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TITLE:

Real-World Event-Free Survival and Real-World Pathological Complete Response in Early-Stage Triple-Negative Breast Cancer: Concordance with Estimates from the control arm of the KEYNOTE-522 Trial

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ABSTRACT

Background: Clinical outcomes such as event-free survival (EFS) and pathological complete response (pCR) have the potential to support medical product development for early-stage breast cancer. Replicability of trial estimates for these endpoints in the real world is needed.

Objective: To assess the concordance of real-world (RW) EFS and pCR for early-stage triple negative breast cancer (eTNBC) with estimates from the KEYNOTE-522 clinical trial control arm.

Methods: This retrospective study used electronic health record data from US community oncology practices within The US Oncology Network. It applied a target trial emulation framework to develop a RW cohort aligned with KEYNOTE-522, with eligibility determined at the date of neoadjuvant treatment initiation. Patients newly diagnosed with eTNBC between 1/1/2020 and 3/30/2022 were followed through 7/18/2023. To balance baseline characteristics

between the RW and clinical trial populations, a matching-adjusted indirect comparison (MAIC) was implemented using inverse probability of treatment weighting (IPTW). Relative risks (RRs) for rwpCR and hazard ratios (HRs) for rwEFS were calculated, before and after MAIC-weighting.

Results: A total of 311 patients in the RW cohort met eligibility criteria aligned with the KEYNOTE-522 clinical trial. The adjusted HR for rwEFS and RR for rwpCR were 1.00 (95% CI: 0.72, 1.38; p=0.980) and 0.96 (95% CI 0.80, 1.14; p=0.627), respectively. A sensitivity analysis for rwEFS that censored RW patients at the time of immunotherapy treatment gave consistent results.

Conclusion: EFS and pCR were concordant between the RW cohort and the KEYNOTE-522 control arm. RW results can reflect clinical trial outcomes in a matched real-world population. These findings increase confidence in the replicability of early-stage trial estimates in RW settings.

KEYWORDS: Triple-negative breast cancer, Event-free survival, Pathological complete response, Real-world evidence, Trial emulation

BACKGROUND

In oncology, primary endpoints used to evaluate therapy often include response rate, overall survival (OS), and progression-free survival (PFS).(1) Previous studies evaluating the alignment between cancer progression endpoints from randomized controlled trials (RCT) and their real-world data (RWD) counterparts have focused on advanced-stage cancers, including non-small cell lung cancer, melanoma, breast cancer, and thyroid cancer.(2-4) With advances in therapy and better outcomes for patients, intermediate assessments of clinical outcomes for progression and recurrence are also needed in real-world (RW) settings.(2) This may be especially important

in cancers with high survival rates, such as breast cancer. In the United States, localized triple-negative breast cancer (TNBC) has a 5-year relative survival around 92%.⁽⁵⁾ TNBC is an aggressive subtype of breast cancer for which intermediate endpoints such as event-free survival (EFS) and pathological complete response (pCR) can provide timely insights into treatment outcomes.⁽⁶⁾ For instance, in 2013, the FDA recognized the utility of pCR as an endpoint to support accelerated approval of therapy in breast cancer in neoadjuvant settings and released guidelines for its use in industry in July 2020.⁽⁷⁾ Population-based studies have supported the use of pCR as a surrogate survival endpoint in real-world settings, especially in aggressive tumor subtypes such as triple-negative early breast cancer.^(8, 9) Nonetheless, the validity of pCR as a surrogate survival endpoint remains to be confirmed.^(10, 11) EFS has been identified by the FDA as a surrogate endpoint for OS, but its concordance with RW settings has not been evaluated.^(12, 13) KEYNOTE-522 demonstrated improved EFS and pCR when pembrolizumab was added to standard neoadjuvant chemotherapy and continued as adjuvant monotherapy, compared with chemotherapy alone in patients with high-risk, early-stage TNBC.^(14, 15)

Reliable early-stage real-world endpoints, such as rWEFS and rwpCR for breast cancer, can help bridge the gap between clinical trial efficacy and real-world effectiveness, accelerate product development, inform regulatory decisions, payer and post-approval needs, as well as improve clinical practice. Studies are needed to evaluate the extent to which real-world endpoints can replicate RCT-based estimates, and to validate estimates generated using equivalent real-world definitions for specific trial endpoints.^(2, 4) To date, no studies have examined the replicability of rWEFS and rwpCR in real-world early TNBC population. This study adopted a target trial emulation framework⁽¹⁶⁻¹⁹⁾ to evaluate RW estimates of EFS and pCR in early-stage TNBC and compare them with published clinical trial results from the KEYNOTE-522 trial control arm as a benchmark. The goal of this study was to evaluate concordance

