outcomes. Patients were included in treatment groups according to their assigned treatment strategy. We employed a landmark approach in which analyses were timed from 4 months after surgery (defined as the landmark time point), to allow for treatment to be started and reduce the risk of immortal time bias [24]. Patients were included if they had at least 4 months' follow-up from surgery and had not experienced the outcome of interest (death) within the first 4 months.

To balance the study variables across the treatment groups and thereby minimise bias due to measured confounders, a propensity score analysis employing the inverse probability of treatment weighting (IPTW) method was used [25]. The IPTW method used all patients in the cohort, and the propensity score corresponded to the probability of a patient receiving trastuzumab. The score was calculated for each patient using a logistic regression model that included all factors that could confound the relationship between treatment and the outcome, along with factors prognostic of the outcome [26]. The model included age, deprivation, patient fitness, tumour stage, nodal involvement, invasive grade, hormone receptor status, type of surgery, radiotherapy. Covariate balance was assessed using the standardised mean difference (SMD) with a value of greater than 0.1 taken to indicate significant imbalance [27]. Stabilised weights were calculated for each patient on the basis of the estimated propensity score [28].

Survival curves were created with IPTW-adjusted Kaplan-Meier plots. IPTW-weighted Cox proportional hazard models with a robust "sandwich" variance estimator were used to calculate an IPTW-adjusted HR as an estimate of the relative effect of trastuzumab-based treatment on OS. IPTW-weighted Fine and Gray regression models were used for competing risk analysis of BCSS, with non-breast cancer death as the competing event. An HR below 1·00 favoured the use of trastuzumab. To determine whether the effect of trastuzumab varied by age and patient fitness, interaction terms with treatment were included in the weighted models.

Sensitivity analyses were carried out looking at the impact of including patients with a record of chemotherapy initiation but not trastuzumab; patients were first included in the "trastuzumab" group and then in the "no trastuzumab" group. Further sensitivity analyses were carried out to consider the impact of the landmark time point (specifically looking at 2/3/5 month time points) and the inclusion of year of diagnosis within the models.

All tests were two-sided, with confidence intervals presented at the 95 % level.

3. Results

A total of 156,375 women aged 50 + years were diagnosed with EIBC between 1 January 2014 and 31 December 2019. There were 14,936 women with HER2-positive EIBC, of whom 11,584 (77.6 %) women proceeded to surgery within 6 months of diagnosis.

A total of 2014 women who received trastuzumab in combination with another HER2-targeting therapy, started adjuvant treatment more than 4 months after surgery or had received neoadjuvant treatment were excluded, along with 40 women who died within four months of surgery, and 187 women with incomplete data. This left 5238 women who received adjuvant trastuzumab-based treatment with no prior treatment and 3421 who received no adjuvant treatment (supplementary Fig. S1). 684 women who received adjuvant chemotherapy but no trastuzumab contributed to the sensitivity analysis of treatment assignment.

Among 5238 women receiving trastuzumab-based treatment median trastuzumab duration was 11.7 months (IQR 11.0–12.1). 22.2 % received chemotherapy prior to starting trastuzumab. 20.2 % were aged 70 + years, 30.6 % were recorded to have node-positive EIBC. 68.3 % had BCS and 79.3 % received radiotherapy.

3.1. Overall survival among patients receiving trastuzumab-based treatment

Median follow-up from initiation of adjuvant trastuzumab-based treatment was 59.0 months (interquartile range: 41.5–73.9), at which point 6.5 % (n = 338/5238) of the cohort had died. OS estimates were 99.5 %, 96.7 % and 92.9 % at 1, 3 and 5 years respectively from the start of treatment.

Supplementary Fig. S2 shows Kaplan-Meier OS estimates overall and stratified by patient and tumour characteristics. For analyses stratified by age at diagnosis, 5 year OS estimates decreased with increasing age, being 96.2 %, 94.2 %, 84.8 % and 64.3 % for women aged 50–59, 60–69, 70–79 and 80 + respectively (supplementary Table S2). Estimates were lowest among those with any comorbidity (86.1 %) or moderate-severe frailty (81.7 %). OS estimates also decreased with increasing grade, increasing tumour stage, nodal involvement and negative/unknown hormone receptor status. Where chemotherapy was given, there was no difference in OS according to whether this was given sequentially or concurrently with trastuzumab.

Adjusted hazard ratios (aHRs) of OS according to patient subgroups (supplementary Table S2), estimated from proportional hazard models, highlighted differences by age with worse OS as age increased ($p < 0.0001$). Worse OS was also associated with the presence of any comorbidity (aHR 1.55, 95 %CI 1.14–2.11), nodal involvement (aHR 2.00, 95 %CI 1.58–2.53), and larger tumours (T2/3 compared to T1), independently of other factors. Conversely hormone receptor-positive EIBC, use of radiotherapy and use of taxanes were independently associated

with improved OS.

3.2. Association of trastuzumab-based treatment with overall survival

Comparison of patients who received adjuvant trastuzumab-based treatment with those who did not receive treatment, among a total of 8659 patients, highlighted substantial differences in characteristics (Table 1). Differences were seen in relation to age, fitness (CCI and SCARF Index), grade, nodal involvement, surgery type, use of radiotherapy. Specifically a higher percentage of women not receiving treatment were older, had at least one comorbidity, had some level of frailty, had grade 1 tumours, no nodal involvement, had had mastectomy and didn't have radiotherapy.

Median follow-up from the landmark time (4 months after surgery) was comparable among women who received adjuvant trastuzumab-based treatment and those who did not receive treatment (overall 56.7 months, interquartile range: 38.2–71.9). Unadjusted OS estimates differed by treatment group, at 92.8 % at five years from the landmark time among women who received trastuzumab-based treatment compared with 75.8 % among women who did not.

Of the ten variables used to produce the propensity score, seven exhibited substantial imbalance (SMD >0.1) pre-weighting. Following IPTW, the intra-group differences were substantially reduced, and a SMD of < 0.1 was achieved for all variables (supplementary Fig. S3). The distribution of propensity scores in the two groups is shown in supplementary Fig. S4.

In the IPTW Cox regression landmark analysis, we found use of adjuvant trastuzumab-based treatment was associated with improved OS, compared with no treatment (HR 0.56, 95 %CI: 0.45–0.70). Use was also associated with improved BCSS (subHR 0.62, 95 %CI: 0.47–0.82).

Fig. 1 presents overall survival estimates for treatment groups, by dichotomised age (50–69/70 +). Fig. 2 shows the effect of treatment on OS across patient subgroups. We found no statistical evidence of effect modification by age (interaction p = 0.431), and no evidence of a difference by the presence of comorbidity (interaction p = 0.822) or frailty (interaction p = 0.923). Additionally, tumour stage (T1/T2/T3; interaction p = 0.773), nodal involvement (N0/N +; interaction p = 0.535), grade (G1/G2/G3; interaction p = 0.212), or hormone receptor-positive status (interaction p = 0.853) were not associated with differences in OS. Similar associations were seen when looking at BCSS (Fig. 3).

Sensitivity analyses which included those women who received adjuvant chemotherapy but no trastuzumab firstly in the trastuzumab group and secondly in the no trastuzumab group demonstrated associations for both OS and BCSS comparable with the main findings (supplementary Fig. S5 & S6), as did considering both shorter and longer grace periods/landmark points (supplementary Fig. S7). Finally, estimates for OS or BCSS were unchanged with inclusion of year of diagnosis in the survival models.

4. Discussion

This population-based cohort study investigated the impact of factors including patient age and fitness on survival outcomes following initiation of adjuvant trastuzumab-based treatment, among women aged 50 + years diagnosed with HER2-positive EIBC in England.

