NOVARTIS

CLEE011AGB02 Study Results Abstract for Public Disclosure

Title

Epidemiology and treatment of HR+/HER2- breast cancer in England (ROTOR)

Keywords

Breast cancer; progression; cyclin-dependent kinase 4/6 (CDK4/6) inhibitors

Rationale and Background

Globally, breast cancer (BC) is the most diagnosed cancer and leading cause of cancer-related death among women. In England, over 80% of BC cases are diagnosed at stage I or II. The recurrence rate for early breast cancer (eBC) is about 20%, with 5-10% of women diagnosed with metastatic breast cancer (mBC) initially, and over 10% of eBC cases progressing to mBC. Hormone receptor-positive (HR+)/ Human epidermal growth factor receptor 2 negative (HER2-) BC is the most common subtype, making up 70% of cases, with a 20% distant recurrence rate within 5 years. Endocrine therapy (ET) is the preferred treatment for HR+/HER2- mBC, but approximately 50% of patients develop resistance. Adding CDK4/6 inhibitors (CDK4/6i) to ET improves outcomes and is now standard care. This study aimed to describe the epidemiology, treatment pathways, access, wastage of CDK4/6i, and healthcare resource use among HR+/HER2- BC patients in England, focusing on progression from eBC to mBC.

Research Objectives

Epidemiology

Primary Objective

To describe and estimate the risk of progression from HR+/HER2- eBC to non-metastatic recurrence, mBC, and death.

Secondary Objectives

1. To describe the baseline (i.e., at earliest BC diagnosis) demographic and pertinent clinical characteristics of patients with HR+/HER2- eBC, who receive adjuvant treatment.
2. To summarise the time from diagnosis of HR+/HER2- eBC to presentation with metastatic disease (time from ≤ stage III to stage IV).
3. To describe the baseline (i.e., at mBC diagnosis) demographic and pertinent clinical characteristics of patients with HR+/HER2- mBC.

Treatment Decisions and Pathway

Primary Objective

To describe the post-diagnosis treatment pathway of patients with HR+/HER2- eBC who receive adjuvant treatment.

Secondary Objectives

1. To describe the post-diagnosis treatment pathway of patients with HR+/HER2- mBC by: 1) number of lines of therapy received; and 2) systemic therapies received in each line of therapy (LOT) for first line (1L), second line, and third line and beyond.
2. To describe the rate of discontinuation for adjuvant treatment among patients with HR+/HER2- eBC.
3. To describe adherence to adjuvant treatment among patients before progression to HR+/HER2- mBC.
4. To describe the number and proportion of patients with HR+/HER2- mBC and treated with each of ribociclib, palbociclib, and abemaciclib who receive electrocardiograms (ECGs) outside of standard of care recommendations.
5. To summarise the duration of CDK4/6i (ribociclib, palbociclib, and abemaciclib) treatment by LOT among patients with HR+/HER2- mBC.

Access to Treatment

Primary Objectives

1. For recent years, defined as 2020–2022, and by region, calculate the total number and proportion of people with HR+/HER2- eBC, eBC treated with adjuvant therapy who progress to mBC, mBC, mBC who receive more than one LOT, and mBC treated with a CDK4/6i.
2. To describe and compare age, ethnicity, and deprivation differences in treatment choice for 1L treatment among patients with HR+/HER2- mBC.

Secondary Objectives

1. To describe and compare age, ethnicity, and deprivation differences in progression-free survival (PFS) of 1L treatment among patients with HR+/HER2- BC.
2. To describe and compare the characteristics of patients with HR+/HER2- mBC who are and are not treated within the cancer wait time targets set by National Health Service (NHS) England.
3. To describe the regional differences in CDK4/6i usage among treatment-eligible patients with HR+/HER2- mBC.
4. To describe and compare regional differences in PFS among patients with HR+/HER2- mBC adjusted for other signals of inequality including age, ethnicity, and deprivation, then stratified by 1L treatment class.
5. To describe and compare age, ethnicity, and deprivation differences between patients with HR+/HER2- mBC who were and were not metastatic at first presentation.

