Ann Surg Oncol (2023) 30:3166–3169
https://doi.org/10.1245/s10434-023-13267-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ASO PERSPECTIVES

Preoperative Immunotherapy Combined with Chemotherapy for Triple-Negative Breast Cancer: Perspective on the KEYNOTE-522 Study

Stephanie Downs-Canner, MD, FACS[1], and Elizabeth A. Mittendorf, MD, PhD, MHCM, FACS[2,3,4]

[1]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA; [3]Breast Oncology Program, Dana-Farber Brigham Cancer Center, Boston, MA; [4]Harvard Medical School, Boston, MA

Improved understanding of breast tumor biology has led to significant advances in treatment. Targeted therapy for hormone-receptor-positive and HER2-overexpressing breast cancers has led to improvements in both survival and quality of life for patients with these subtypes of breast cancer. Until recently, few advances have been made in the treatment of triple-negative breast cancer (TNBC), which disproportionally affects young, African American women[1] and has an aggressive clinical course marked by greater metastatic potential, higher recurrence rates, and worse overall survival than other breast cancer subtypes.[2]

Immune checkpoint blockade with anti-programmed death receptor 1/programmed death receptor 1 ligand (anti-PD1/PD-L1) or anti-CTLA4 monoclonal antibodies works by "releasing the brakes" on the immune system imposed by the tumor microenvironment. Initially shown to be successful in the treatment of patients with highly immune-infiltrated cancers, such as melanoma and non-small cell lung cancer, where higher mutational burden correlates with response to immunotherapy, evaluation of efficacy in TNBC, the most highly immune-infiltrated subset of breast cancer, was a logical next step. Clinical trials of anti-PD-L1 and/or anti-PD-1 monoclonal antibodies atezolizumab and pembrolizumab, in combination with chemotherapy, in locally advanced and metastatic TNBC showed promise and the positive results of the KEYNOTE-355 study led to US Food and Drug Administration (FDA) approval of pembrolizumab for PD-L1 positive metastatic TNBC.[3,4]

Subsequent to the approval of pembrolizumab in the metastatic setting, the KEYNOTE-522 study evaluated the role of preoperative immunotherapy combined with chemotherapy for early-stage TNBC. The trial randomized 1174 patients with clinical T1cN1–2 or T2–4N0–2 TNBC to preoperative pembrolizumab (eight cycles given every 3 weeks) plus chemotherapy (paclitaxel and carboplatin, followed by doxorubicin or epirubicin, and cyclophosphamide), or placebo plus chemotherapy. All patients proceeded to surgery, followed by completion of nine additional cycles (27 weeks) of adjuvant pembrolizumab or placebo (Fig. 1). The coprimary endpoints were pathologic complete response (pCR) and event-free survival (EFS). At a preplanned interim analysis, patients treated with pembrolizumab had a statistically significantly higher rate of pCR (64.8%) compared with those treated with placebo (51.2%).[5] The fourth planned interim analysis demonstrated improved EFS in patients treated with pembrolizumab (84.5% vs. 76.8%), resulting in FDA approval based on positive results for both primary endpoints.[6]

While multidisciplinary evaluation and management is critical for patients being selected for neoadjuvant chemo-immunotherapy, it is often the surgical oncologist who has first contact with patients with breast cancer who may be eligible for treatment with neoadjuvant therapy. It is therefore critical that surgeons are aware of eligibility criteria of the KEYNOTE-522 study so that eligible patients can be considered for the chemotherapy plus immunotherapy regimen, and potentially benefit from the

First Received: 9 January 2023
Accepted: 9 February 2023
Published Online: 10 March 2023

