Developing and Evaluating Definitions of Real-World (rw) Clinical Endpoints for Patients With Early-Stage Triple-Negative Breast Cancer Using a US Secondary Database

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Background

- Triple-negative breast cancer (TNBC), characterized as lacking expression of human epidermal growth factor receptor 2 (*HER2*, also known as *ERBB2*) and of both estrogen and progesterone receptors, represents ~15% of all breast tumors and tends to be more aggressive, difficult to treat, and likely to recur than other breast cancer types, including in early stages[1]
- Pembrolizumab, an immune checkpoint inhibitor, was studied in the KEYNOTE-522 clinical trial for patients with previously untreated early-stage TNBC (esTNBC), leading to a July 2021 regulatory approval in the US for administration in combination with chemotherapy as neoadjuvant therapy before surgical resection and then continued as a single agent as adjuvant therapy after surgery
- In KEYNOTE-522, a benefit in pathological complete response (pCR) was evident at the first interim analysis in 2019 among patients who received pembrolizumab plus neoadjuvant chemotherapy, as compared with neoadjuvant chemotherapy alone,[2] and significant improvements in both event-free survival (EFS) and overall survival in the pembrolizumab arm were recorded in subsequent analyses[3,4]
- As therapies are expanding for early stages of TNBC, when cure is the intent, an understanding of treatment effectiveness in real-world settings is also needed to evaluate the generalizability of trial results for patients treated outside the clinical trial setting
- Real-world databases can serve as rich sources of clinical information to supplement clinical trial findings

Objectives

- To develop and evaluate real-world early clinical endpoints for patients with esTNBC receiving care in the US

Methods

Study design

- Retrospective database study supplemented with manual chart review
- Data source: Syapse Learning Health Network, Enriched Breast Cohort, a longitudinal database integrating multiple sources of patient care information at US community practices, including cancer registries, electronic medical records, laboratory reports, and external sources, enriched with manual abstraction from patient charts by Syapse Oncology Data Specialists

Patients

- Adult patients (≥18 years old) with a first diagnosis of esTNBC from January 1, 2016, to December 31, 2021, and at least two medical encounters, including at least one after the initial diagnosis
  - Confirmed TNBC at diagnosis, documented as HER2-negative (by immunohistochemistry [IHC] 0, 1+, 2+/in situ hybridization [ISH]-negative or a nonamplified ISH alone, or annotated as being negative) with estrogen- and progesterone receptor-negative status (≤1% positivity)
  - Early-stage was defined per American Joint Committee on Cancer (AJCC) TNM clinical staging as combined primary tumor (T) and regional lymph node (N) of T1c N1-N2 *or* T2-T4 N0-N2 and nonmetastatic (M0)
- Eligible patients received neoadjuvant therapy (NAT) regimens similar to those for the control arm of the KEYNOTE-522 trial (ie, neoadjuvant carboplatin + paclitaxel followed by an anthracycline + cyclophosphamide):
  - Carboplatin + taxane, followed by anthracycline (doxorubicin or epirubicin) + cyclophosphamide
  - Anthracycline + cyclophosphamide, followed by carboplatin + taxane
  - Carboplatin + taxane followed by another regimen
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or unknown
- Excluded: Patients participating in a clinical trial, with unknown surgical history, or who had received immunotherapy
- Follow-up: Through December 31, 2022

Endpoints and analyses

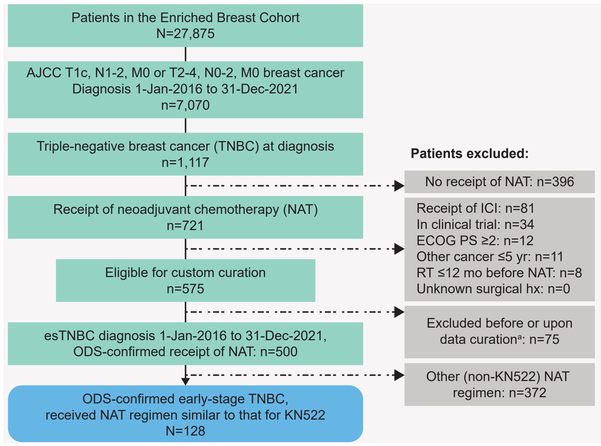
- Descriptive summaries of patient characteristics and NAT were contrasted with those for the KEYNOTE-522 control arm
- Real-world pCR (rwpCR) was derived from pathology reports and/or clinician's notes, including both rwpCR1 and rwpCR2, and was compared with pCR results for the KEYNOTE-522 control arm using Fisher's exact test:
  - rwpCR1: Post-NAT pathologic stage ypT0 ypN0 (no tumor detected, lymph node-negative) or clinician assessment of pCR
  - rwpCR2: Post-NAT pathologic stage ypT0/Tis ypN0 (no tumor detected/carcinoma in situ, lymph node-negative) or clinician assessment of pCR with in situ disease explicitly noted
- The Kaplan-Meier product-limit estimator was used to estimate the distribution of real-world EFS (rwEFS) from NAT initiation and compared with EFS results from KEYNOTE-522 using the log-rank test
  - Events were defined as progression in the NAT period that precluded surgery and/or with surgical margins with residual disease, local or distant recurrence at any site, second primary cancer, or death from any cause