Wastage and dose reduction

1. To describe the number and proportion of patients with HR+/HER2- mBC treated with ribociclib, palbociclib, or abemaciclib who experience a dose reduction.
2. To describe the number and proportion of patients with HR+/HER2- mBC treated with ribociclib, palbociclib, or abemaciclib who experience a second dose reduction.
3. To describe and compare the frequency of dose reduction for patients with HR+/HER2- mBC for ribociclib, palbociclib, and abemaciclib.
4. To describe and compare the length of treatment for patients with HR+/HER2- mBC with no dose reduction, one dose reduction, and two dose reductions for ribociclib, palbociclib, and abemaciclib.
5. To describe at which treatment cycle and timepoint within the given cycle patients with HR+/HER2- mBC treated with ribociclib, palbociclib, or abemaciclib experience a dose reduction.
6. To describe the costs associated with wastage (dose reduction) for each of ribociclib, palbociclib, and abemaciclib.
7. To describe the number and proportion of patients with HR+/HER2- mBC who switch CDK4/6 inhibitors, and to describe what treatment patients switch from and to.

Healthcare Resource Use (HCRU)

1. To quantify the total all-cause and BC-related secondary care HCRU events and associated costs for patients with HR+/HER2- BC while in specified disease states, e.g., eBC (including recurrences) to remission, remission to mBC, mBC to death.
2. To quantify the chemotherapy toxicity-related secondary care HCRU events and associated costs of patients with HR+/HER2- BC.

Study Design

This study was a retrospective cohort study using linked registry and administrative data.

Setting

All individuals with a diagnosis of HR+/HER2- eBC or mBC aged ≥18 years between 01 April 2012 and 31 December 2022 in England, as captured in a national registry.

Subjects and Study size, Including Dropouts

Individuals with eBC or mBC were defined based on a registered tumour diagnosis with an International Classification of Diseases, 10th Revision (ICD-10) code C50: malignant neoplasm of the breast with oestrogen receptor-positive (ER+) or progesterone receptor-positive (PR+), i.e., HR+ and HER2-.

Additional inclusion criteria for individuals with mBC were defined as tumour stage IV or Tumour, Nodes, Metastases (TNM) staging indicative of M1 at diagnosis or on subsequent treatment, or ICD-10 codes indicating secondary malignant neoplasm, or initiation of ribociclib or palbociclib from 01 January 2017 to the end of the study period or abemaciclib from 01 January 2017 to 31 May 2022, or treatment for distant/metastatic recurrence. Individuals with mBC were further

classified into de novo or progressed mBC. De novo mBC was defined as <100 days between the first BC tumour diagnosis and first evidence of metastatic disease. For de novo mBC, diagnosis date was the earliest of first BC diagnosis or first evidence of mBC. For progressed mBC, diagnosis date was the date of first evidence of mBC.

We excluded patients with unknown sex, ductal carcinoma in situ or lobular carcinoma in situ, non-malignant disease, co-positive disease before or within 6 months after diagnosis (i.e., HR+ and HER2+), or any registered BC tumour or evidence of metastatic cancer prior to index date.

A subgroup analysis within the eBC cohort was performed, with the aim of generating a real-world population that closely resembles that of the NATALEE trial population. The following additional criteria were applied: stage IIa BC at diagnosis (i.e., T0 N1, T1 N1, or T2 N0 with Grade 3 tumour); stage IIb BC at diagnosis (i.e., T2 N1, T3 N0), and stage III BC at diagnosis (i.e., T* N2, T* N3, T3 N1, T4 N*). In the NATALEE trial, the enrolment of patients with stage II BC was capped at 40%. Therefore, from all eligible patients, we randomly sampled to ensure the final NATALEE sub-cohort included 40% of patients with stage II BC and 60% of patients with stage III.

Variables

Baseline Demographic and Clinical Characteristics

- Age, gender, ethnicity, deprivation quintiles, body mass index (BMI), Charlson comorbidity index, geographical location, tumour staging, TNM staging at diagnosis, years between first eBC diagnosis and mBC diagnosis, performance status (Eastern Cooperative Oncology Group [ECOG] score), and select comorbidities (e.g. cardiovascular disease [CVD], hypertension, diabetes, renal insufficiency).

Epidemiology Outcomes

- Progression states: non-metastatic recurrence, metastatic recurrence, non-breast invasive, cancer and death (all-cause, BC-related and toxicity-related, based on pre-specified ICD-10 codes), invasive disease-free survival' (iDFS), defined as start of ET to first of other non-breast invasive cancer, non-metastatic recurrence, metastatic recurrence, or death from any cause.

Treatment Decisions and Pathway Outcomes

- Lines of therapies (LOTs): defined based on changes in core anti-cancer treatments (termed category A treatments here) between regimens.
- Use of radiotherapy.
- Discontinuation (within six months of first systemic anti-cancer therapy [SACT]) for adjuvant therapy (yes/no): defined when the number of cycles completed in a regimen was less than the number of cycles planned, applicable to regimens containing category A or category B (treatments used alongside category A treatments) therapies or if any regimen outcome has a flag indicating discontinuation.
- Adherence to adjuvant therapy (yes/no): patients were considered adherent when the number of completed cycles was greater than or equal to the number of planned cycles per patient, applicable to regimens containing category A or category B therapies.
- ECG use in patients with mBC treated with a CDK4/6i.