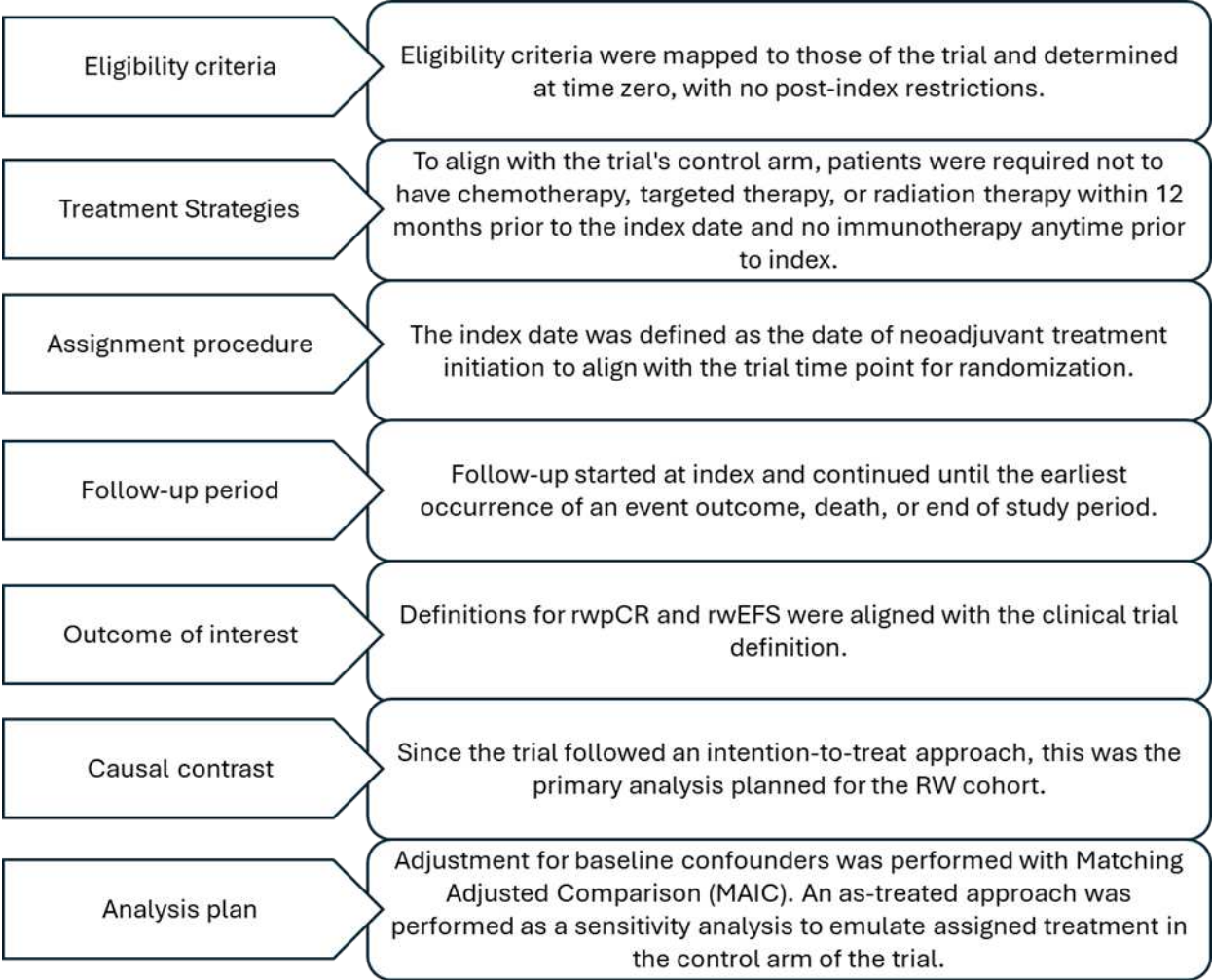
between the RW and clinical trial findings to advance our understanding of data quality and readiness to support product development.

METHODS

Study Design

This retrospective observational cohort study used iKnowMed® (iKM) EHR data from US community oncology practices within The US Oncology Network. The design followed seven key features of a target trial emulation framework to establish eligibility, treatment strategy, assignment procedure, follow-up period, outcomes, causal contract, and analysis plan (Figure 1).

Figure 1: Study Design following steps from a target trial emulation framework



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The US Oncology Network includes over 2,700 affiliated physicians operating in over 600 sites of care across states. Approximately 1.2 million US cancer patients are treated annually in The US Oncology Network.(20) In addition to the de-identified data available in structured fields, a custom chart abstraction was conducted to gather additional information about clinical trial-based eligibility criteria. The study was reviewed and approved by the Castle Institutional Review Board (IRB). Since this study is based on secondary, retrospective data and published data, the IRB granted a waiver of informed consent.

Population

The real-world cohort was developed using eligibility criteria aligned with those of the KEYNOTE-522 trial (Table 1). Eligibility was determined at the date of neoadjuvant treatment initiation (index date) to align with the trial's randomization time point. Eligible patients were ≥ 18 years and had received a diagnosis of HER2-negative disease with a pathology report available for the initial breast cancer diagnosis (Stage II-III). All patients were diagnosed during the study identification period, 1 January 2020 to 31 March 2022. To align with the intent of replicating the trial's control arm, RW patients were required not to have received chemotherapy, targeted therapy, or radiation therapy within 12 months prior to the index date and to have no prior exposure to immunotherapy (IO). No restrictions on post-index treatment for eTNBC were imposed on the eligibility criteria for the RW cohort, in accordance with target trial emulation methodology to avoid selection bias. Patients were excluded if they were diagnosed with or received treatment for another primary cancer before the study observation period, or if they participated in an interventional clinical trial before the study observation period (18 July 2023).

Endpoints

EFS was defined as the time interval from initiation of neoadjuvant therapy until the first of the following events: 1) progression of disease, if the patient did not have surgery for breast cancer before the end of follow-up, 2) locoregional or metastatic recurrence, 3) additional primary cancer diagnosis, or 4) death due to any cause. Additional criteria defining EFS are shown in Table 2.

pCR was met if there was no evidence of tumor in the resected specimen following initiation of neoadjuvant therapy. Timing of surgery was defined as the first surgery for breast cancer after initiation of neoadjuvant treatment. While documentation of residual tumor was assessed by a local pathologist for the clinical trial, in the RWD, this criterion relied on either pathology report, scan report, or physician documentation, as available within the patients' charts. Additional criteria defining pCR are shown in Table 2.

KEYNOTE-522 Data

EFS data for the control arm of KEYNOTE-522 were extracted from the published paper(14) using digitizing methods(21, 22) and Web Plot Digitizer(23). pCR results from the first interim analysis of KEYNOTE-522 control arm(15) were used to assess concordance with the RW population, as this was the prespecified time point to statistically evaluate pCR in the clinical trial.

Patients in the control arm of KEYNOTE-522 received neoadjuvant placebo plus chemotherapy. After definitive surgery, they received adjuvant placebo plus chemotherapy.

EFS

Unadjusted and MAIC-adjusted Kaplan-Meier (KM) curves were produced for the control arm of the trial and the RW cohort. Since KEYNOTE-522 followed an intention-to-treat (ITT) approach, this was used as the primary analysis. For this analysis, patients were censored at the time of an event, death, or the end of the study period. An as-treated (AT) analysis was also conducted in which patients were censored when they initiated immunotherapy to further align the real-world treatment journey for eligible patients with that of the trial control arm. Unadjusted and MAIC-adjusted hazard ratios (HRs), 95% confidence intervals (CIs), and p-values were calculated using Cox modeling, with the trial control arm as the reference group.

pCR

As pCR is a proportion, relative risks were calculated from a generalized linear model with a log-link function and a binomial distribution. Risk ratios (RRs), 95% CIs, and p-values were reported, with the trial comparator arm as the reference group.