E. A. Mittendorf, MD, PhD, MHCM, FACS
e-mail: emittendorf@bwh.harvard.edu

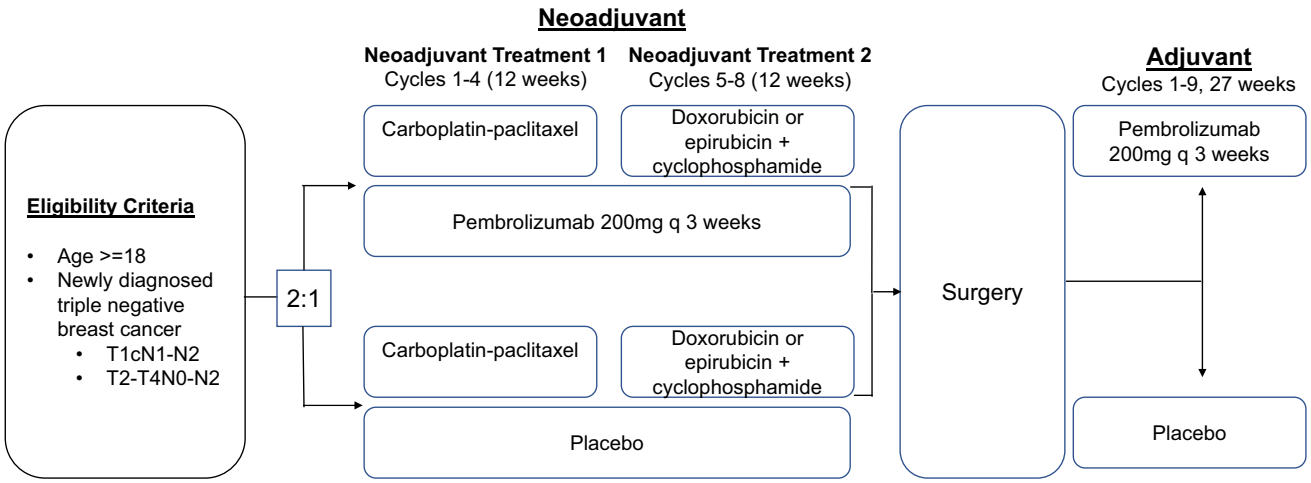

FIG. 1 KEYNOTE-522 Study schema. Adapted from Schmid et al.[5]

improved pCR rate and EFS. Unlike in the metastatic setting, early-stage patients are eligible for pembrolizumab regardless of PD-L1 status, with an improvement in the pCR rate and EFS benefit demonstrated in both PD-L1-positive and PD-L1-negative patients.[6] Therefore, PD-L1 staining is not necessary to confirm eligibility for preoperative immunotherapy. Careful assessment by the surgeon of clinical T and N categories can also optimize patient selection for treatment with immunotherapy. The trial enrolled patients with T2 and greater disease, regardless of nodal status, as well as those with cT1c tumors and clinically node-positive disease. A recent report has shown that a significant percentage of patients with clinical T1c disease, initially assessed as clinically node negative on physical examination, may have N1 disease. In a study of 175 clinical T1cN0 patients undergoing initial surgery at the Dana-Farber Brigham Cancer Center, 15% had pathologically node-positive disease. In a similar group of over 18,000 patients captured in the National Cancer Database, 11% were pathologically node positive.[7] While many centers deliberately omit the use of preoperative axillary ultrasound in patients who may otherwise be eligible for omission of axillary dissection, according to the ACOSOG Z0011 trial, routine use of pretreatment axillary ultrasound in patients with T1c TNBC may identify patients eligible for preoperative immunotherapy. Axillary ultrasound is our preferred imaging modality, as it is recommended by the National Comprehensive Cancer Network guidelines version 1.2023 to evaluate for axillary metastases.[8]

The unique side-effect profile of immunotherapeutic agents is particularly relevant for the surgical oncologist. Immune-related adverse events (irAEs) of any grade in early studies of anti-PD1/PD-L1 and anti-CTLA4 therapy have been reported to be as high as 70%, with up to half of patients in some studies discontinuing (at least temporarily) immunotherapy due to irAEs.[9] In the KEYNOTE-522 trial, 33.5% of patients receiving pembrolizumab experienced an irAE, and 12.9% of these were at least grade 3. However, many common irAEs have important implications for surgeons. In KEYNOTE-522, 15.1% of patients experienced hypothyroidism, 5.2% experienced hyperthyroidism, and 2.6% developed adrenal insufficiency. Importantly, while many irAEs manifest within the first 8–12 weeks of treatment, late-onset and lifelong irAEs are relatively common and likely under-reported.[10] Many irAEs have vague presentations, and a missed diagnosis of adrenal insufficiency or thyroid dysfunction could negatively impact anesthetic outcomes. Recommendations for a standardized approach to evaluation and treatment of irAEs was published by the Society for Immunotherapy of Cancer prior to the approval of neoadjuvant chemo-immunotherapy for TNBC.[11] At our institutions, it is standard practice to monitor for irAEs, particularly thyroid dysfunction and adrenal insufficiency, in the perioperative period. Thyroid-stimulating hormone (TSH) and free T4 is measured at baseline, halfway through neoadjuvant treatment, at the last dose of neoadjuvant therapy, at the first postoperative appointment, every 12 weeks while on adjuvant pembrolizumab, and for 12 months thereafter. An AM cortisol is measured at the last dose of neoadjuvant therapy. The onus is often on the surgeon to recognize and appropriately refer patients with irAEs and ensure adequate measures are taken to make certain a safe anesthetic is delivered, especially when some irAEs could develop in the time between completion of neoadjuvant therapy and surgery. Data regarding perioperative outcomes of patients treated with immunotherapy are limited to small series describing patients with metastatic disease undergoing surgery after treatment with immunotherapy, and are an active area of investigation for patients being treated in the neoadjuvant setting.[12,13]