Access to Treatment Outcomes

- Geographical distribution, defined by region of residence for patients with eBC, eBC progressing to mBC, mBC, mBC with more than one LOT, and mBC treated with CDK4/6i.
- Treatment use for 1L therapy in patients with mBC, defined as anthracycline without taxane, taxane without anthracycline, anthracycline and taxane, CDK4/6i, or other.
- PFS for patients with eBC, defined as the time from date of first breast surgery (or diagnosis if no surgery) until the earliest of: new surgical procedures (breast surgery); change in category A SACT treatment or new radiotherapy at least 3 months after initial surgery (or diagnosis if no surgery); non-metastatic recurrence, metastatic recurrence, death.
- PFS for patients with mBC, defined as the time from date of diagnosis with mBC until the earliest of: change in category A SACT treatment or new radiotherapy at least 3 months after diagnosis with mBC; a new metastasis record after diagnosis with mBC; death.
- Timeliness of treatment for patients with mBC, defined as having received treatment within 31 days of decision to treat for mBC diagnosis.
- First presentation of metastatic disease, defined as de novo or progressed.

Wastage and Dose Reduction Outcomes

- CDK4/6i dose reductions, defined as a change in administered dose between consecutive records of abemaciclib, palbociclib, or ribociclib.
- Length of treatment for CDK4/6i, calculated based on a cycle length of 28 days for each of the CDK4/6is.
- Cycle and timepoint of CDK4/6i dose reduction: cycles were numbered consecutively based on each administration of the individual CDK4/6is, and the cycle numbers for records containing a dose reduction with respect to the previous cycle were identified. The time to dose reduction was calculated as the number of days from the start of the previous cycle to the date of the dose reduction.
- Costs associated with CDK4/6i wastage: Cycles were considered interrupted if a dose reduction occurred fewer than 21 (ribociclib, palbociclib) or 28 (abemaciclib) days after the start of the cycle. The cost of wastage was calculated for interrupted cycles, assuming the patient started the new lower dose on its administration date and continued at the lower dose for the remaining number of treatment days in the cycle.
- Number of patients who switch CDK4/6i.

HCRU Outcomes

- Secondary care HCRU were obtained from inpatient admissions, outpatient specialist appointments, and emergency care attendances.
- Inpatient and outpatient HCRU were classified as all-cause (any activity), BC-related (BC diagnosis, BC surgery, or admission for chemotherapy or radiotherapy), and toxicity-related, using relevant procedure and diagnosis codes.

Statistical methods

Epidemiology

Baseline demographic and clinical characteristics were described in the eBC cohort, NATALEE-aligned sub-cohort, and mBC cohort using summary statistics. Continuous variables were described using means, standard deviations (SDs), medians, interquartile ranges (IQRs), and minimum/maximum values. Categorical variables were described using numbers and percentages.

The number and percentage of patients in the eBC cohort and NATALEE-aligned sub-cohort who experienced disease progression was described. Deaths occurring during follow-up were identified and reported by type (all-cause, BC-related, and toxicity-related). Kaplan-Meier curves were used to graphically represent progression and survival time after diagnosis and to calculate the median time to progression states, along with corresponding 95% confidence intervals (CI). Cox proportional hazards regression models were used to estimate the association between sociodemographic/clinical characteristics and transition probabilities of each progression state of interest.

Treatment Decisions and Pathway

Post-diagnosis treatment pathways including LOTs and radiotherapy were summarised in the eBC and mBC cohort. A subgroup of patients with mBC who initiated treatment (first LOT or radiotherapy record) on or after 01 January 2017 was also included. To illustrate treatment pathways, the total number of LOTs per person, the time from diagnosis to first, second, and third LOT, and the number and percentage of people receiving radiotherapy were summarised. Sankey diagrams were constructed to display treatment pathways across LOTs. The time (days) on each CDK4/6i treatment (ribociclib, palbociclib, and abemaciclib), and the time from diagnosis to start of treatment mBC were summarised using descriptive statistics. The number and percentage of patients with eBC who discontinued treatment within 6 months of first SACT was summarised and calculated among all patients with eBC and among those who had a record of SACT. The percentage of patients who were adherent to treatment was calculated among patients with eBC who were treated with SACT and subsequently progressed to mBC. Finally, the number and percentage of patients with mBC who received an ECG during treatment with ribociclib, palbociclib and abemaciclib was described. For ribociclib, the number and proportion of patients who received an ECG outside of standard of care (i.e., one before start of treatment, one repeated approximately on day 14 of first cycle, one at the beginning of second cycle) was reported.