Statistical Analysis

To balance the clinical trial and RW patient populations on available baseline characteristics, a matching adjusted indirect comparison (MAIC) was implemented (Signorovitch 2010 & 2012), which adjusted for age group, sex, race, ethnicity, and ECOG score. The average treatment effect on the treated in the trial was estimated from the published results of KEYNOTE-522.(24)

In this approach, each patient in the control arms of the clinical trial will be assigned a weight of 1, and the patients in the RW cohorts will be assigned a weight of $ps/(1-ps)$ where ps is the patient's propensity score, calculated from a multivariable logistic regression model with the dependent variable being receiving the treatment (ie, clinical trial=1 and RW=0), and the baseline variables as covariates.

Comparison between the estimates from the control arm of KEYNOTE-522 and RW endpoints was done in a descriptive manner (i.e. without formal hypothesis testing) by visually describing outcomes in each population using Kaplan Meier curves, and comparing outcomes by study design using Cox proportional hazard models and generalized linear models, setting the KEYNOTE-522 control arm as the reference group, to generate effect estimates, and their associated 95% CIs and p values. In this descriptive analysis, concordance was assessed based on: (1) Visual inspection of overlap of the KM curves for the RW cohort and the KEYNOTE-522 control arm, (2) Examination of the HRs and RRs and their corresponding 95% confidence intervals (CI) to describe the range of estimates compatible with the data.

RESULTS

Baseline Characteristics

A total of 311 patients met RW eligibility criteria aligned with the KEYNOTE-522 clinical trial. Compared to the KEYNOTE-522 control arm, patients in the RW cohort were older (24% were aged ≥ 65 years vs. 12%) and included a greater proportion of patients with stage III (45% vs. 25%) and ECOG ≥ 1 (41% vs. 13%). After MAIC adjustment, the resulting effective sample size (ESS) was 185, and the baseline characteristics of the RW cohort were similar to the KEYNOTE-522 control arm (Table 3).

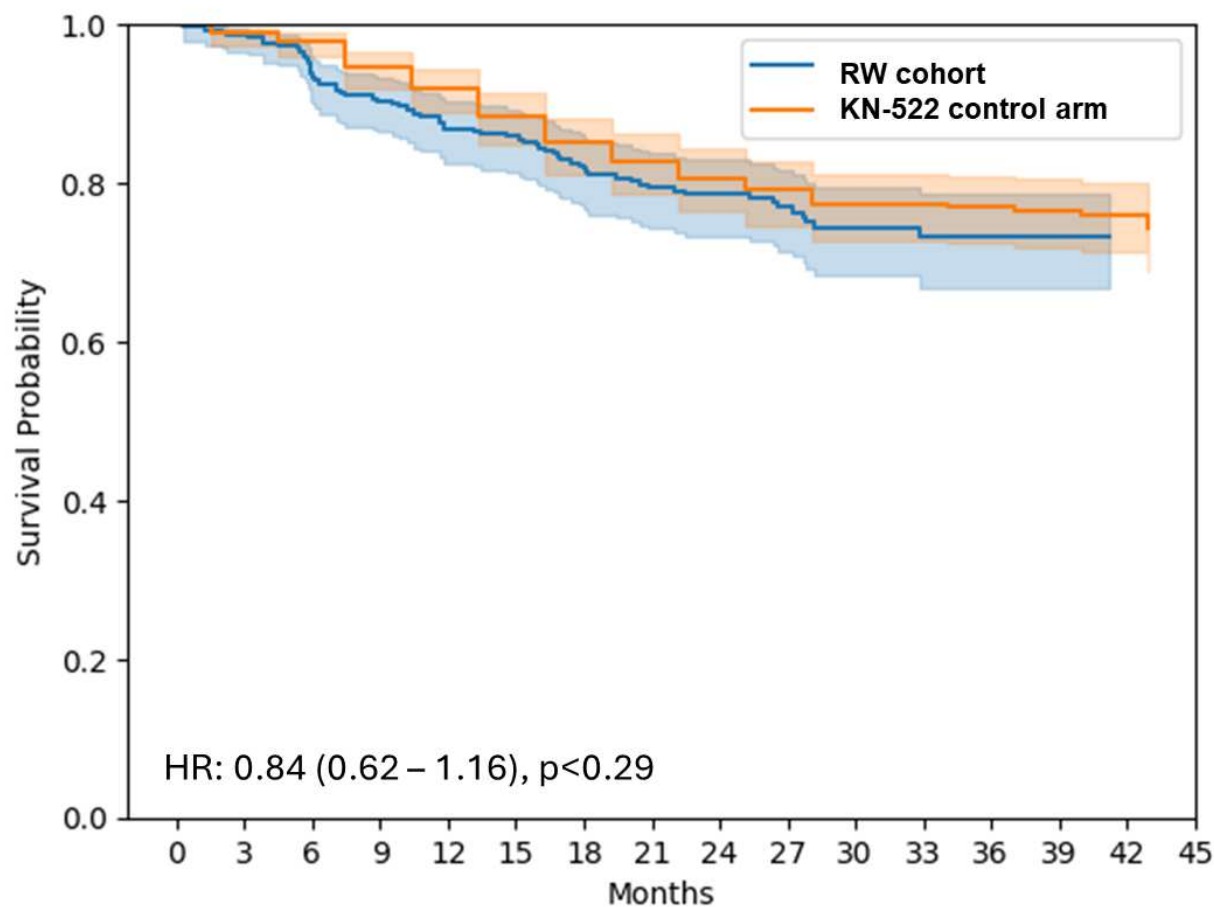
Endpoint Concordance

Concordance was achieved between the RW cohort and the KEYNOTE-522 control arm in all analyses, with the strongest concordance observed after MAIC adjustment and in the ITT analysis.