Results

Patients

- A total of 128 patients with esTNBC were eligible for the study (**Figure 1, Table 1**)

Figure 1. Selection of eligible patients in the database with early-stage TNBC



[a]*Eligibility criteria were confirmed during manual data curation.*

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; hx, history; KN, KEYNOTE; ICI, immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1); NAT, neoadjuvant therapy; ODS, Oncology Data Specialist; RT, radiation therapy.

Table 1. Baseline characteristics of patients with esTNBC who received neoadjuvant therapy in the real-world cohort and in the control arm of KEYNOTE-522

Characteristic	Real-world cohort (n=128)	KEYNOTE-522[2,3] control arm (n=390)
Age, median (range), years	54 (28–89)	48 (24–79)
Age <65 years	107 (84)	342 (88)
Female sex	128 (100)	390 (100)
Race		
White	96 (75)	242 (67)
Black or African American	28 (22)	15 (4)
Asian	4 (3)	89 (25)
Other	0	13 (4)
Unknown	0	31
Premenopausal[a]	46 (38)	221 (57)
Postmenopausal	75 (62)	169 (43)
ECOG PS of 1	23 (23)	49 (13)
ECOG PS unknown	30	0
Positive PD-L1 status[b]	12 (63)	317 (82)
PD-L1 unknown	110	4
Primary tumor classification		
T1 to T2	85 (66)	290 (74)
T3 to T4	43 (34)	100 (26)
Positive nodal involvement	69 (54)	200 (51)
Stage group at diagnosis		
I	2 (2)	1 (<1)
II	56 (44)	291 (75)
III	70 (55)	98 (25)
HER2 status		
IHC 0–1+	91 (100)	286 (73)
IHC 2+ and ISH negative	0	104 (27)
Unknown	37	0

Data are n (%) unless otherwise noted. Percentages represent the percentages with data and may not add up to 100% because of rounding.

[a]Menopausal status was missing for 7 patients in the real-world cohort.

[b]In the real-world cohort, PD-L1 positivity was defined as a combined positive score (CPS) of ≥10% or as positive according to the laboratory interpretation.

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PD-L1, programmed death-ligand 1.

Therapy and outcomes

- NAT regimens administered:
  - 81 patients (63%) received doxorubicin + cyclophosphamide → carboplatin + taxane
  - 34 (27%) received carboplatin + taxane → anthracycline (all but 1 patient received doxorubicin) + cyclophosphamide
  - 13 (10%) received carboplatin + taxane → other regimen
- First primary site surgery: 85 patients (66%) underwent mastectomy and 41 (32%) breast-conserving surgery
  - 2 patients (2%) refused surgery
- Follow-up time, (rw)pCR rates, and (rw)EFS rates are reported in **Table 2** and **Figure 2** for the real-world cohort and patients in the KEYNOTE-522 control arm
- Adjuvant capecitabine was administered to 42 patients (33%) in the real-world cohort but was not allowed in KEYNOTE-522
  - 1 of the 42 patients (2.4%) who received capecitabine had achieved rwpCR2 (ypT0/Tis ypN0)
  - The 36-month rwEFS rate was 59.5% (95% CI, 45.1–78.5) among those who received adjuvant capecitabine and 84.2% (95% CI, 76.1–93.1) among those who did not (**Figure 3**)

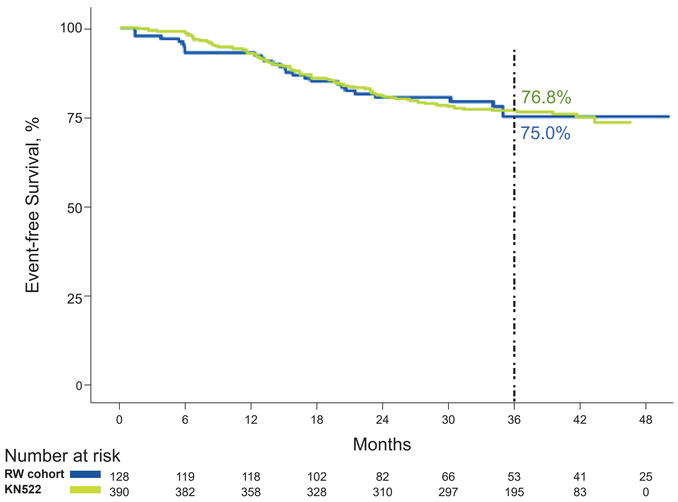
Table 2. Follow-up time, pathologic complete response, and event-free survival in the real-world cohort and KEYNOTE-522 control arm[2,3]