Access to Treatment

The number and percentage of patients diagnosed with BC in 2020, 2021, or 2022 was reported by index year and stratified by region. For comparison, the estimated mid-year adult population of England (males and females aged 18 or over) was reported for each year and by region. Age groups, ethnicity, and deprivation quintiles stratified by class of 1L treatment were described for patients with mBC who received at least one non-endocrine category A SACT treatment. The class of therapy for 1L treatment was categorised as anthracyclines with a taxane, anthracyclines without a taxane, taxane without an anthracycline, CDK4/6i, and other. Chi-square goodness-of-fit tests were used to compare differences in age groups, ethnic groups, and deprivation quintiles between the 1L treatments of interest.

Cox proportional hazards regression models were used to assess the association between sociodemographic characteristics and the following dependent variables: PFS, timeliness of starting treatment following metastatic diagnosis, and regional differences in metastatic status at first presentation (as de novo or progressed metastatic disease). Univariable models were performed, followed by adjusted models including all relevant explanatory variables. Ethnicity was not included in adjusted models due to collinearity between ethnicity and deprivation. Further models were performed including interaction terms between deprivation and 1L treatment, or age and region.

Wastage and Dose Reduction

Wastage and dose reduction statistics were calculated for patients with mBC who initiated a CDK4/6i on or after 01 January 2017. For each of ribociclib, palbociclib, and abemaciclib, the number and percentage of patients with 0–2 dose reductions was reported out of the total number of patients with valid doses and following the recommended dose reductions. The proportion of patients with 0–2 dose reductions was compared across the three CDK4/6is using a Chi-squared goodness of fit test. The cycle number for the first and second dose reductions was summarised, and the time to dose reduction (days) from the start of the previous cycle was also summarised. The total number of dose reductions per CDK4/6i was reported, and the cost (£) associated with wastage due to dose reduction was summarised. The number of patients with each of the CDK4/6is who subsequently switched to a different CDK4/6i was reported, and the CDK4/6i to which they switched was summarised, counting patients more than once if they switched more than once. The length of treatment (days) for each CDK4/6i was summarised. Univariable linear regression models were used to compare the length of treatment for each CDK4/6i, stratified by the number of dose reductions (0–2).

HCRU

Secondary care HCRU and costs during health state transition periods were calculated. For each treatment setting, the number of admissions/attendances per person per month (PPPM) were calculated. For inpatient admissions, the standardised cumulative inpatient bed days PPPM was estimated from the total number of nights spent in hospital.

In inpatient admissions, specified toxicity-related admissions were defined as those with a record of a chemotherapy side effect, including but not limited to neutropenic sepsis, cardiotoxicity and arrhythmia, diarrhoea and vomiting causing dehydration requiring admission to hospital, and fragility fractures. In outpatient appointments, toxicity-related care was defined as an outpatient appointment with a specialty that corresponds to the specified toxicity, including but not limited to cardiology, gastroenterology, and rheumatology or orthopaedic surgery.

All secondary care costs were calculated based on healthcare resource groups (HRGs) using the annually published national cost collection schedule (otherwise known as ‘reference costs’). Inpatient costs were generated by mapping ICD-10 and Office of Population Censuses and Surveys (OPCS) codes to the HRG code using a ‘grouper’ software provided by NHS Digital. Costs were inflated to 2023-24 pounds sterling using the NHS cost inflation index available from Jones and Burns 2021. Total costs for inpatient, outpatient, and emergency care attendance, as well as summary statistics monthly cost of attendances (PPPM) were reported. For inpatient and outpatient attendances, the unit cost of toxicity-related attendances was reported.

Results

Participants

We identified 221,008 adults with an HR+/HER2- BC diagnosis recorded in the registry between 01 April 2012 and 31 December 2022. After applying the remaining eligibility criteria, we identified 206,854 patients with an eBC diagnosis, 28,920 patients with an mBC diagnosis, and 29,311 patients who met the eligibility criteria and randomisation for proportional distribution between stage II and stage III for the NATALEE-aligned sub-cohort. The median follow-up duration was 75.6 months among patients with eBC, 65.5 months for those included in the NATALEE-aligned cohort, and 23.6 months for patients with mBC.