176 **EFS**

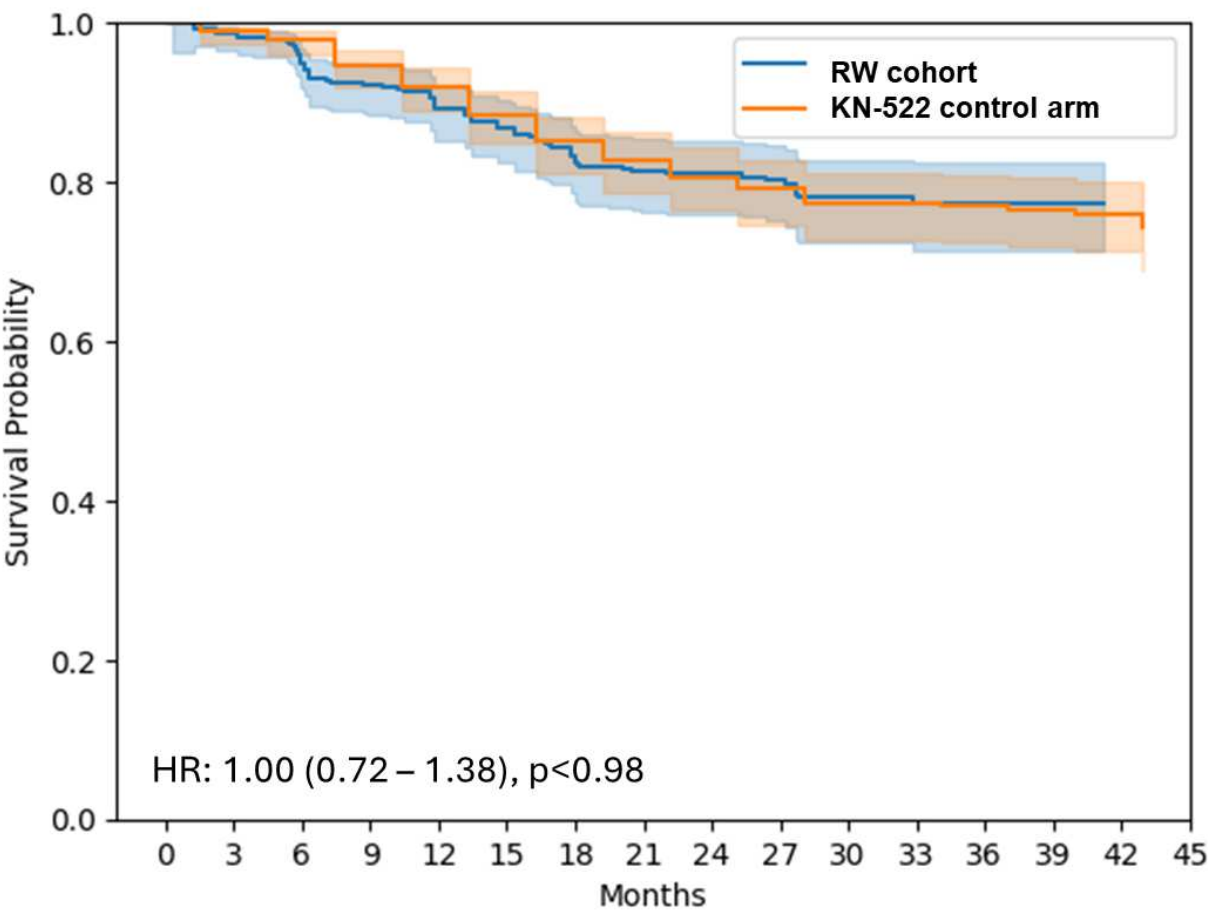
177 Median EFS was not reached in the KEYNOTE-522 trial control arm(14), and it was not reached
178 in the RW cohort. Figure 2 shows the unadjusted and MAIC-adjusted Kaplan-Meier EFS curves
179 for both the ITT and AT analyses.

180 **Figure 2: Kaplan-Meier Curves of Event-Free Survival for the KEYNOTE-522 Control Arm**
181 **(N=311) and RW Cohort (unadjusted N=311, adjusted ESS N=185)**

182 **a. Unadjusted Intention-To-Treat Analysis**

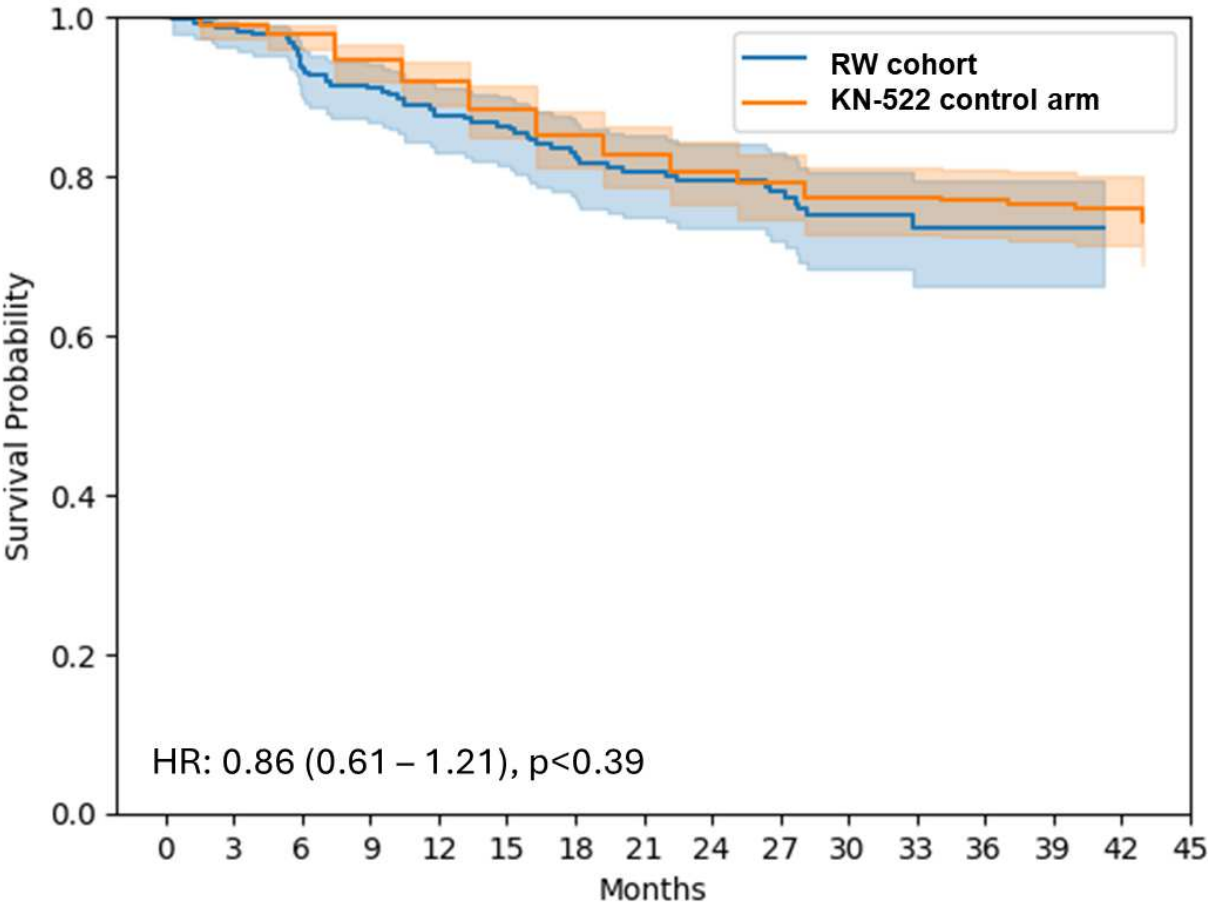
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184 **b. MAIC-Adjusted Intention-To-Treat Analysis**



