Three-Year Event-Free Survival from a Phase 2 Study of Peri-Operative Immune Checkpoint Inhibition and Cryoablation in Women with Hormone Receptor-Negative, HER2-Negative Early Stage/Resectable Breast Cancer (Ipilimumab/Nivolumab Cohort)

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Background

- In 2011, our group initiated the first curative-intent immune-therapy study in breast cancer, evaluating pre-operative immune checkpoint inhibition (ICI) ± cryoablation (cryo) in early-stage TNBC[1]
- This current phase 2 study builds upon the results of the 2011 pilot, which demonstrated that the combination of pre-operative ICI and cryo generates robust local and systemic immune activation, providing the first mechanistic evidence that peri-operative immune modulation could reshape long-term outcomes[2]
- These early curative-intent immunotherapy studies have been investigator-initiated and sustained through foundation and philanthropic support, advancing despite the absence of broader investment in this space
- Although initial cohorts were necessarily small, they established the foundation for a continuous research program in curative-intent immunotherapy
- As a historical benchmark, the KEYNOTE-522 NAC-alone arm demonstrated a 3-year EFS of 56.8% in patients with residual TNBC, highlighting the high-risk nature of this population[3]
- Approximately 1/3 of non-pCR TNBC patients will experience a recurrence and die of disease within 3 years, underscoring the need for improved peri-operative strategies[3]
- We conducted a multi-center, single-arm, phase 2 study evaluating peri-operative ICI and cryo in patients with early-stage, resectable TNBC
- The study was originally launched using ipilimumab/nivolumab (ipi/nivo); the protocol was amended after KEYNOTE-522 to allow for pembrolizumab as SOC for high-risk, early-stage TNBC

Study Design

- The primary endpoint was 3-year EFS defined as the time from enrollment to disease progression that precluded definitive surgery, local or distant recurrence, or death from any cause
- Secondary endpoints included invasive disease-free survival (IDFS), distant disease-free survival (DDFS), overall survival (OS), and safety
- The pembrolizumab cohort is not yet mature for analysis; here, we report 3-year EFS for the ipi/nivo cohort

Methods and Materials

- Patients aged ≥18 years with early-stage, resectable, hormone receptor–negative (ER <10%, PR <10%), HER2-negative breast cancer and ≥1.0 cm residual disease following taxane-based NAC were enrolled and treated with peri-operative ipi/nivo in combination with cryo, followed by definitive breast surgery and adjuvant nivo
- Patients underwent percutaneous, image-guided cryo with concurrent research core biopsy 7–10 days prior to surgery and received a single dose of ipi (1 mg/kg IV) and nivo (240 mg IV) 1 to 5 days prior to cryo

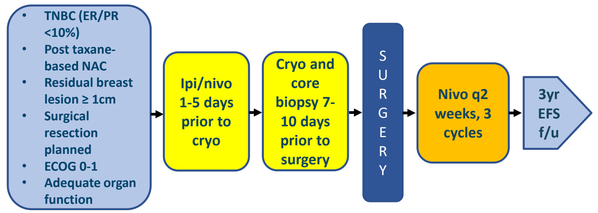


Figure 1. Study Schema
Following surgery, patients received three additional doses of nivo (240 mg IV) every two weeks. Adjuvant capecitabine was recommended for all patients in accordance with local SOC . Adjuvant RT was recommended per local SOC. Patients were evaluated every 3 (+/-1) months until month 36 .

Results

Table 1. Baseline Characteristics of the Patients

Characteristic, n(%)	N=15
Age	
Median (range) – yr	55 (32–75)
<65 yr – no. (%)	10 (66.7)
Race/Ethnicity – no. (%)	
White/non-Hispanic	10 (66.7)
White/Hispanic	2 (13.3)
Black or African American	1 (6.7)
Asian	2 (13.3)
Residual Tumor Size, median (range) – cm	3 (1.1–7.5)
Neoadjuvant Chemotherapy	
Taxane + Anthracycline	4 (26.7)
Taxane + Platinum	10 (66.7)
Taxane-only	1 (6.7)