Epidemiology

Baseline demographic characteristics

Among patients with eBC, the mean (SD) age at index was 63.3 (13.4) years and most were white (88.2%). Among all patients with eBC (including NATALEE-aligned sub-cohort), a higher percentage were from the least deprived population quintile than from the most deprived quintile (23.2%; 47,914 vs. 15.2%; 31,461 for all patients with eBC). Among patients with mBC, the mean (SD) age at index was 65.9 (14.5) years and most patients were white (89.7%). The distribution of patients across deprivation quintiles was reasonably equal (least deprived: 20.6% vs. most deprived: 18.1%).

Baseline clinical characteristics

In the eBC cohort, most patients had a Charlson Comorbidity Index (CCI) score of zero (74.4%) and were initially diagnosed with a stage I tumour (47.3%). In the eBC cohort and NATALEE aligned sub-cohort, the prevalence of baseline comorbidities was low, with the most frequent being hypertension (all eBC: 2.4%). In the mBC cohort, most patients (67.1%) had CCI score >2. The most prevalent baseline comorbidity was hypertension (24.2%), followed by cardiomyopathy (11.5%), diabetes (7.9%), and CVD (6.3%). Most initially presented with eBC before progressing to mBC (59.1%). The mean (SD) time between initial diagnosis and mBC was 3.23 (2.34) years.

Progression

In the eBC cohort, a small proportion experienced a non-metastatic recurrence (6.8%) or a metastatic recurrence (9.1%), while nearly one-fifth (18.6%) died (due to any cause) during follow-up. The median time from ET initiation to non-metastatic recurrence was 37.1 (95% CI: 36.6 to 37.7) months and the median time to metastatic recurrence from ET initiation was 36.9 (95% CI: 36.2 to 37.5) months. The median time from ET initiation to death was 46.7 (95% CI: 46.2 to 47.2) months. Overall, when iDFS was considered, 29.6% of patients had an event. Compared with the eBC cohort, in the NATALEE-aligned sub-cohort, a higher proportion of patients experienced progression; 9.9% had a non-metastatic recurrence and 20.9% had a metastatic recurrence, while more than one-quarter (27.8%) died during follow-up. The median time from ET initiation to non-metastatic recurrence was 30.1 (95% CI: 29.0 to 31.3) months, while the median time to metastatic recurrence from ET initiation was 32 (95% CI: 31.0 to 33.1) months. The median time from ET initiation to death was 45 (95% CI: 44.0 to 46.0) months. Overall, when iDFS was considered, 43.4% of patients had an event (n=11,260).

Patients with eBC who had a non-metastatic recurrence during follow-up were more likely to have a higher level of deprivation (quintile 5 HR: 1.11; 95% CI: 1.05 to 1.18 vs. quintile 1), have an initial stage 2 BC diagnosis (HR: 1.44; 95% CI: 1.39 to 1.50) or stage 3 (HR: 2.46; 95% CI: 2.33 to 2.60), and be from the North East (HR: 1.42; 95 CI: 1.30 to 1.54) or South West (HR: 1.21, 95% CI: 1.12 to 1.31) of England. Patients who experienced a metastatic recurrence during follow-up were more likely to be post-menopausal (HR: 1.19, 95% CI: 1.16 to 1.23), have a higher level of deprivation (quintile 4 HR: 1.16; 95% CI: 1.10 to 1.22 and quintile 5 HR: 1.27; 95% CI: 1.21 to 1.34 vs. quintile 1), and have an initial BC diagnosis of stage 2 (HR: 2.55; 95% CI: 2.46 to 2.65 [vs. stage 1]) or stage 3 (HR: 7.16; 95% CI: 6.86 to 7.48 [vs. stage 1]). Geographical region did not appear to be a factor significantly associated with metastatic recurrence.

A total of 26,635 (12.9%) patients in the eBC cohort died during follow-up without progressing to mBC; 21.9% of these deaths were attributable to cancer, whereas 29.3% were toxicity related. In sharp contrast, 20,440 (70.7%) patients died in the mBC cohort during follow-up; 80.6% were attributable to cancer, while 9.1% were toxicity related.

Treatment Decisions and Pathway

Most patients with eBC did not receive any SACT (80.5%) or received one LOT (18.8%) during follow-up, while 69.1% received radiotherapy. Among those who received SACT, the mean (SD) time between diagnosis and first treatment was 91 (58.9) days. The proportion of patients who received SACT increased with stage of diagnosis (diagnosed stage I: 94.9% vs. diagnosed stage III: 30.6% with no SACT). Among patients with mBC, more than half (53.7%) received no SACT, more than one-quarter (27.2%; 7,880) received one LOT, and nearly one-fifth (19.0%) received ≥2 LOTs. Among patients with mBC who initiated treatment on or after 01 January 2017, the percentage of patients who received ≥2 LOTs increased to 30.8%, with a much lower percentage of patients receiving no SACT (24.6%). Overall, 44.8% of patients with mBC had radiotherapy, with this percentage increasing to 63.3% among those who initiated treatment on or after 01 January 2017. The time (SD) between diagnosis and first SACT treatment was 159 (384.6) days.