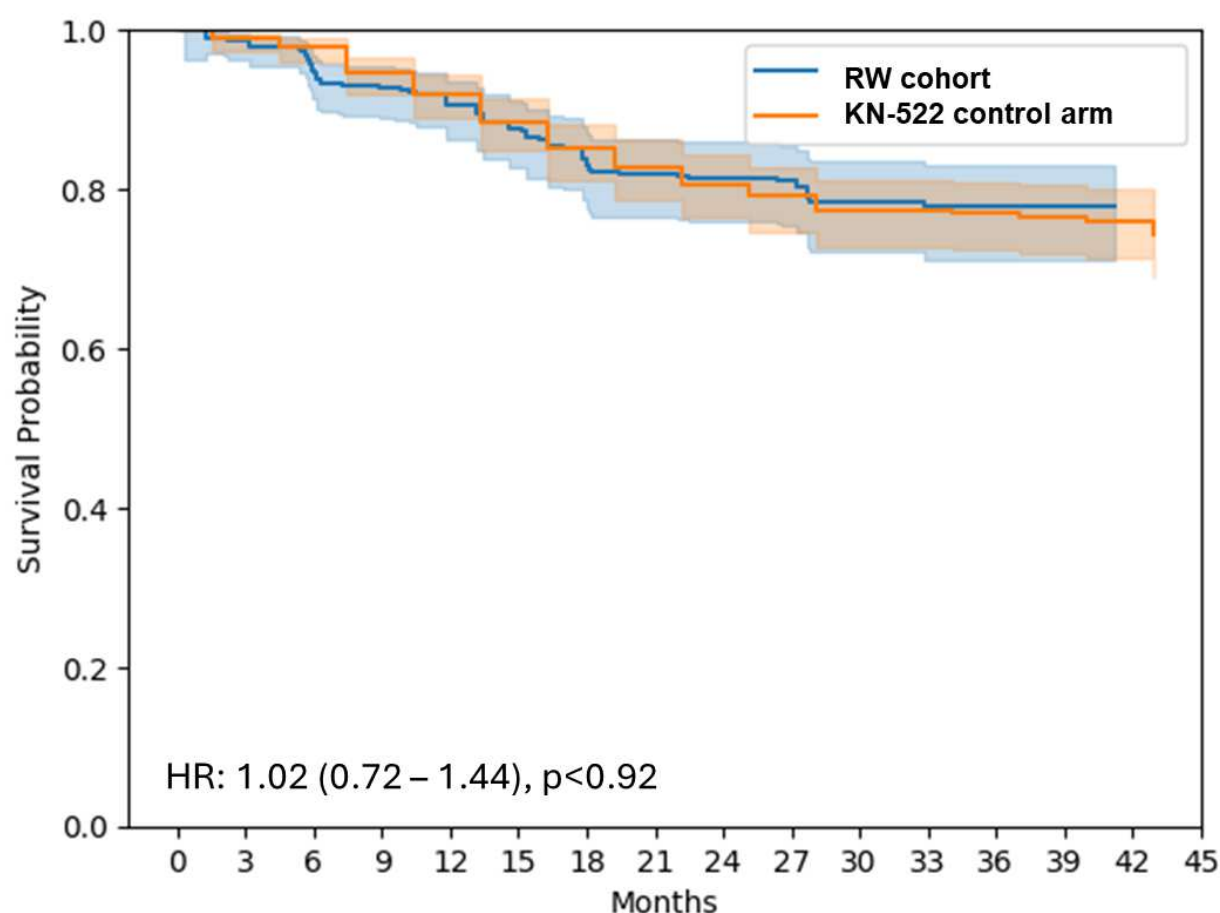
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186 **c. Unadjusted As-Treated Analysis**



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188 **d. MAIC-Adjusted As-Treated Analysis**



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 190 In the primary (ITT) analysis of EFS, the unadjusted and MAIC-adjusted HRs were 0.84 (95% CI
 191 0.62, 1.16; $p=0.289$) and 1.00 (95% CI 0.72, 1.38; $p=0.980$), respectively. Median follow-up time
 192 in the ITT analysis was 24.6 months. In the AT analysis, the unadjusted and MAIC-adjusted HRs
 193 were 0.86 (95% CI 0.61, 1.21; $p=0.387$) and 1.02 (95% CI 0.72, 1.44; $p=0.918$), respectively.
 194 Median follow-up time in the AT analysis was 19.8 months.