Five-year OS of women treated with adjuvant trastuzumab-based treatment (93 %) was consistent with estimates from RCTs (89 % 4-year OS in HERA, ~90 % in N9831 and NSABP B-31, 91–92 % 5-year OS in BCIRG-006) and several other population-based studies [1, 29–34]. Increasing age, comorbidity, nodal involvement and larger tumour size were linked to worse OS, whilst hormone receptor-positive EIBC, use of radiotherapy and use of taxanes were independently associated with improved OS. These findings are consistent with those reported by an Italian study which considered predictors of survival [35].

Adjuvant trastuzumab-based treatment was associated with improved OS (HR 0.56) and BCSS (subHR 0.62), when patients who

Table 1
Distribution of patient, tumour and treatment characteristics in women with HER2-positive, early invasive breast cancer, by receipt of adjuvant trastuzumab-based treatment.

Total	Trastuzumab-based treatment N = 5238	No treatment N = 3421	*Chemotherapy only N = 684*
Age			
50 −59 years	2226 (42.5 %)	587 (17.2 %)	*293 (42.8 %)*
60 −69 years	1952 (37.3 %)	913 (26.7 %)	*235 (34.4 %)*
70 −79 years	970 (18.5 %)	1010 (29.5 %)	*147 (21.5 %)*
80 + years	90 (1.7 %)	911 (26.6 %)	*9 (1.3 %)*
IMD			
1 - Most deprived	794 (15.2 %)	486 (14.2 %)	*141 (20.6 %)*
2	886 (16.9 %)	579 (16.9 %)	*131 (19.2 %)*
3	1119 (21.4 %)	678 (19.8 %)	*130 (19.0 %)*
4	1200 (22.9 %)	833 (24.3 %)	*146 (21.3 %)*
5 - Least deprived	1239 (23.7 %)	845 (24.7 %)	*136 (19.9 %)*
CCI			
0	4744 (90.6 %)	2760 (80.7 %)	*609 (89.0 %)*
1	395 (7.5 %)	416 (12.2 %)	*59 (8.6 %)*
2 +	99 (1.9 %)	245 (7.2 %)	*16 (2.3 %)*
SCARF Index			
Fit	4478 (85.5 %)	2453 (71.7 %)	*579 (84.6 %)*
Mild frailty	492 (9.4 %)	450 (13.2 %)	*71 (10.4 %)*
Moderate - severe frailty	268 (5.1 %)	518 (15.1 %)	*34 (5.0 %)*
Grade			
G1	100 (1.9 %)	232 (6.8 %)	*11 (1.6 %)*
G2	1925 (36.8 %)	1631 (47.7 %)	*279 (40.8 %)*
G3	3213 (61.3 %)	1558 (45.5 %)	*394 (57.6 %)*
Tumour stage			
T1	2954 (56.4 %)	1923 (56.2 %)	*341 (49.9 %)*
T2	2113 (40.3 %)	1385 (40.5 %)	*314 (45.9 %)*
T3	171 (3.3 %)	113 (3.3 %)	*29 (4.2 %)*
Nodal stage			
N0	3633 (69.4 %)	2607 (76.2 %)	*404 (59.1 %)*
N +	1605 (30.6 %)	814 (23.8 %)	*280 (40.9 %)*
Hormone receptor-positive			
Yes	3601 (68.7 %)	2519 (73.6 %)	*487 (71.2 %)*
No/Unknown	1637 (31.3 %)	902 (26.4 %)	*197 (28.8 %)*
Surgery type			
Breast conserving surgery	3577 (68.3 %)	2072 (60.6 %)	*432 (63.2 %)*
Mastectomy	1661 (31.7 %)	1349 (39.4 %)	*252 (36.8 %)*
Radiotherapy			
No	1082 (20.7 %)	1333 (39.0 %)	*160 (23.4 %)*
Yes	4156 (79.3 %)	2088 (61.0 %)	*524 (76.6 %)*
Endocrine therapy			
No	1627 (31.1 %)	984 (28.8 %)	*199 (29.1 %)*

(*continued on next page*)

Table 1 (*continued*)

Total	Trastuzumab-based treatment N = 5238	No treatment N = 3421	*Chemotherapy only N = 684*
Yes	3611 (68.9 %)	2437 (71.2 %)	*485 (70.9 %)*
Chemotherapy			
No	72 (1.4 %)	3421 (100 %)	*0 (0 %)*
Other chemotherapy	51 (1.0 %)	-	*327 (47.8 %)*
Taxanes	2120 (40.5 %)	-	*52 (7.6 %)*
Anthracyclines	969 (18.5 %)	-	*179 (26.2 %)*
Taxane & anthracycline	2026 (38.7 %)	-	*126 (18.4 %)*
Death reported (Y)	338 (6.5 %)	741 (21.7 %)	*76 (11.1 %)*

Key: IMD = Index of Multiple Deprivation; CCI = Charlson Comorbidity Index; SCARF = Secondary Care Administrative Records Frailty.
Note: Anthracyclines = doxorubicin, epirubicin, mitoxantrone recorded in SACT. Taxanes = docetaxel, cabazitaxel, paclitaxel, nab-paclitaxel recorded in SACT.

received adjuvant trastuzumab-based treatment were compared with those who did not. Overall findings were consistent with evidence from RCTs. In particular, the HERA trial reported an unadjusted HR of 0.53 for OS at 4-year follow-up [36]. This study however included more than twice as many patients than were in the HERA trial. The findings are also consistent with other real-world studies estimating the effect of treatment on OS. A study in the Netherlands among patients diagnosed from 2005 to 2007 reported comparable 5-year OS estimates and an associated adjusted HR of 0.48, whilst another study among women in the Netherlands from 2006–12 found adjuvant trastuzumab considerably improved OS for small tumours (adjusted HR 0.35) [30,37].

This study included patients with an upper age range older than in the RCTs, with 20.2 % of women aged 70 + years. We found no evidence that the impact of treatment varied by patient age at diagnosis or fitness, as measured using comorbidity and frailty scores.

The study has a number of strengths. Use of a large, population-based sample of women diagnosed with HER2-positive EIBC over a period of six years (2014–2019) with mortality data to October 2021 means the findings reflect the diversity of women with breast cancer in routine care and current survival outcomes. The evidence from this study is more representative of the general population than previously published small observational studies or randomised trials. Use of the propensity score weighting and landmark analysis are recognised methods to reduce bias introduced by patient selection for treatment. The study demonstrated good balance among the prognostic factors associated with treatment selection and clinical outcomes, and this provides confidence in the possible treatment effect estimates.

There are various limitations of this study. Firstly, the use of routine data raises the potential of bias from treatment misclassification, unmeasured confounding, and missing data. Misclassification might arise because some hospitals may not enter data into SACT on all treatments, however we used HES-APC data to identify patients who received treatment and thereby reduced misclassification. SACT provides data on prescribed therapies and some patients may not have received trastuzumab; which means that the approach used in this paper is analogous to an intention-to-treat analysis as would be carried out within an RCT. There is potential for errors in patient and tumour characteristics within the England Cancer Registry and COSD datasets, however the cancer registration service has various validation steps when compiling national registration data and the overall effect of coding errors should therefore be minimal. Secondly, with data only available for women aged 50 years and over, it was not possible to look at differences in survival outcomes in younger women. Third, propensity score analysis will not account for unmeasured confounding, and there may be residual unrecognised bias. This should be small in comparison to the estimated treatment effect because of the large number of variables used to derive the propensity score; equally, with the estimated effect being large, we would not expect this to change considerably. Clinically relevant prognostic factors not captured in the model are minimal, with specific aspects of severe health problems which would be contraindications for treatment being detected within the measures of fitness used. However, there is likely to be some residual confounding which would impact the study estimates of effect. We expect this to have limited impact on the conclusion that there was no evidence of differences by age or patient