In the eBC cohort, the most common first LOT consisted of a combination of anthracyclines, fluoropyrimidines, other alkylating agents, and a taxane, while the most common second LOT consisted of CDK4/6is. In the mBC cohort, the most common first LOT consisted of CDK4/6is, while the most common second LOT was fluoropyrimidines. For those who initiated treatment from 01 January 2017 onwards, the percentage of patients who received a CDK4/6i in the first and second LOT settings increased. Among the mBC subcohort of patients who initiated treatment from 01 January 2017 onwards (n=12,939), 50.2% patients used a CDK4/6i. The most frequently used CDK4/6i was palbociclib (34.8%) followed by abemaciclib (10.5%), and ribociclib (6.8%). The median time from mBC diagnosis to treatment with any of these three CDK4/6is ranged from 43 to 58 days. The median treatment duration ranged from 336 to 461 days.

Among all patients in the eBC cohort (n=206,854), 3.5% discontinued an SACT regimen containing a category A or category B treatment within 6 months of initiation. Among those who had SACT, 14.4% discontinued treatment within 6 months. In the eBC cohort, 20,365 patients progressed to mBC during follow-up, of whom 38.0% received at least one regimen in SACT during follow-up. Among patients who received at least one regimen in SACT, 49.3% were adherent to treatment, although adherence was unknown for 30.8% of patients. There were 24,528

patients in the mBC cohort with follow-up extending beyond 01 January 2017. Among these patients, 922 were treated with ribociclib, of whom 10.6% received ECG outside of standard of care during ribociclib treatment.

Access to Treatment

A total of 48,652 and 9,849 patients were diagnosed with eBC and mBC, respectively, between 2020 and 2022. Generally, the distribution of patients between regions of England was similar to the overall adult aged population in each region, although the proportion of mBC in London was higher (10.6%) and slightly lower in the North East (7.1%). The distribution of patients with mBC and treated with a CDK4/6i was similar to the overall mBC regional distribution.

Among patients with mBC who started a category A SACT from 01 January 2017 onwards (n=10,127), the distribution of age categories was significantly different between categories of first LOT (chi-squared $P<0.001$); the proportion of patients from older age groups was higher among those who received a CDK4/6i (n=5,860) or 'other' (non-anthracycline or non-taxane) SACT as first LOT. There were significant differences in ethnicity by first LOT as well ($P=0.005$). There was no statistically significant difference in deprivation ($P=0.089$).

In the eBC cohort, patients aged 18–39, 40–49 and ≥80 years were less likely to experience a progression event, compared with those aged 50-59 years. Patients who received a taxane without an anthracycline as the first LOT were more likely to experience a progression event compared with those who received an anthracycline without a taxane. Deprivation quintile was not associated with progression. Compared with patients resident in London, progression was more likely in most regions except for the East of England and the North West.

Among patients with mBC who started category A SACT from 01 January 2017, patients aged between 60–69 and 70–79 years were less likely to experience a progression event than those aged 50–59 years. Patients who received an anthracycline with a taxane or a CDK4/6i as the first LOT were less likely to experience a progression event compared with those who received anthracycline without a taxane. Deprivation quintile was not associated with progression. Progression was less likely in the East Midlands and the North West than London and more likely in the East of England and West Midlands.

Comparing patients with mBC who initiated treatment within 31 days and those initiating after 31 days, age and deprivation were not associated with treatment timeliness. Those residing in the East Midlands, East of England, North West, or West Midlands were more likely to initiate treatment within 31 days than those residing in London. Comparing the sociodemographic characteristics of patients who presented with de novo mBC vs. progressed to mBC, there was no association with age or deprivation and mBC presentation. Patients residing in the West Midlands were more likely to present with de novo mBC than those in London.