195 **pCR**

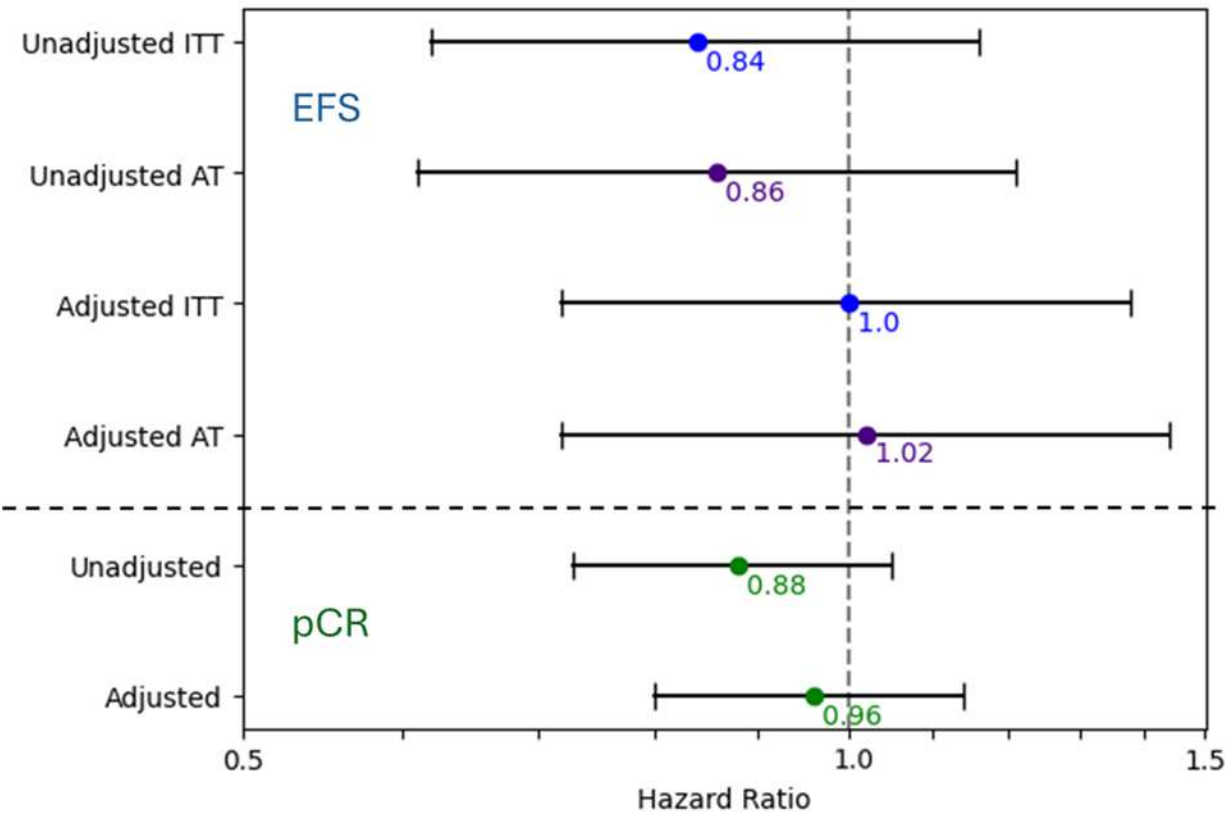
196 pCR in the control arm of the KEYNOTE-522 trial was 51.2%(15), and it was 44.3% in the real-
 197 world cohort. The unadjusted and MAIC-adjusted RRs were 0.88 (95% CI: 0.73, 1.05; $p=0.156$)
 198 and 0.96 (95% CI: 0.80, 1.14; $p=0.627$), respectively (Table 4).

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A forest plot illustrating the unadjusted and MAIC-adjusted estimates for pCR and EFS is provided in Figure 3.

Figure 3: Forest Plot of Endpoints Comparing the Real-World Cohort and KEYNOTE-522

Control Arm



Legend: Ratio measures are hazard ratios for EFS and risk ratios for pCR. All estimates include the KEYNOTE-522 control arm as the reference group. Error bars represent 95% confidence intervals.

It shows how confounding is statistically adjusted through MAIC for both endpoints, as well as the impact of the sensitivity analysis (intention-to-treat vs. as-treated approach) for EFS.

DISCUSSION

This study of real-world data from community oncology demonstrated that, with the application of a target trial emulation framework, real-world endpoints can approximate clinical trial

estimates in eTNBC patients in a matching population. The current findings increase confidence in the reliability and replicability of rwEFS and rwpCR in eTNBC.

After applying eligibility criteria that aligned with the KEYNOTE-522 clinical trial, real-world patients were slightly older, with marginally higher disease burden and lower performance status. This points to the greater heterogeneity of patients in the RW setting. Other studies have also observed that patients in community settings are generally older, more racially diverse, and of lower socioeconomic status than those enrolled in cancer clinical trials.(25-29) The greater heterogeneity of patients in RW practice highlights the importance of estimating clinical outcomes in this setting in addition to estimates from RCTs.

MAIC adjustment improved the balance of baseline characteristics across the clinical trial and RW populations. Median observed follow-up was longer in the ITT analysis of EFS compared to the AT analysis (24.6 months versus 19.8 months) as patients who received subsequent IO therapy in the adjuvant setting were censored. Nonetheless, the AT analysis did not appreciably change the survival estimates, suggesting that censoring was non-informative, and that receipt of IO was not confounded by disease progression and did not distort the RW survival estimates. In KEYNOTE-522, median EFS was not reached(14), and pCR was 51.2% in the control arm(15). These results are comparable to those of the BrighTNess, NeoSTOP, and CALGB40603 clinical trials, supporting the choice of KEYNOTE-522 as a benchmark trial for evaluating the concordance of real-world endpoints in TNBC.(30-32)

The replication of early-stage cancer endpoints using RW evidence is a rapidly evolving area of research to better understand treatment effectiveness outside the clinical trial setting.(33)

Despite guidance from the Food and Drug Administration (FDA) and other regulatory bodies, as well as ongoing initiatives to validate RW response from groups such as Friends of Cancer Research, no consensus exists on the specific methods for demonstrating concordance with trial endpoints in RW settings.(34-36) This study used a target trial emulation framework to ensure a robust methodological approach, minimizing potential sources of bias.(37, 38)

Previous studies have replicated clinical trial results for late-stage endpoints with mixed results. For instance, Ton *et al.* showed that overall survival can be replicated with RWD in NSCLC.(4) Chesang *et al.* broadly emulated survival outcomes from a prostate cancer trial and highlighted challenges like the timing of treatment.(39) Tan *et al.* identified variability in endpoint concordance, emphasizing the importance of analytic decisions.(40) The current study is among the first to contribute to the validation of rwEFS and rwpCR in early-stage TNBC. Reliable early-stage endpoints are needed for timely, actionable insights into treatment effectiveness.

Limitations

Although a target trial emulation framework and MAIC adjustment address confounding by balancing baseline characteristics between the RW cohort and clinical trial arm, adjustment was limited to data available for both populations, and residual and unmeasured confounding may remain. For example, based on KEYNOTE-522 reporting, ten potential confounders were available for adjustment. BMI, BRCA status, and Ki-67 expression are potential confounders that could not be included in the MAIC. Nonetheless, the impact of the MAIC adjustments was relatively small on the unadjusted versus adjusted hazard ratios and risk ratios, indicating that residual confounding may be minimal, so that their impact on endpoint estimates is likely minor. This study may be limited by differences in the timing of assessments, particularly as events underlying rwEFS endpoint were not evaluated on a fixed schedule, as patients in the trial were. Misclassification bias is possible as the study used iKM EHR data, which are collected for clinical practice and subject to missingness and coding errors. This may introduce some level of misclassification of diagnoses, events, or procedures of interest in the study. Likewise, some variables of interest may not be complete across the entire population. For instance, patients missing key matching variables were not included in the RW cohort (e.g., ECOG was poorly documented, and patients missing ECOG performance status were excluded).

