A Real-World Correlation Analysis on the Age at Diagnosis, Pathologic Complete Response, Germline Mutations, and Toxicity in Early Triple-Negative Breast Cancer Patients Treated with the Neoadjuvant Therapy KEYNOTE-522

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Introduction

Age at diagnosis can significantly impact treatment outcomes and toxicity profiles in breast cancer. Pathologic complete response (pCR) following neoadjuvant therapy in triple-negative breast cancer (TNBC) is an established surrogate for long-term outcomes. While clinical and genetic factors have been explored as predictors of pCR, the relationship between age at diagnosis and pCR, especially in the context of immune checkpoint inhibitor-based therapy such as KEYNOTE-522 (KN522), remains unclear. The KEYNOTE-522 regimen (neoadjuvant pembrolizumab combined with a four-drug chemotherapy backbone, followed by adjuvant pembrolizumab) is a standard of care for stage II-III TNBC. We evaluated the correlations between age and pCR, germline mutation status, and treatment-related toxicities in a cohort of breast cancer patients treated with the neoadjuvant therapy, KN522 regimen.

Methods and Demographics

A total of **78 patients** with early-stage, triple-negative breast cancer (TNBC) were evaluated from a single-institution clinical registry.

Treatment distribution:

KN522-based neoadjuvant therapy: 66 patients (84.6%)
Other chemotherapy regimens: 2 patients (2.6%)
Upfront surgery: 10 patients (12.8%)

Patient Characteristics:

Age at diagnosis: 23–85 years (mean 52.9 ± 14.9 years)
Pathologic complete response (pCR): binary outcome (yes/no)
Other variables assessed: Germline testing, HER2 status, ECOG performance status, BMI, and treatment-related toxicity
Pathologic response data: 72 patients (92.3%)

Results

- **Pathologic Response:**
  - pCR achieved in 51.4% (37/72) of evaluable patients
- **Age and pCR:**
  - Median age similar between pCR vs. non-pCR groups (52 vs. 53 years).
  - No significant linear correlation (point biserial, $r = -0.08$, $p > 0.3$).
- **Germline BRCA1/2 Status:**
  - 13/70 patients (18.6%) carried BRCA1/2 mutations.
  - These patients demonstrated a numerically higher pCR rate, though the difference was not statistically significant due to small sample size.
- **Toxicity and Treatment Modifications:**
  - Patients >65 years experienced higher toxicity and more frequent treatment modifications.
  - Despite this, pCR rates were not reduced in older patients.
- **KN522 Subgroup:**
  - Slightly higher pCR rates observed in patients receiving KN522-based therapy, consistent with previous trial data.
  - Age did not significantly modify response in this subgroup.
- **Cohort Demographics:**
  - **Sex:** 100% female
  - **Race/Ethnicity:** 87% non-Hispanic, 65% Hispanic
  - No significant correlation between age and race or ethnicity.

Figure 1: Treatment Distribution

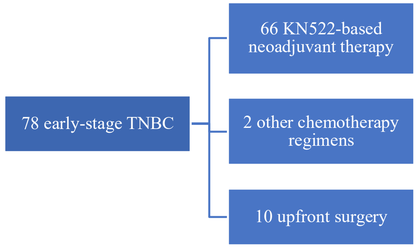


Figure 2: Cohort Results

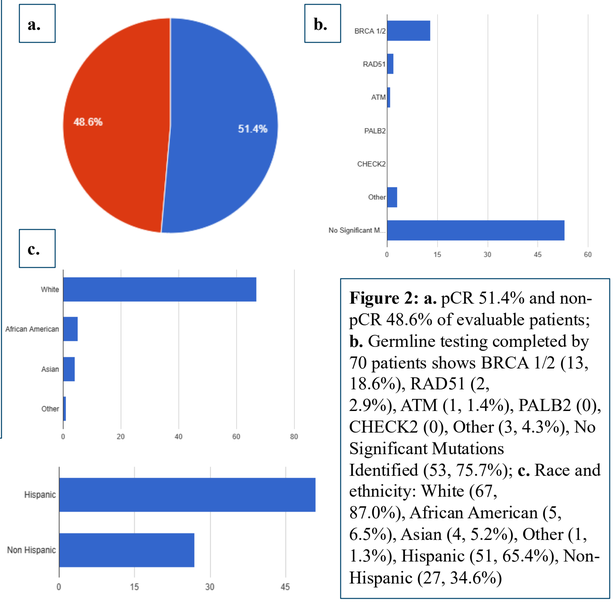


Figure 2: a. pCR 51.4% and non-pCR 48.6% of evaluable patients; **b.** Germline testing completed by 70 patients shows BRCA 1/2 (13, 18.6%), RAD51 (2, 2.9%), ATM (1, 1.4%), PALB2 (0), CHECK2 (0), Other (3, 4.3%), No Significant Mutations Identified (53, 75.7%); **c.** Race and ethnicity: White (67, 87.0%), African American (5, 6.5%), Asian (4, 5.2%), Other (1, 1.3%), Hispanic (51, 65.4%), Non-Hispanic (27, 34.6%)

Discussion

- Age at diagnosis does not predict response.
- Despite higher toxicity in older patients, pCR rates were comparable across age groups, suggesting age alone should not be used to predict response to KN522-based therapy.
- Toxicity and increased treatment modifications in older patients did not translate to inferior outcomes.
- These findings reinforce that chronological age should not be a barrier to offering aggressive chemotherapy when clinically indicated.
- Real-world outcomes align with KN522 trial data, supporting the regimen is generalizability beyond clinical trial populations.
- Higher pCR in BRCA1/2 carriers suggests a potential biologic sensitivity to the KN522 regimen.
- Additional prospective research is needed characterize age-related toxicity and to optimize supportive care approaches that preserve therapeutic efficacy.

Conclusions

In this real-world, retrospective cohort of early-stage TNBC patients receiving neoadjuvant therapy with KN522, pathologic complete response (pCR) was achieved in over half (51.4%) of evaluable patients with no significant association between age at diagnosis and pCR outcomes. Toxicities were common during KN522 treatment, with 100% of patients experiencing at least one toxicity. Although older patients experienced increased toxicity and treatment modifications, this did not translate into lower response rates. Germline BRCA1/2 mutation carriers showed a trend toward higher pCR, though statistical power was limited. These findings suggest age alone should not be a determining factor in predicting treatment response in early-stage breast cancer, consistent with existing KN522 trial data. These findings also emphasize the importance of incorporating age and genetic testing in personalized treatment planning.

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