Variable	Real-world cohort (n=128)	KEYNOTE-522 control arm (n=390)
Follow-up, median (range), months	31.2 (1.3–83.4)	15.5 (2.7–25.0)[2]
(rw)pCR2 (ypT0/Tis ypN0), n (%)	48 (38)	103 (51)[a]
(rw)pCR2 by baseline TN status, n (%)		
Tumor size T1-T2	38 (45)	84/149 (56)
Tumor size T3-T4	10 (23)	19/52 (37)
Nodal status, positive	22 (32)	45/102 (44)
Nodal status, negative	26 (44)	58/99 (59)
(rw)pCR1 (ypT0 ypN0), n (%)	41 (32)	91 (45)[a]
Follow-up, median (range), months	31.2 (1.3–83.4)	39.1 (30.0–48.0)[3]
Median (rw)EFS (95% CI), mo	Not reached	Not reached
(rw)EFS rate, % (95% CI)		
At 12 months	93.0 (88.6–97.5)	–
At 24 months	80.4 (73.7–87.8)	–
At 36 months	75.0 (67.1–83.8)	76.8 (72.2–80.7)
Any first event, n (%)	28 (22)	93 (24)
Distant recurrence	15 (12)	51 (13)
Local recurrence	4 (3)	17 (4)
Distant progression in neoadjuvant period	4 (3)	0
Disease progression precluding surgery	1 (<1)	15 (4)
Second primary cancer	3 (2)	4 (1)
Positive surgical margin (R1)	1 (<1)	0
Death	0	6 (2)

[a]*P*<0.05 (Fisher's exact test) for comparisons of pCR between real-world cohort and KEYNOTE-522. In KN522, pCR was calculated for 201 of 390 patients who had definitive surgery after 6 months of protocol-specified neoadjuvant therapy and had no missing data with respect to pCR.

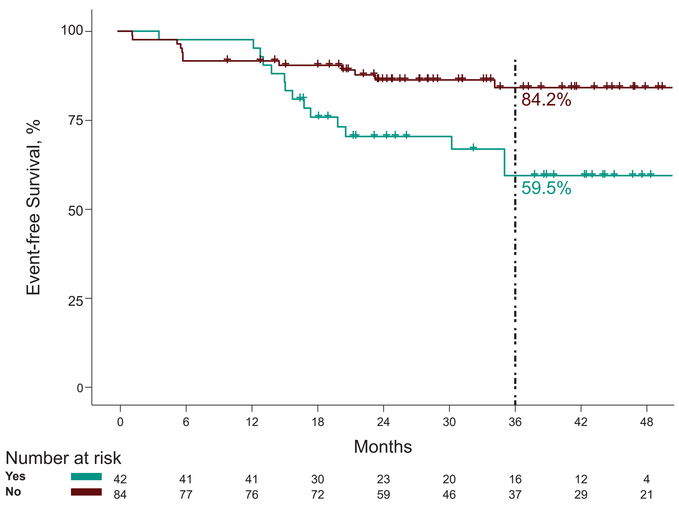
(rw)EFS, (real-world) event-free survival; (rw)pCR, (real-world) pathologic complete response.

Figure 2. Real-world event-free survival (rwEFS) Kaplan-Meier curve with overlying EFS curve from KEYNOTE-522 control arm (log-rank *P*=0.97)



RW, real-world; KN, KEYNOTE.

Figure 3. Real-world event-free survival: Kaplan-Meier curve by adjuvant capecitabine receipt (yes or no) in the real-world cohort



Conclusions

- In this real-world study, we observed that the rwpCR rate among patients with esTNBC was 38%, while the pCR rate in the KEYNOTE-522 trial control arm was 51%; instead, the 36-month rwEFS/EFS rates (75% and 77%, respectively) were similar, raising the need for further study to understand the basis for divergence/convergence of the results across the two analyses
- Differences between the real-world cohort and the KEYNOTE-522 control arm in rwpCR/pCR may result from differences in neoadjuvant regimens and possibly from differences in the distribution of patient and tumor characteristics between the real-world cohort and the trial population
- The majority of patients who received adjuvant capecitabine (98%) did not achieve rwpCR2, which could explain both why they were prescribed adjuvant therapy and the 36-month rwEFS rate of 60% (vs 84% among those who did not receive adjuvant capecitabine)
- Limitations of this study include the relatively small size of the real-world cohort and missing clinical data, such as ECOG performance status and HER2 status
- Continued study is planned to evaluate rwpCR and rwEFS results with a larger real-world cohort and over a longer follow-up period

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