Finally, results from this study may be most generalizable to other community oncology practices and those using the iKM EHR, as data collection varies across health systems.

CONCLUSIONS

Real-world endpoints rwEFS and rwpCR for eTNBC are concordant with clinical trial estimates when key study design aspects are aligned and high-quality EHR data are leveraged. These findings increase confidence in the replicability of trial estimates in a matched RW population for clinical decision-making.

List of Abbreviations:

- Disease / clinical context
 - TNBC: Triple-negative breast cancer
 - eTNBC: Early-stage triple-negative breast cancer
- Endpoints
 - EFS: Event-free survival
 - rwEFS: Real-world event-free survival
 - pCR: Pathological complete response
 - rwpCR: Real-world pathological complete response
 - OS: Overall survival
 - PFS: Progression-free survival
 - RR: Response rate / Risk ratio (clarify at first use per journal preference)
- Study design / methods
 - RWD: Real-world data
 - RWE: Real-world evidence

- 289 ○ RCT: Randomized controlled trial
- 290 ○ MAIC: Matching-adjusted indirect comparison
- 291 ○ IPTW: Inverse probability of treatment weighting
- 292 ○ KM: Kaplan–Meier
- 293 ○ HR: Hazard ratio
- 294 ○ CI: Confidence interval
- 295 ○ ITT: Intention-to-treat
- 296 ○ AT: As-treated
- 297 ○ ESS: Effective sample size
- 298 • Data / setting
- 299 ○ EHR: Electronic health record
- 300 ○ iKM: iKnowMed®
- 301 ○ ECOG: Eastern Cooperative Oncology Group (performance status)
- 302 • Biomarkers / clinical
- 303 ○ HER2: Human epidermal growth factor receptor 2
- 304 ○ ER: Estrogen receptor
- 305 ○ PR: Progesterone receptor
- 306 • Regulatory / organizations
- 307 ○ FDA: Food and Drug Administration
- 308 ○ IRB: Institutional Review Board

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310 **DECLARATIONS**

311 **Ethics approval and consent to participate:**

This retrospective study was reviewed and approved by the Castle IRB. As the study involved secondary use of existing, de-identified data, a waiver of informed consent was granted by the IRB.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets generated and analyzed during the current study are not publicly available as they are subject to a contractual agreement with Ontada. This is legally required in order to safeguard patient information and follow compliance rules under HIPAA. The underlying code for this study is not publicly available for proprietary reasons.

Competing interests:

Authors JRE, AH, and KD were employed by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc., Rahway, NJ, USA. Authors declare no financial or non-financial competing interests.

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Authors' contributions

All authors (CB, JP, MC, ZS, PC, JRE, AH, KD) made substantial contributions to the conception and design of the study. MC and ZS performed statistical analyses. All authors (CB, JP, MC, ZS, PC, JRE, AH, KD) participated in the interpretation of results and reviewed and approved the final manuscript.

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Table 1: KEYNOTE-522 and Real-world Eligibility Criteria of Patients with eTNBC

KEYNOTE-522 Trial Eligibility Criteria	Corresponding Real-World Eligibility Criteria
Inclusion criteria from KEYNOTE-522	
Newly diagnosed, locally advanced, centrally confirmed TNBC, as defined by the most recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines.	Documentation of all the following: - Pathology report available at the time of initial breast cancer diagnosis - Disease stage II or III at diagnosis - Negative results for biomarkers ER, PR, and HER2 Patients were ineligible if disease stage was IA, IB, I, IV for breast cancer during the study identification period.
Previously untreated locally advanced non-metastatic (M0) TNBC defined as the following combined primary tumor (T) and regional lymph node (N) staging per	Documentation of T1c, N1-N2, T2, N0-N2, T3, N0-N2 or T4a-d, N0-N2 closest to diagnosis.

current American Joint Committee of Cancer (AJCC) staging criteria for breast cancer as assessed by the investigator based on radiological and/or clinical assessment: • T1c, N1-N2 • T2, N0-N2 • T3, N0-N2 • T4a-d, N0-N2	
Core needle biopsy consisting of at least 2 separate tumor cores from the primary tumor at screening to the central laboratory.	Not Applicable ¹
Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 performed within 10 days of treatment initiation.	Documentation of performance status ECOG (or Karnofsky converted to ECOG) score of 0 or 1 closest to index date.
Adequate organ function.	Not Applicable ¹
Males and female participants of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 12 months after the last dose of study treatment for participants who have	Not Applicable ¹

received cyclophosphamide, and 6 months after the last dose of study treatment for participants who did not.	
Exclusion criteria from KEYNOTE-522	
History of invasive malignancy ≤ 5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.	Excluded patients diagnosed with or who received treatment for another primary cancer following initial diagnosis through the index date
Received prior chemotherapy, targeted therapy, and radiation therapy within the past 12 months.	Excluded patients who received systemic anticancer treatment or radiation for breast cancer within 12 months prior to index
Received prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), anti-programmed death - ligand 1 (anti-PD-L1), or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g., cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4], OX-40, CD137 [tumor necrosis factor receptor superfamily member 9 (TNFRSF9)]) or previously participated in a pembrolizumab (MK-3475) clinical study.	Excluded patients who received neo-adjuvant or adjuvant immunotherapy at any time before and including the index date

Currently participating in or has participated in an interventional clinical study with an investigational compound or device within 4 weeks of the first dose of treatment in this current study.	Excluded patients who participated in an interventional clinical trial following diagnosis and through index date
Received a live vaccine within 30 days of the first dose of study treatment.	Not Applicable ¹
Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs).	Excluded patients with documentation of any of the following autoimmune diseases during the 2 years prior to index: rheumatoid arthritis, psoriasis, multiple sclerosis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, Hashimoto's autoimmune thyroiditis, sarcoidosis, polymyalgia rheumatica, scleroderma, psoriatic arthritis, Sjogren's syndrome, Guillain-Barre syndrome, Graves' disease, Addison's disease, Idiopathic thrombocytopenia, Myasthenia gravis, Ankylosing spondylitis
Diagnosis of immunodeficiency or is receiving systemic steroid therapy (i.e., dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within	Not Applicable ¹