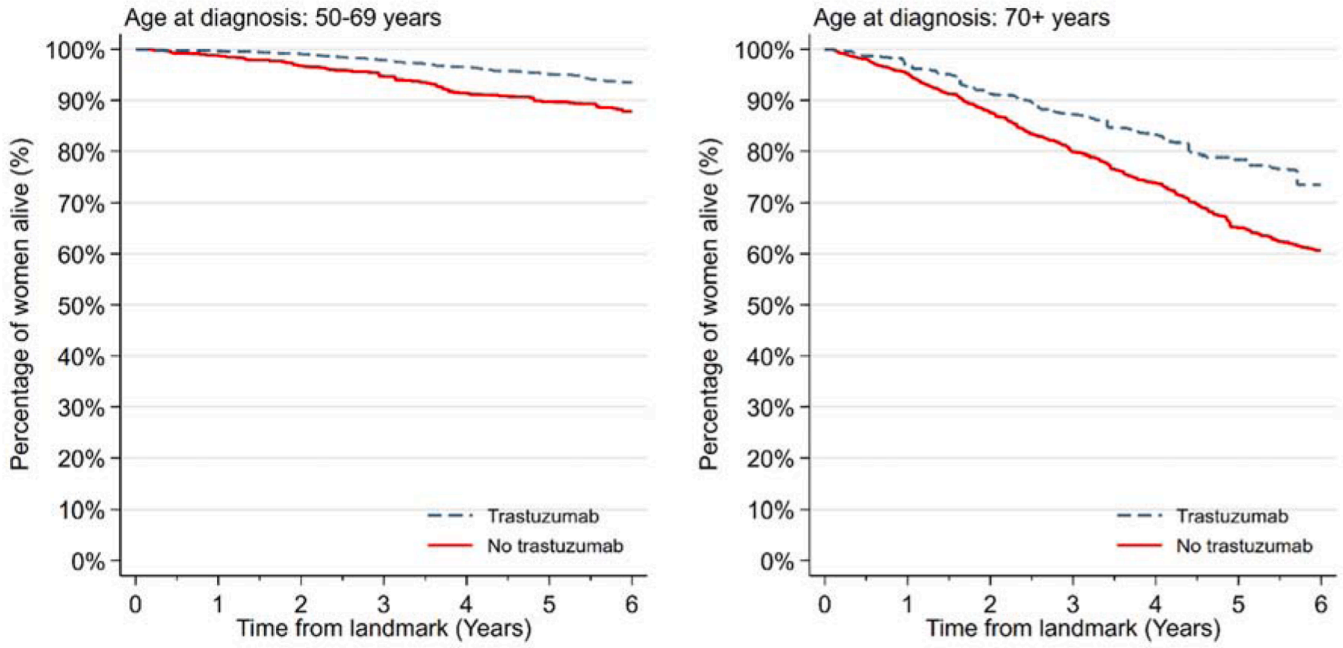

Fig. 1. Weighted Kaplan-Meier curves (including 95 % confidence intervals) for overall survival in patients with HER2-positive EIBC receiving adjuvant trastuzumab-based treatment compared with no treatment, by age at diagnosis. Note: Kaplan-Meier survival curves are provided to visually show OS across patient groups; patient group numbers can be seen in Table 1, treatment differences across age decade groups can be seen in Fig. 2.

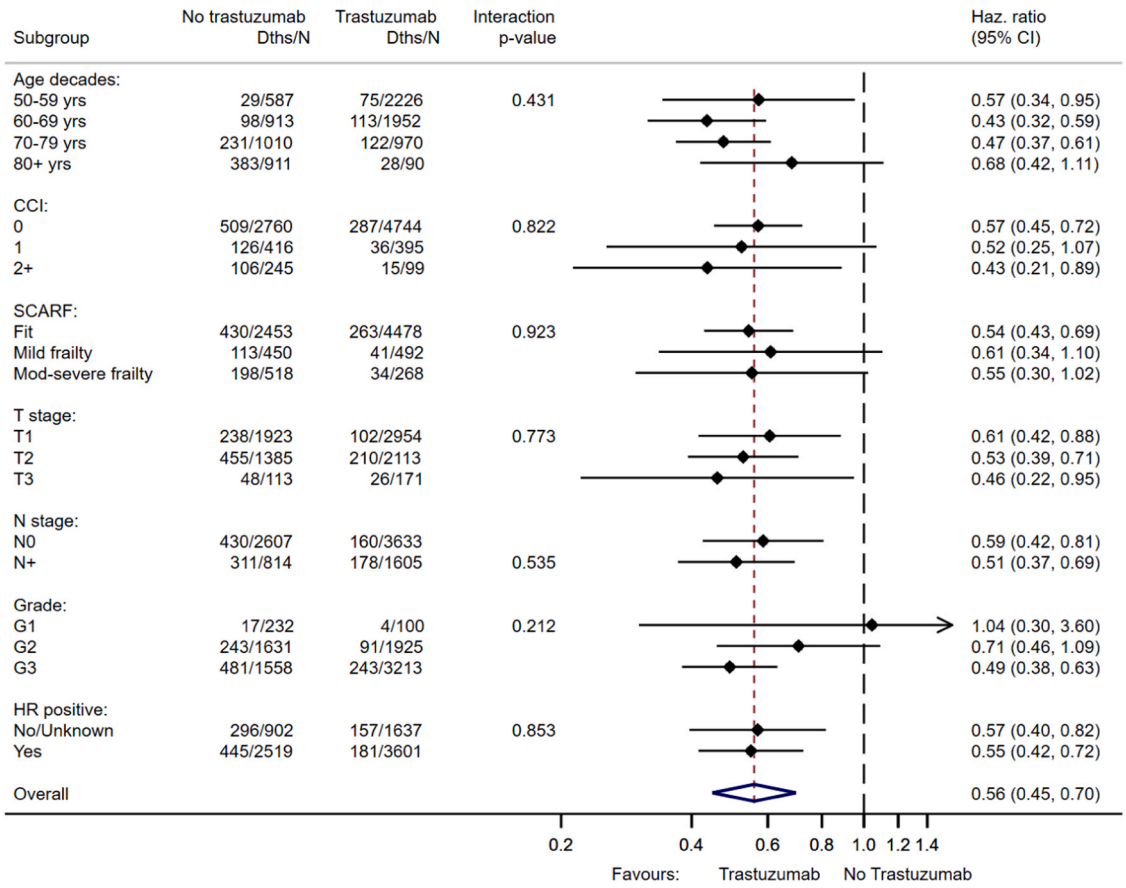

Fig. 2. Forest plot of estimated hazard ratios for overall survival (trastuzumab versus no trastuzumab) in patients with HER2-positive EIBC.

fitness. Finally, current NICE guidance (NG101) was changed in 2018 and recommended patients are offered neoadjuvant chemotherapy/HER2-targeting therapy for HER2-positive EIBC [4]. This might have had the effect of changing who was offered adjuvant therapy in later years, and increased the number of treated patients with a better prognosis. However, inclusion of year of diagnosis as a sensitivity analysis demonstrated no impact on the findings.

Although trastuzumab is a well-established standard treatment for HER2-positive breast cancer, there are still many women not receiving this treatment in routine clinical practice [11]. While the primary aim of this study was to assess whether the survival benefit of adjuvant trastuzumab varies by patient age and fitness, it is noteworthy that the observed uptake of 60.5 % (5238/8659), among those eligible for the study, was lower than anticipated and we here discuss some possible explanations. The study findings reveal disparities in treatment utilisation across patient subgroups including those based on age and fitness. A clinician's approach to giving trastuzumab-based treatment may be more cautious among older patients, as well as those with higher levels of comorbidity and frailty (as seen within the CCI and SCARF Index results). The prior lack of comprehensive research exploring the impact of patient age and fitness on survival outcomes, especially among subgroups underrepresented in RCTs, may partially explain these disparities. We also observed lower uptake among patient groups where tumour characteristics had less aggressive features (G1, N0) which are traditionally less likely to receive chemotherapy. With a higher numbers of deaths among those patients not receiving trastuzumab-based treatment, there is also the possibility of there being other confounding health issues. In addition, it is well known that real world practice can show fewer interventions than guideline recommended practice might expect. However, this real-world data encompasses a population that includes older patients with some comorbidities who successfully receive treatment, which can hopefully inspire confidence in the clinical community to broaden their treatment base.