Wastage and Dose Reduction

Among the 6,803 patients with mBC who initiated a CDK4/6i on or after 01 January 2017, 62% of patients treated with ribociclib had no dose reduction, while 54.1% of those treated with palbociclib and 52.8% treated with abemaciclib had no dose reduction. 29.5% of patients treated with ribociclib, 26.2% (969) treated with palbociclib, and 35.0% (369) treated with abemaciclib had one dose reduction; and 8.5% treated with ribociclib, 19.7% treated with palbociclib, and

12.2% with abemaciclib had two dose reductions (chi-squared $P<0.001$). The median number of cycles received before a first dose reduction for ribociclib and abemaciclib was 3 and was 4 for palbociclib. The median number of cycles until second dose reduction was eight for all CDK4/6is. The mean (SD) cost associated with wastage due to dose reduction was lower for ribociclib (£390 [£27]) than palbociclib (£3,127 [£708]) or abemaciclib (£1,707 [£694]). A higher proportion of all patients treated with ribociclib (9.1%; 85 of 939) switched to another CDK4/6i than those treated initially with palbociclib (2.5%; 117 of 4,861) or abemaciclib (6.2%; 90 of 1,449). Patients most frequently switched to palbociclib; 63.5% for those starting on ribociclib and 86.7% for abemaciclib. The length of treatment, regardless of the number of dose reductions was longer in those treated with palbociclib than ribociclib, and there was no difference between those treated with abemaciclib compared with ribociclib.

HCRU

All-cause and BC related:

The median rate of all-cause admissions ranged from 0.09 and 0.20 admissions PPPM across most transition periods, except for the period between non-metastatic recurrence and metastatic recurrence, which was higher (0.43 [IQR: 0.15 to 1.38] admissions PPPM). The mean number of all-cause bed days PPPM was higher for transitions from non-metastatic recurrence to metastatic recurrence (3.91 [SD 29.2] bed days PPPM) and metastatic recurrence to death (5.93 [SD 10.1] bed days PPPM) than other transitions. The median (IQR) cost associated with all-cause inpatient admissions was also higher for the transition from non-metastatic recurrence to metastatic recurrence (£550 [£204 to £1,555]) than other transitions. The proportion of patients with BC-related inpatient admissions was low across all transitions, with a maximum of 1.4% (transition from start of ET to death).

The median rate of all-cause outpatient appointments across most transition periods ranged from 0.09 to 0.75 appointments PPPM. Similar to inpatient admissions, the highest rate of patients with at least one all-cause outpatient appointment was during the transition from non-metastatic recurrence to metastatic recurrence, with a median (IQR) of 1.35 (0.51 to 3.09) appointments PPPM. The highest median all-cause cost was also during this period (£236 [£90 to £558] PPPM compared with £127 or less for the other transitions). The rate of emergency care attendance PPPM was low compared with inpatient and outpatient attendance, and was highest during the period of metastatic recurrence to death (median 0.22 PPPM, or approximately one visit per 4.5 months).

Toxicity-related:

Across all health state transition periods, infection (including tuberculosis reactivation) was the condition for which the highest proportion of patients had at least one related inpatient admission. Regardless of the toxicity-related condition, the median costs PPPM were higher for transitioning to metastatic recurrence than transitioning to death. For example, for cardiotoxicity or arrhythmias, the median (IQR) cost of admissions was £429 (£112 to £976) PPPM for non-metastatic recurrence to metastatic recurrence and £196 (£63 to £456) PPPM for non-metastatic recurrence to death. Across all health state transition periods, fragility fractures and cardiotoxicity or arrhythmia (i.e., cardiology) were the conditions for which the highest proportion of patients had at least one related outpatient appointments. In most cases, median numbers of appointments and costs PPPM were highest for those transitioning to metastatic recurrence.

Discussion

Key Results

- Using the registry and linked datasets from England, 95% of individuals with HER2- HR+ BC were diagnosed with eBC and 5% had mBC at the time of diagnosis between 2012 and 2022.
- Overall, iDFS was about 70% in the eBC cohort. Specifically, 7% experienced a non-metastatic recurrence, 9% progressed to mBC, 9% experienced a non-breast invasive cancer, and 19% died due to any cause. Our progression estimates were generally consistent with published real-world studies.
- In the NATALEE-aligned cohort, the iDFS was approximately 43%. Specifically, 10% experienced a non-metastatic recurrence, 21% progressed to mBC, 10% experienced a non-breast invasive cancer, and 28% died due to any cause. However, in comparison to the NATALEE trial, the real-world iDFS this study estimated was worse than that of the trial population. This discrepancy can be partly explained by the study population selection criteria among the entire eBC cohort (such as no exclusion of prior cancer) as possible differences that are present in the NATALEE-aligned sub-cohort used in this analysis, which yielded worse results than the main eBC cohort.
- Use of CDK4/6i as first LOT for mBC has been widely and generally consistently adopted across the country.
- While a mix of anthracyclines and taxane regimens are still the predominant treatment for eBC, the approval of abemaciclib shows rapid uptake of this treatment.
- Generally, the distribution of patients with eBC and mBC between the regions of England was similar to the overall adult aged population residing in each region. Furthermore, the regional breakdown of patients with mBC was similar to the one observed among patients with eBC. However, a slightly higher proportion of mBC cases was observed in London (10.6% compared to 8.2% for eBC) and a slightly lower proportion of mBC cases was observed in the North East at (7.1%. vs. 8.1% for eBC).
- However, these differences may be related to a younger population residing in London. There was also some indication of regional differences in progression risk among patients with eBC and mBC. However, these regional differences were not consistent between the eBC and mBC analysis and were not associated with deprivation, making it hard to draw any clinically relevant conclusions. Nevertheless, some age differences in progression risk were also observed among eBC patients, with lower risk in younger ages.
- This study found limited sociodemographic differences in event free survival among patients with eBC or PFS among patients with mBC; however, patients with eBC who experienced a metastatic recurrence during follow-up were more likely to have a higher level of deprivation. Given that there are important links between race/ethnicity and economic deprivation, this finding aligns with prior studies conducted in the United States (US), which have reported that racial and ethnic minority groups, including Black women and American Indians, experience persistent inequities in BC outcomes. In our analysis, deprivation and ethnicity were collinear, so ethnicity was not included in multivariable models.