7 days prior to the first dose of study treatment.	
Known history of Human Immunodeficiency Virus (HIV).	Excluded patients with documentation of AIDS/HIV within 6 months prior to or on index.
Known active Hepatitis B or Hepatitis C.	Excluded patients with documentation of hepatitis B or hepatitis C infection within 6 months prior to or on index.
History of (non-infectious) pneumonitis that required steroids or current pneumonitis.	Excluded patients with documentation of pneumonitis any time prior to index, on index date, or 30 days post index.
Active infection requiring systemic therapy.	Excluded patients with documentation of active infection requiring systemic therapy 30 days pre or post and including index.
Significant cardiovascular disease, such as: history of myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months OR congestive heart failure (CHF) New York Heart Association (NYHA) Class II-IV or history of CHF NYHA Class III or IV.	Excluded patients with documentation of congestive heart failure (CHF), acute myocardial infarction (MI) or history of myocardial infarction within 6 months prior to or on index.
Pregnant or breastfeeding or expecting to conceive children within the projected duration of the study, starting with the screening visit through 12 months after the	Not Applicable ¹

last dose of study treatment for participants who have received cyclophosphamide, and for 6 months after the last dose of study treatment for participants who have not.	
Known hypersensitivity to the components of the study treatment or its analogs.	Not Applicable ¹
Known history of active tuberculosis (TB, Bacillus Tuberculosis).	Excluded patients with documentation of tuberculosis within 6 months prior to or on index

¹Not applicable to real-world settings as these are not reliably documented in the EHR.

Table 2. Real-World Elements to Define Pathological Complete Response (pCR) and Event-Free Survival (EFS) Based on the KEYNOTE-522 Clinical Trial Definitions

KEYNOTE-522 Endpoint Elements		Corresponding Real-World Endpoint Elements
pCR		
Time of definitive surgery		Date of first surgery for breast cancer after initiation of neoadjuvant treatment (index date)
(ypT0/Tis) No invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement following completion of neoadjuvant systemic therapy by the		Documentation of pathological complete response with no documentation of residual tumor in breast

American Joint Committee on Cancer (AJCC) staging criteria (7 th edition) assessed by the local pathologist at the time of definitive surgery.	
(ypT0 ypN0) No residual invasive and in situ cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sample regional lymph nodes following completion of neoadjuvant systemic therapy by AJCC staging criteria (7 th edition) assessed by the local pathologist at the time of definitive surgery.	Documentation of pathological complete response with no documentation of residual tumor in breast and lymph nodes
EFS	
Randomization date	Initiation of neoadjuvant treatment (index date)
Progression of disease that precludes definitive surgery	Earliest date of documented disease progression or recurrence that occurs during neoadjuvant therapy and results in no surgery for breast cancer prior to the end of follow-up
Date of progression of disease (Subjects who had locoregional progressive disease (PD) - as assessed radiologically during the neoadjuvant treatment phase, but underwent definitive surgery and had clear margins, will	Date of documented disease progression If patients had surgery for breast cancer during the study observation period with no mention of positive margins, they were not classified as having an EFS event.

not be classified as having an EFS event. If the subject had pCR, then the PD will be considered pseudoprogression. Subjects who did not have PD during the neoadjuvant treatment phase, but had positive margins at their last surgery, will be classified as having an EFS event at surgery.)	If patients did not have disease progression during the study observation period but had resection with positive margins, they were classified as having an EFS event at the time of surgery.
Local or distant recurrence (Subjects who had locoregional PD - as assessed radiologically - during the neoadjuvant treatment phase, but went to surgery and ended up with positive margins at their last surgery, will be classified as having an EFS event at the time of diagnosis of locoregional PD. Subjects who had distant PD (metastasis, confirmed by biopsy or 2 imaging studies at least 4 weeks apart, if a biopsy was not feasible) during the neoadjuvant treatment phase had an EFS event at the time of diagnosis of distant PD, even if the subjects had palliative breast surgery. Subjects who had cytological, histological, and/or radiological evidence of local or distant recurrence during the adjuvant phase had an EFS event at the time recurrence was diagnosed.)	Date and type (locoregional or metastatic) of recurrence If patients had locoregional recurrence during the study observation period but underwent resection with positive margins, they were classified as having an EFS event at the time of diagnosis of locoregional recurrence. If patients had metastatic recurrence, they were classified as having an EFS event.

Date of surgery	Date of surgery
Margins	Extent of surgical resection (complete resection with no mention of positive margins, resection with positive margins, not documented)
Second primary malignancy	Record of diagnosis and/or treatment for another primary cancer and date.
Death due to any cause	Date of death due to any cause

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485 **Table 3. Baseline Characteristics of the KEYNOTE-522 Control Arm and Real-World**486 **Cohort**

Variable	KEYNOTE-522	Unadjusted	MAIC-Adjusted
	control arm (N=390)	RW Cohort (N=311)	RW Cohort (ESS N=185)
Age group (years), N (%)			
<65	342 (88%)	237 (76%)	88.4%
≥65	48 (12%)	74 (24%)	11.6%
Race, N (%)			
White/Caucasian	242 (62%)	184 (59%)	68.2%
Other	117 (30%)	86 (28%)	22.5%
Not documented	31 (8%)	41 (13%)	9.3%
Ethnicity, N (%)			
Hispanic	39 (10%)	24 (8%)	7.7%
Not Hispanic	307 (79%)	43 (14%)	80.1%

Not documented	44 (11%)	244 (78%)	12.2%
Clinical Cancer Stage at Initial Diagnosis, N (%)			
Stage I, Stage II	292 (75%)	173 (56%)	77.5%
Stage III	98 (25%)	138 (44%)	22.5%
ECOG, N (%)			
0	341 (87%)	185 (59%)	88.4%
1	49 (13%)	126 (41%)	11.6%

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Table 4: Unadjusted and MAIC-Adjusted Estimates of Pathological Complete Response (pCR)

Pathological Complete Response (pCR)	Total N	Number of events	Unadjusted Risk Ratio	95% Confidence Interval	p-value	MAIC-Adjusted Risk Ratio	95% Confidence Interval	p-value
KEYNOTE-522 (reference)	201	103	0.88	0.73, 1.05	0.1559	0.96	0.80, 1.14	0.627
Real-world Cohort	301*	135						

*10 patients did not have recorded pCR results and were excluded from this analysis