While the KEYNOTE-522 study has been a practice-changing advance for the treatment of TNBC, multiple important questions remain unanswered. The chemotherapy backbone used in the KEYNOTE-522 trial included paclitaxel and carboplatin, followed by doxorubicin or epirubicin and cyclophosphamide. This combination is relatively toxic and must be balanced with patient quality of life. While patient-reported outcome data from the KEYNOTE-522 study demonstrated no detriment to the quality of life of those treated with pembrolizumab compared with placebo, real-world data are needed to more accurately capture the impact of immunotherapy on patients likely less fit than a clinical trial population.[14] Other studies, including GeparNuevo, I-SPY2, and IMpassion-031, have demonstrated increased pCR rates using a chemotherapy backbone of nab-paclitaxel, followed by epirubicin/doxorubicin and cyclophosphamide.[15–17] The phase II NeoPACT trial showed a promising 60% pCR rate using an anthracycline-free neoadjuvant regimen of pembrolizumab plus carboplatin and docetaxel.[18] Results from these and future studies are needed to determine the optimal chemotherapy backbone for use with preoperative immunotherapy.

A substantial number of patients treated with the KEYNOTE-522 regimen may not benefit, either because pCR would have been achieved with chemotherapy alone ($\sim$ 50–55%), or because the addition of PD-1 inhibition does not induce pCR (30–35%). There are currently no biomarkers that predict response to neoadjuvant chemo-immunotherapy in TNBC. In the GeparNuevo study, investigators showed that PD-L1 expression, the presence of stromal tumor-infiltrating lymphocytes (TIL), tumor mutational burden, and immune gene expression profiles were predictive of response to preoperative systemic therapy, but did not differentiate response to chemotherapy plus immunotherapy from response to chemotherapy alone.[19] Other promising potential biomarkers include mRNA-based signatures, spatial distribution of TIL subsets within a tumor, microbiome-informed selection, and circulating-tumor DNA.[11] In other cancers, the presence of tertiary lymphoid structures is one of the best predictive biomarkers of response to immunotherapy, although this remains to be seen in TNBC.[20,21] Ongoing studies, including a multicenter effort through the Immuno-Oncology working group of the Translational Breast Cancer Research Consortium (TBCRC), will provide important insights into biomarkers for patient selection.

Finally, the need to complete the year of adjuvant pembrolizumab in those who experience a pCR is an area of active investigation. The OptimICE-PCR study, led by the Alliance for Clinical Trials in Oncology, will randomize patients treated in the neoadjuvant setting with chemotherapy plus pembrolizumab experiencing a pCR to complete 1 year of adjuvant pembrolizumab or observation. The primary objective is to determine if observation is noninferior to 1 year of pembrolizumab.

Preoperative immunotherapy combined with chemotherapy is a major breakthrough for the treatment of patients with early-stage TNBC. Surgical oncologists play a critical role in identifying appropriate patients for treatment and in the active surveillance of irAEs, which may have important implications for the timing and conduct of surgery. Further work is needed to better understand the impact of irAEs in a real-world and preoperative setting. The optimal chemotherapy backbone and duration of pembrolizumab, as well as biomarker-based patient selection, are active areas of research, which will result in precisely tailored treatments for optimal individual patient outcomes that maximize oncologic benefit and minimize impact on quality of life.