- Timeliness of treatment as well as having de novo vs. progressed mBC were also not associated with age or deprivation.
- Among patients with mBC and treated with a CDK4/6i, wastage and the associated cost due to dose reduction was lower for ribociclib than palbociclib or abemaciclib. Specifically, the mean (SD) cost associated with wastage due to dose reduction was lower for ribociclib (£390 [£27]) than palbociclib (£3,127 [£708]) or abemaciclib (£1,707 [£694]). These results are in line with prior studies conducted in the US and Europe. Dose reductions for palbociclib and abemaciclib are expected to result in drug wastage, as capsules must be discarded to achieve a lower dose. On the other hand, ribociclib dose adjustment can be accomplished by altering the number of tablets taken, without the need for a new prescription, thus resulting in less drug wastage.
- HCRU and associated costs varied by progression transition states but were generally more extensive as progression worsened, particularly for non-metastatic recurrence and metastatic recurrence.

Limitations

- ET is unreliably recorded in the registry and linked datasets; with fewer than 25% of patients identified having ET recorded among the study population, this data was therefore not included in the analysis (a priori methodological decision). Other treatment-related variables, such as adherence, are also poorly recorded within the datasets.
- Secondary care data are currently only available for 60 days preceding the earliest BC diagnosis. This period may have been too short to comprehensively capture all comorbidities and other covariates. As the mBC cohort includes those who progressed, baseline data was available from eBC diagnosis and may account for the higher prevalence of comorbidities among patients with mBC. Secondary care data are primarily generated for reimbursement purposes; therefore, data may not always meet the rigorous needs of real-world evidence research.
- Dose reduction and associated costs may be underestimated for ribociclib. Unlike palbociclib and abemaciclib, ribociclib is only available in one strength and extra tablets are prescribed to make the target dose. Stepping down doses would, therefore, use fewer tablets rather than being issued a new box. Therefore, a change in dose of ribociclib mid-cycle, and the wastage costs, are less likely to be identified in the data. Nevertheless, due to ribociclib single strength, wastage costs should be lower.
- Reference costs were used in the calculation of healthcare costs. There was a large degree of missingness when mapping HRGs to reference cost recording that was not anticipated prior to analysis. Median costs among healthcare interactions with an HRG were used to impute missing values; however, the accuracy of this method cannot be determined.

Generalisability

These results should be generalisable among all patients with HR+/HER2- BC in England given the national dataset used and minimal exclusion criteria applied. However, results may have limited generalisability in geographies with a different healthcare system (England has a national

healthcare system) where diagnosis and treatment processes may be different, affecting outcomes among patients.

Conclusion

This study provides a contemporaneous analysis of the clinical and economic burden of HR+/HER2- eBC and mBC in England using real-world data. Approximately 10% of patients with eBC progressed to mBC and nearly a third (30%) of patients with eBC had an invasive disease event. The analysis reported limited evidence on sociodemographic inequalities in care and treatment access. As expected, CDK4/6is are now the mainstay of treatment for mBC, and used in all regions of England. Furthermore, use of ribociclib is associated with lower wastage than palbociclib or abemaciclib. Due to the substantial costs of oncology drugs and the potential for significant drug wastage from dose adjustments and early discontinuation, drug wastage is a crucial factor in the economic evaluations of these medications. Further research is required to evaluate the effect of CDK4/6i use on long-term clinical and economic outcomes.