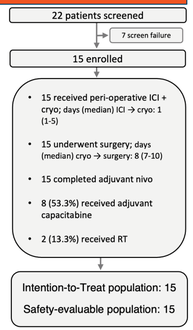


Figure 2. Disposition of Pts

Results

Median follow-up of 49.5 months (data cutoff: June 1, 2025)

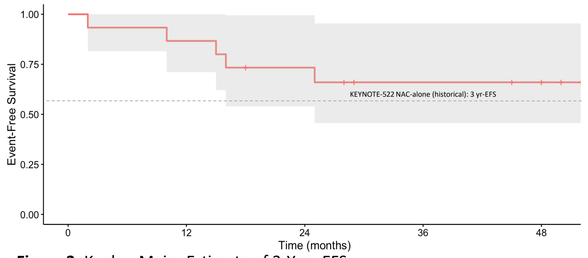


Figure 3. Kaplan-Meier Estimate of 3-Year EFS
The 3-year EFS was 66.7% (95% CI, 45.7 to 95.4). Five events were observed: 4 distant recurrences at 2, 10, 15, and 16 months, and one loco-regional recurrence at 25 months.

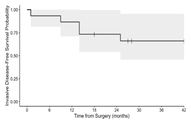


Figure 4. 3-year IDFS 66.7%

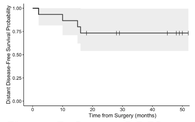


Figure 5. 3-year DDFS 73.3%

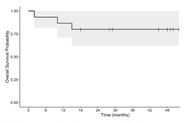


Figure 6. 3-year OS 80.0%

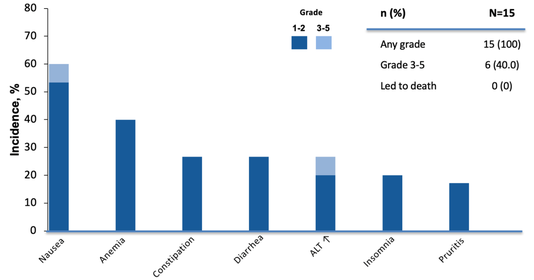


Figure 7. Adverse Events (AEs) with ≥10% Incidence thru 1-Year Post-Surgery

- No grade ≥3 AEs were attributed to cryo
- Grade ≥3 AEs occurred in 6 pts (40%) with none attributed to cryo
- Cryo-related AEs were limited to grade 1 breast pain in 2 pts (13%)

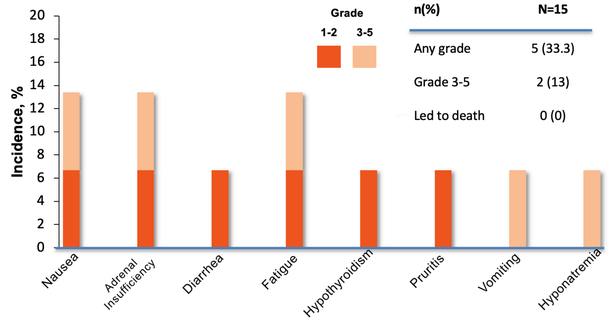


Figure 8. Immune-Related Adverse Events (irAES) Incidence ≥ 1 pt or ≥ grade 3

- irAEs of any grade occurred in 5 pts (33.3%)
- Grade ≥3 irAEs were reported in 2 pts: 1 pt experienced adrenal insufficiency, fatigue, hypothyroidism, and hyponatremia; 1 pt experienced vomiting

Conclusions

- Peri-operative ICI with ipi/nivo combined with cryo demonstrated encouraging long-term outcomes in patients with high-risk, early-stage TNBC who did not achieve a pCR with NAC
- The 3-year EFS of 66.7% exceeds the historical benchmark of 56.8% observed in the NAC-alone arm of KEYNOTE-522
- These findings suggest that cryo may enhance antitumor immunity and may allow for shorter duration of ICI
- The regimen was generally well tolerated, with minimal cryo-related AEs and manageable irAEs, and highly feasible, causing no delays to surgery
- These results support further investigation of cryo as a strategy to augment ICI efficacy in early-stage TNBC

Acknowledgements

This research is supported by Susan G Komen, Bristol-Myers Squibb, Boston Scientific Corp, ASCO/Conquer Cancer Foundation Advanced Clinical Research Award, and Breast Cancer Research Foundation

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