ACKNOWLEDGEMENT E.A.M. acknowledges support as the Rob and Karen Hale Distinguished Chair in Surgical Oncology. S.D.C. is supported by National Institutes of Health Grant 1K08CA259533-01A1. The authors also acknowledge Valerie Hope Goldstein for her editorial assistance.

DISCLOSURES E.A.M. reports compensated service on scientific advisory boards for AstraZeneca, Exact Sciences (formerly Genomic Health), Merck, Roche/Genentech, uncompensated service on steering committees for Bristol Myers Squibb, Lilly, and Roche/Genentech, and institutional research support from Roche/Genentech (via SU2C grant) and Gilead. She receives research funding from Susan Komen for the Cure for which she serves as a Scientific Advisor. She also reports uncompensated participation as a member of the American Society of Clinical Oncology Board of Directors. S.D.C. reports no conflicts of interest.

REFERENCES

1. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. 2006;295(21):2492–502.
2. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res*. 2007;13(15 Pt 1):4429–34.
3. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet*. 2020;396(10265):1817–28.
4. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108–21.
5. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810–21.
6. Schmid P, Cortes J, Dent R, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med*. 2022;386(6):556–67.
7. Mittendorf EA, Kantor O, Weiss A, et al. Nodal positivity in early-stage triple-negative breast cancer: implications for

preoperative immunotherapy. *Ann Surg Oncol*. 2023;30(1):100–6. https://doi.org/10.1245/s10434-022-12357-8.
8. National Comprehensive Cancer Network, Breast Cancer (Version 1.2023), January 27, 2023.
9. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. 2016;13(8):473–86.
10. Ghisoni E, Wicky A, Bouchaab H, et al. Late-onset and long-lasting immune-related adverse events from immune checkpoint-inhibitors: An overlooked aspect in immunotherapy. *Eur J Cancer*. 2021;149:153–64.
11. Emens LA, Adams S, Cimino-Mathews A et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of breast cancer. *J Immunother Cancer* 2021; 9 (8).
12. Bott MJ, Cools-Lartigue J, Tan KS, et al. Safety and feasibility of lung resection after immunotherapy for metastatic or unresectable tumors. *Ann Thorac Surg*. 2018;106(1):178–83.
13. Gyorki DE, Yuan J, Mu Z, et al. Immunological insights from patients undergoing surgery on ipilimumab for metastatic melanoma. *Ann Surg Oncol*. 2013;20(9):3106–11.
14. Dent R. HRQoL with neoadjuvant pembrolizumab + chemotherapy vs placebo + chemotherapy, followed by adjuvant pembrolizumab vs placebo for early-stage TNBC: results from KEYNOTE-522. ESMO Congress 2022, Abstract 135 MO 2022.
15. Loibl S, Schneeweiss A, Huober JB, et al. Durvalumab improves long-term outcome in TNBC: results from the phase II randomized GeparNUEVO study investigating neodjuvant durvalumab in addition to an anthracycline/taxane based neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC). *J Clin Oncol*. 2021;39(15_suppl):506–506.
16. Nanda R, Liu MC, Yau C, et al. Effect of Pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. *JAMA Oncol*. 2020;6(5):676–84.
17. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet*. 2020;396(10257):1090–100.
18. Sharma P, Stecklein SR, Yoder R, et al. Clinical and biomarker results of neoadjuvant phase II study of pembrolizumab and carboplatin plus docetaxel in triple-negative breast cancer (TNBC) (NeoPACT). *J Clin Oncol*. 2022;40(16_suppl):513–513.
19. Karn T, Denkert C, Weber KE, et al. Tumor mutational burden and immune infiltration as independent predictors of response to neoadjuvant immune checkpoint inhibition in early TNBC in GeparNuevo. *Ann Oncol*. 2020;31(9):1216–22.
20. Helmink BA, Reddy SM, Gao J, et al. B cells and tertiary lymphoid structures promote immunotherapy response. *Nature*. 2020;577(7791):549–55.
21. Petitprez F, de Reynies A, Keung EZ, et al. B cells are associated with survival and immunotherapy response in sarcoma. *Nature*. 2020;577(7791):556–60.