The landscape of treatment for EIBC has changed considerably since trastuzumab was first approved for use in the UK. Future research would benefit from understanding whether there are differences in survival outcomes, across patient subgroups and within those patient populations which are poorly represented in the RCTs, for more recently approved treatments. Alongside this, work to understand the associated safety outcomes among patients treated in routine care is necessary to provide a better understanding of the benefits and risks of HER2-targetting therapy to inform discussions with patients. This includes the more recently approved dual HER2-targetting therapy (pertuzumab + trastuzumab) proven to be beneficial in patients with high-risk disease.

Despite the evolution of treatment, including the approval of neoadjuvant trastuzumab for HER2-positive EIBC, use of adjuvant trastuzumab-based treatment remains an important treatment option with clear survival benefits including for patients with smaller, node-negative tumours.

5. Conclusions

This study found the use of adjuvant trastuzumab-based treatment, initiated in routine care for women with HER2-positive EIBC, was associated with improved overall survival. This was seen regardless of patient age or fitness. Chronological age and fitness alone should not be barriers to the receipt of effective adjuvant targeted treatment.

Ethics approval and consent to participate

This study was exempt from NHS Research Ethics Committee

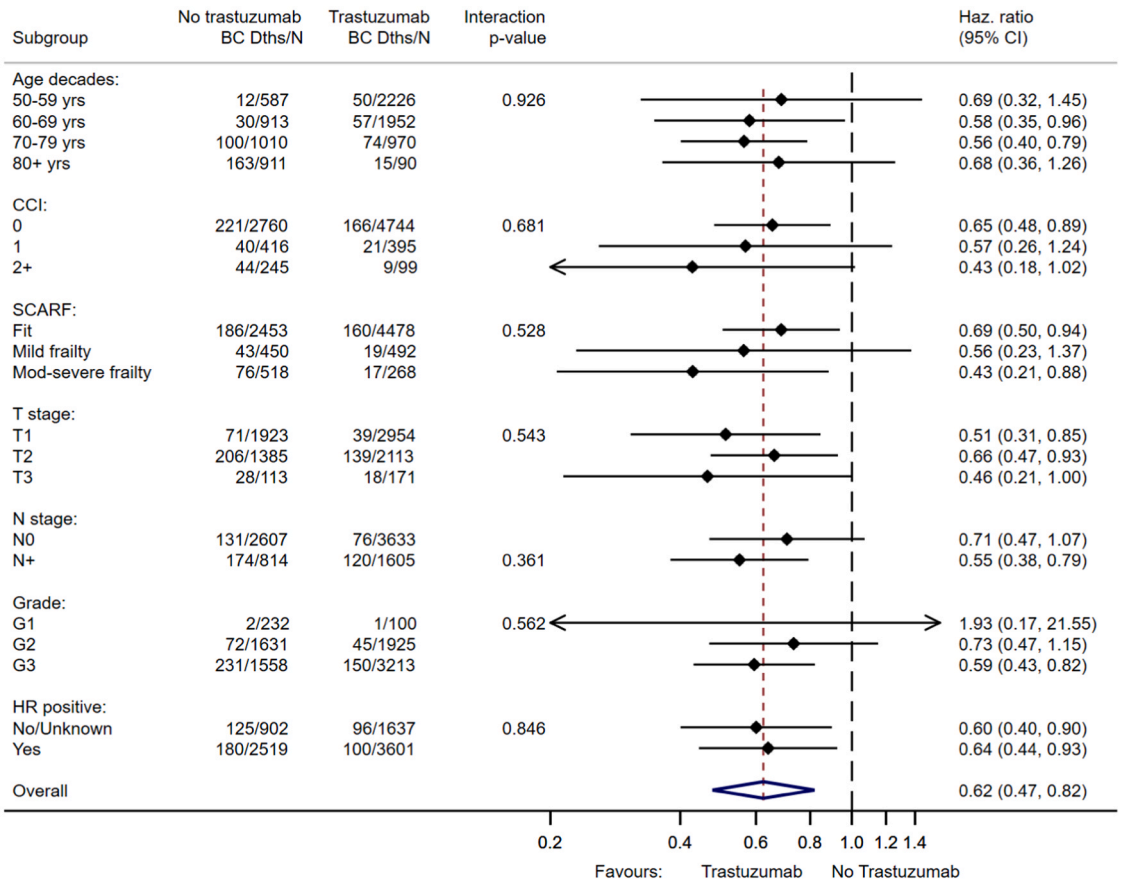

Fig. 3. Forest plot of estimated sub hazard ratios breast cancer-specific survival (trastuzumab versus no trastuzumab) in patients with HER2-positive EIBC.

approval because it involved analysis of pseudonymised linked data collated for the purpose of service evaluation as part of the National Audit of Breast Cancer in Older Patients.

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DD also receives funding from Cancer Research UK (grant C7852–A25447). CRUK had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit the article for publication.

CRediT authorship contribution statement

Min Hae Park: Writing – review & editing, Supervision, Conceptualization. **Kieran Horgan:** Writing – review & editing, Conceptualization. **David Alan Cromwell:** Writing – review & editing, Supervision, Conceptualization. **Katie Miller:** Writing – review & editing, Conceptualization. **Karen Clements:** Writing – review & editing, Conceptualization. **Jibby Medina:** Writing – review & editing, Conceptualization. **David Dodwell:** Writing – review & editing, Conceptualization. **Melissa Ruth Gannon:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

DD receives funding from Cancer Research UK (grant C7852–A25447). CRUK had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit the article for publication.

KH declares being the Chair of the Endonet Trial Steering Committee.

KC declares funding was received for Breast Cancer Research Manager role within NHS England as part of the Cancer Grand Challenges PRECISION team, which was funded by Cancer Research UK and the Dutch Cancer Society (C38317/A24043); the grant was not related to her work on the National Audit of Breast Cancer in Older Patients or this paper.

DAC declares grants/contracts from Healthcare Quality Improvement partnership; participation on the Pregnancy Outcome Prediction Study (POPS2) Trial Steering Committee; being on the Editorial Committee for the Journal of Health Services Research and Policy; being Deputy Chair on the Examination Committee for the MSc, PG Diploma and PG Cert in Public Health distance learning programme at the London School of Hygiene & Tropical Medicine.

All other co-authors have no COI to declare.

Data Availability

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data for England are collated, maintained and quality assured by the National Disease Registration Service (NDRS), which is part of NHS England. Data on English Cancer Registrations can be accessed via the NHS Digital Data Access request Service (DARS) https://digital.nhs.uk/services/data-access-request-service-dars#national-disease-registration-service-ndrs-

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114309.

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Figure S1: Details of patient cohort selection from women aged 50 and over, diagnosed with breast cancer in a NHS organisation in England between 2014 and 2019.

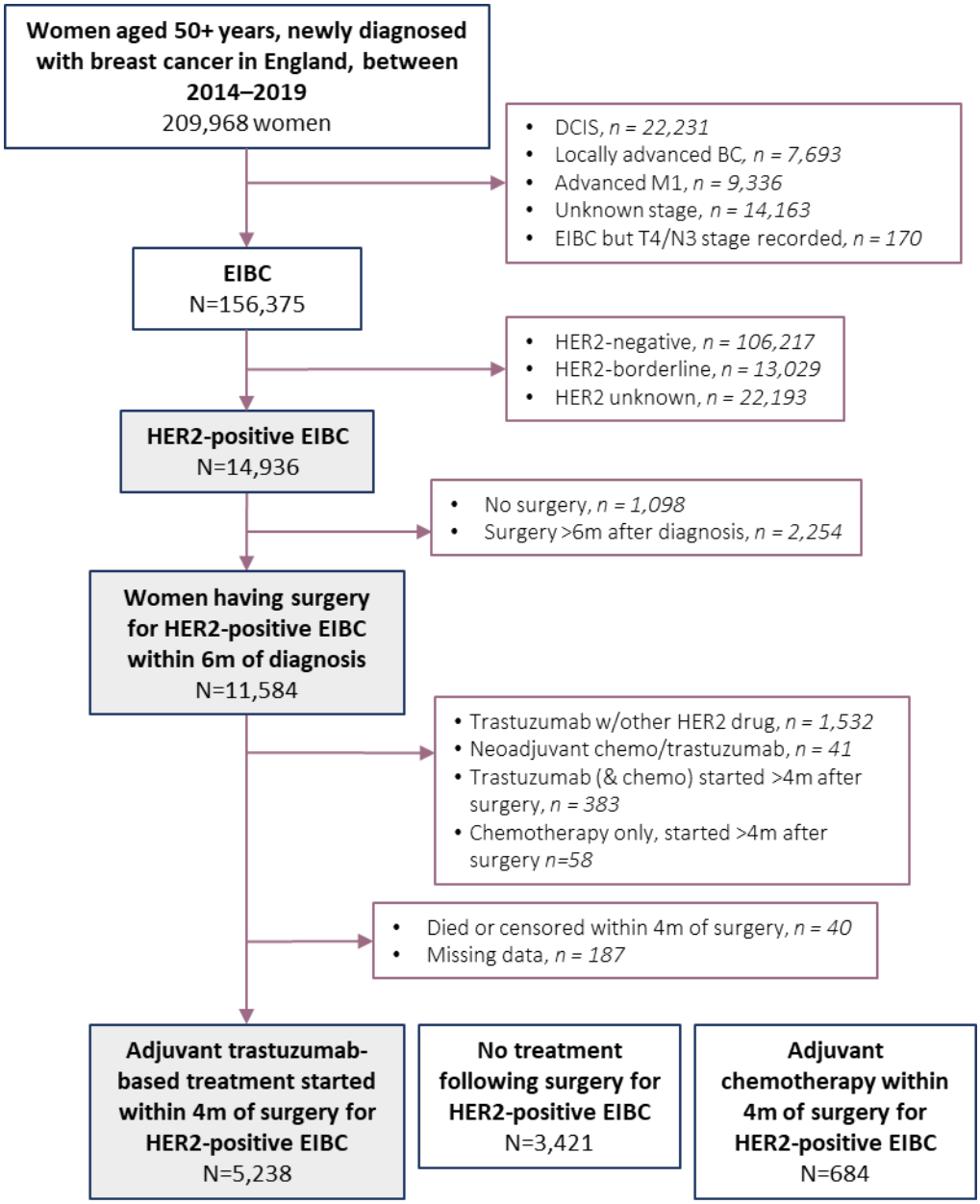
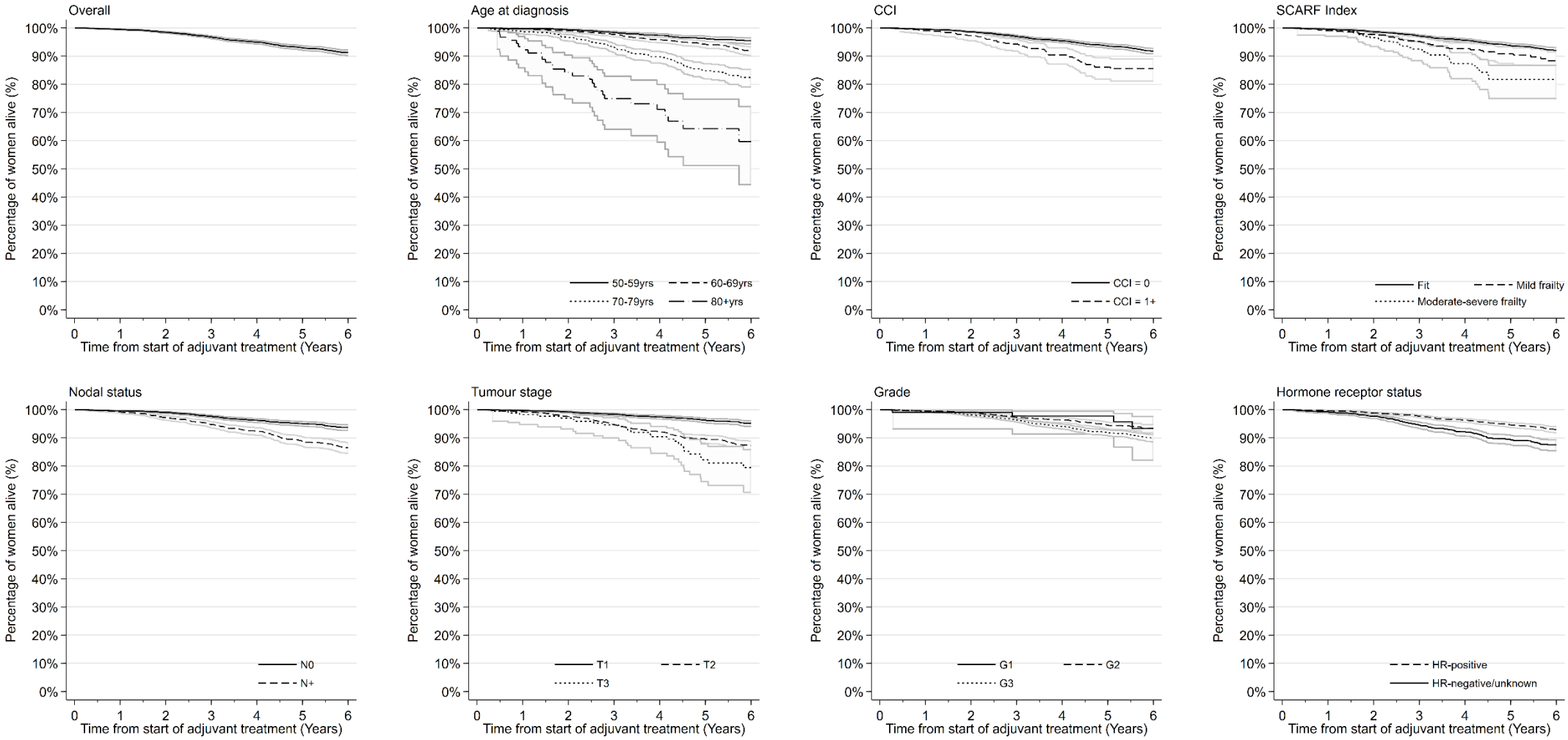


Figure S2: Kaplan-Meier survival curves (including 95% confidence intervals) for overall survival following initiation of adjuvant trastuzumab-based treatment, overall and by patient and tumour characteristics.



Note: Kaplan-Meier survival curves are provided to visually show OS across patient groups; patient group numbers can be seen in Table 1, treatment differences can be seen in Figure 2.

Figure S3: Balance obtained with standardised means difference, while accounting, or not, for selection bias (i.e. weighted and unweighted, respectively)

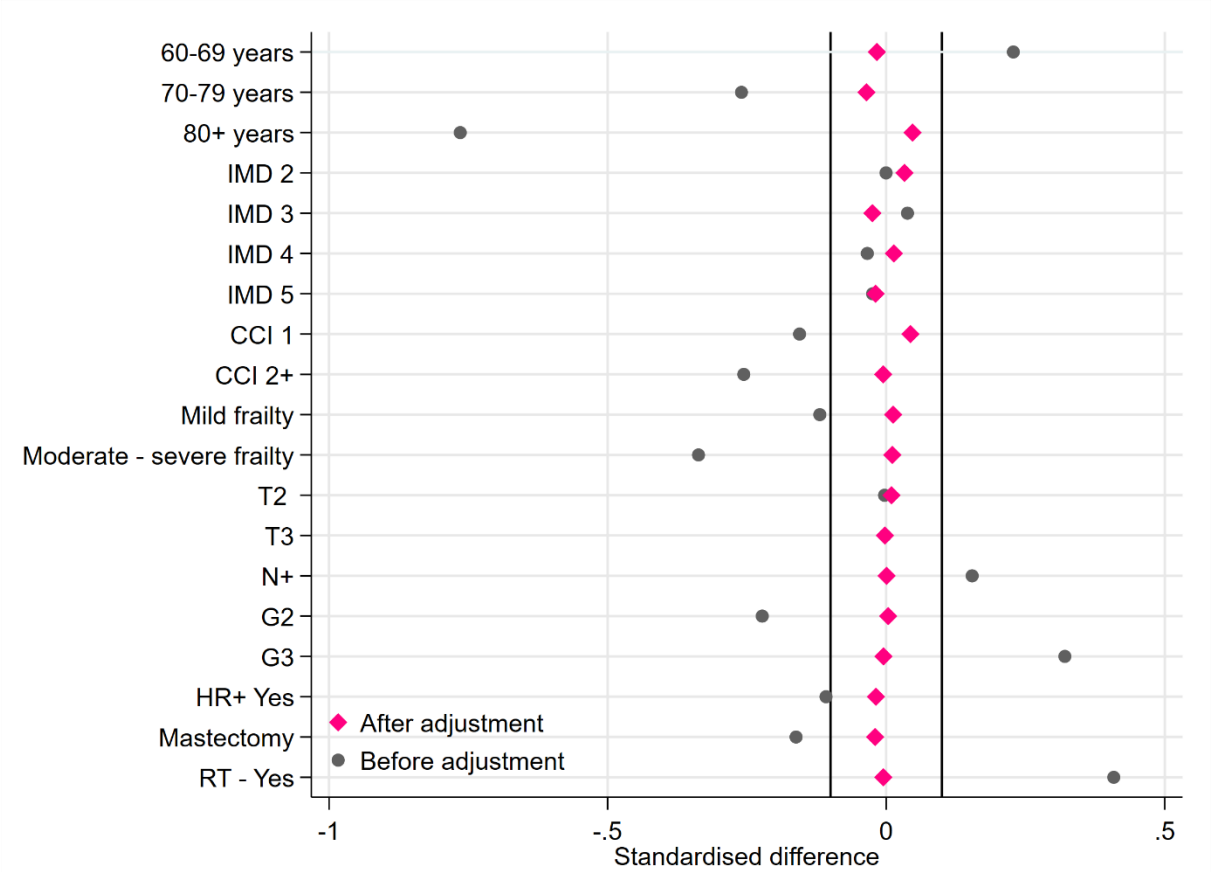


Figure S4: Density plot of propensity score by treatment group

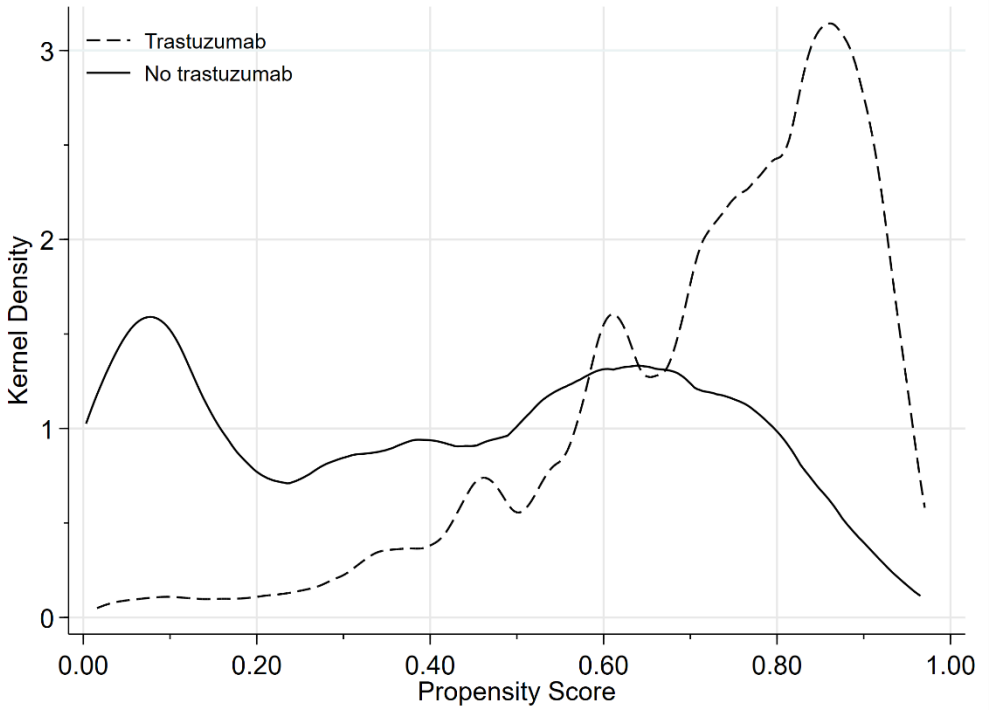


Figure S5: Overall Survival – Results from sensitivity analyses including patients with only adjuvant chemotherapy recorded (i.e. no trastuzumab recorded)

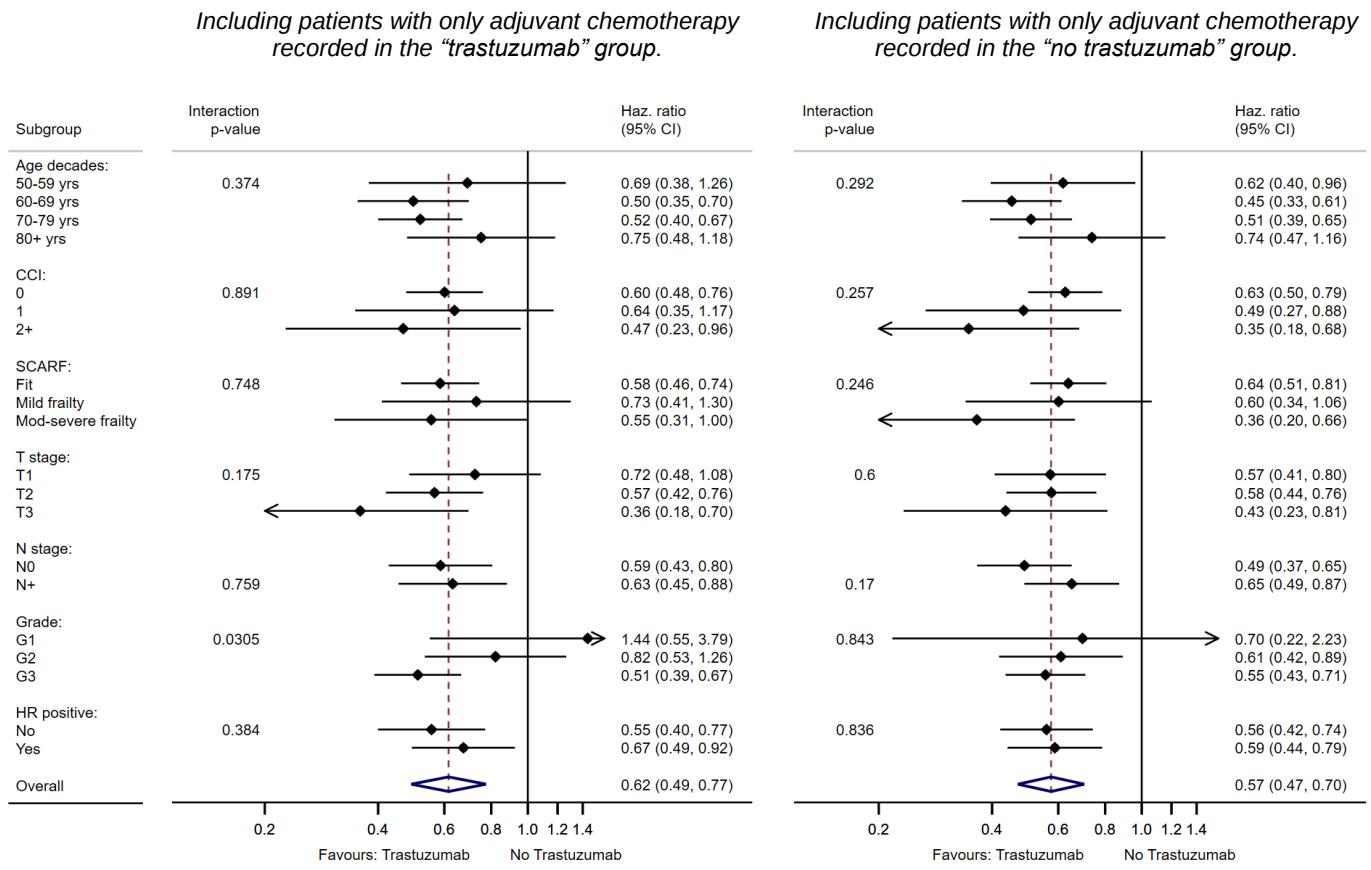


Figure S6: Breast cancer-specific survival – Results from sensitivity analyses including patients with only adjuvant chemotherapy recorded (i.e. no trastuzumab recorded)

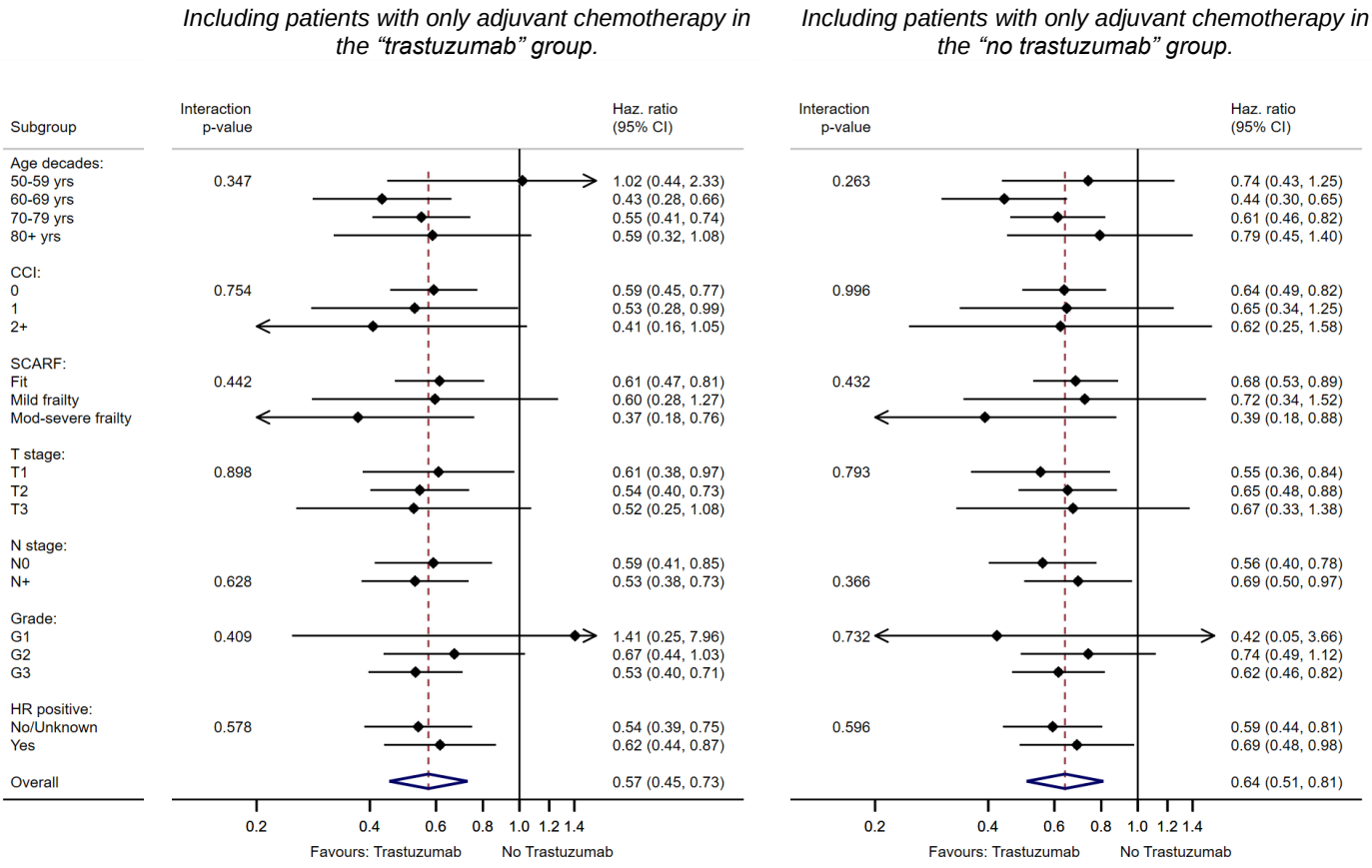
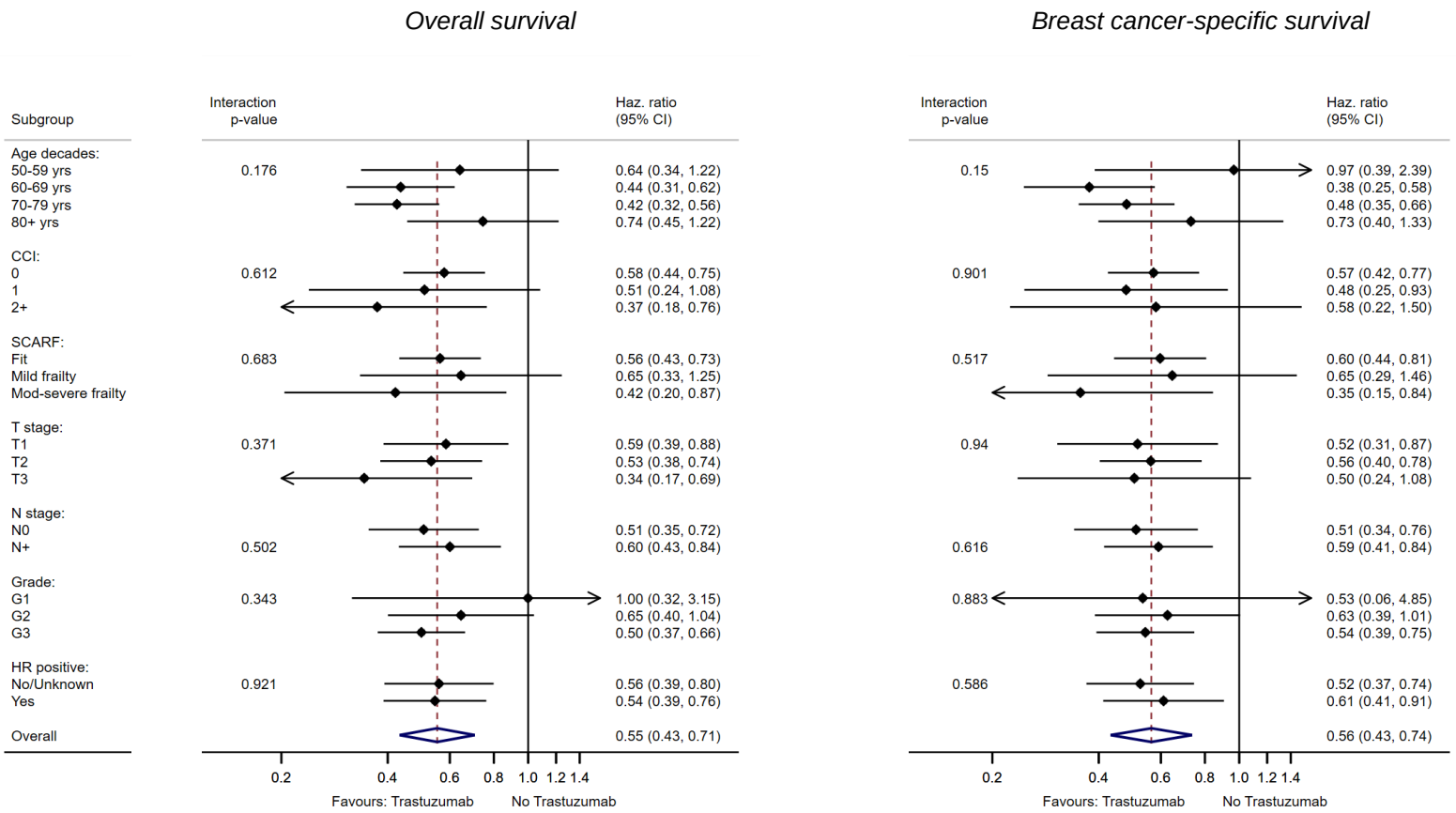


Figure S7: Results from sensitivity analyses around the landmark time point (5-month time point shown)*



* 2 & 3 months looked at and found to be stable with 5-month time point and main results of 4-months.

Table S1: Specification and emulation of a target trial of adjuvant trastuzumab versus no treatment among patients with HER2-positive EIBC between 2014 and 2019 in England

Component	Description of Target trial	Description of Emulated trial using routine healthcare data
Eligibility criteria	Patients with EIBC who receive surgery, with no prior use of chemotherapy or trastuzumab.	Same as target trial
Treatment strategies	1. Initiate trastuzumab-based treatment. 2. Don't initiate trastuzumab-based treatment.	Same as target trial
Treatment assignment	Patients are randomly assigned to either strategy.	We classified individuals according to the strategy their data were compatible with. Randomisation was assumed conditional on baseline covariates, using propensity scores. A 4-month grace period from date of surgery was specified to allow for decision-making (landmark approach).
Follow up	Starts at randomisation and ends at the point of death or administrative censoring.	Starts at landmark time point and ends at the point of death or administrative censoring
Outcome	Death from any cause; Death from breast cancer.	Same as target trial
Causal contrast of interest	Intention-to-treat.	Same as target trial. To be analogous to the target trial, comparison will be of treatment initiation. Some patients allocated to strategy 1 may have been prescribed treatment but never initiated it.
Analysis plan	Intention-to-treat effect estimated via standard survival methods.	Same as target trial. Propensity scores used for balance of baseline prognostic factors.

Table S2: Overall survival by patient, tumour and treatment characteristics among women receiving adjuvant trastuzumab-based treatment for HER2-positive, early invasive breast cancer.

	N	% died	5 year OS (95% CI)	Unadjusted HR	Adjusted HR*	Grouped p-value
Overall	**5238**	**6.5%**	**92.9% (92.1-93.7)**	**-**	**-**	**-**
Age						
50-59 years	2226	3.4%	96.2% (95.2-97.0)	1.00	1.00	<0.0001
60-69 years	1952	5.8%	94.2% (92.9-95.3)	1.72 (1.28-2.3)	1.62 (1.21-2.17)	
70-79 years	970	12.6%	84.8% (81.9-87.3)	4.17 (3.13-5.56)	2.99 (2.18-4.11)	
80+ years	90	31.1%	64.3% (51.1-74.8)	13.76 (8.75-21.63)	6.41 (3.89-10.57)	
IMD						
1 - Most deprived	794	8.2%	91.4% (88.8-93.4)	1.00	*No crude association*	
4	886	7.2%	92.2% (89.9-94.0)	0.93 (0.66-1.31)		
2	1119	5.4%	94.1% (92.3-95.5)	0.67 (0.47-0.96)		
3	1200	6.7%	92.6% (90.7-94.1)	0.84 (0.60-1.16)		
5 - Least deprived	1239	5.6%	93.7% (91.8-95.1)	0.71 (0.50-0.99)		
CCI						
0	4744	6.0%	93.6% (92.7-94.3)	1.00	1.00	0.0053
1+	494	10.3%	86.1% (81.8-89.4)	1.98 (1.47-2.67)	1.55 (1.14-2.11)	
SCARF Index						
Fit	4478	5.9%	93.7% (92.8-94.5)	1.00	*No adjusted association*	
Mild frailty	492	8.3%	90.8% (87.3-93.3)	1.54 (1.11-2.15)		
Mod - severe frailty	268	12.7%	81.7% (74.9-86.8)	2.74 (1.91-3.92)		
Grade						
G1	100	4.0%	97.8% (91.3-99.4)	1.00	*No adjusted association*	
G2	1925	4.7%	94.5% (93.1-95.6)	1.24 (0.46-3.36)		
G3	3213	7.6%	91.8% (90.7-92.9)	1.92 (0.72-5.13)		
Tumour stage						
T1	2954	3.5%	96.3% (95.4-97.0)	1.00	1.00	<0.0001
T2	2113	9.9%	89.5% (87.9-90.9)	2.75 (2.17-3.48)	2.07 (1.62-2.65)	
T3	171	15.2%	82.2% (74.4-87.9)	4.17 (2.72-6.39)	2.60 (1.64-4.12)	
Nodal stage						
N0	3633	4.4%	95.0% (94.1-95.8)	1.00	1.00	<0.0001
N+	1605	11.1%	88.8% (86.9-90.4)	2.26 (1.82-2.79)	2.00 (1.58-2.53)	
HR-positive						
Yes	3601	5.0%	94.6% (93.6-95.4)	0.53 (0.43-0.66)	0.61 (0.49-0.75)	<0.0001
No/Unknown	1637	9.6%	89.3% (87.5-90.9)	1.00	1.00	
Surgery type						
BCS	3577	4.5%	95.0% (94.1-95.8)	1.00	*No adjusted association*	
Mastectomy	1661	10.6%	88.7% (86.9-90.3)	2.25 (1.82-2.79)		
Radiotherapy						
No	1082	8.7%	90.8% (88.7-92.6)	1.00	1.00	0.0012
Yes	4156	5.9%	93.5% (92.5-94.3)	0.67 (0.53-0.85)	0.67 (0.52-0.85)	
Endocrine therapy						
No	1627	9.8%	89.3% (87.4-90.9)	1.00	*No adjusted association*	
Yes	3611	4.9%	94.5% (93.6-95.4)	0.48 (0.39-0.60)		
Chemotherapy						
No	72	18.1%	80.6% (67.9-88.7)	1.00	1.00	0.0017
Other chemo therapy	51	9.8%	87.9% (72.8-94.9)	0.45 (0.16-1.27)	0.69 (0.25-1.89)	
Taxanes	2120	6.7%	91.4% (89.8-92.8)	0.37 (0.20-0.66)	0.49 (0.28-0.86)	
Anthracyclines	969	8.0%	92.5% (90.5-94.1)	0.33 (0.18-0.61)	0.63 (0.35-1.14)	
Taxane & anthracycline	2026	4.9%	94.9% (93.7-95.9)	0.22 (0.12-0.41)	0.37 (0.21-0.67)	

Key: OS = overall survival; CI = confidence interval; HR = hazard ratio; IMD = Index of Multiple Deprivation; CCI = Charlson Comorbidity Index; SCARF = Secondary Care Administrative Records Frailty; HR = hormone receptor; BCS = breast conserving surgery.
Note: Anthracyclines = doxorubicin, epirubicin, mitoxantrone recorded in SACT.
Taxanes = docetaxel, cabazitaxel, paclitaxel, nab-paclitaxel recorded in SACT.
* HRs adjusted for other factors