A Treatment Option for Patients With Triple-Negative Breast Cancer:

A Multidisciplinary Approach

Speaker Name, Degree

Institutional Affiliation

MSD | KEYTRUDA® (pembrolizumab) injection 100 mg

Speaker Disclosures

Disclosures

Presentation Objectives

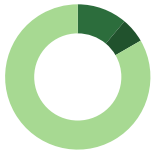
The unmet medical need in triple-negative breast cancer (TNBC)

The addition of KEYTRUDA® (pembrolizumab) as a change in the approach to treatment for patients with TNBC

The significance of a multidisciplinary approach for best patient outcomes

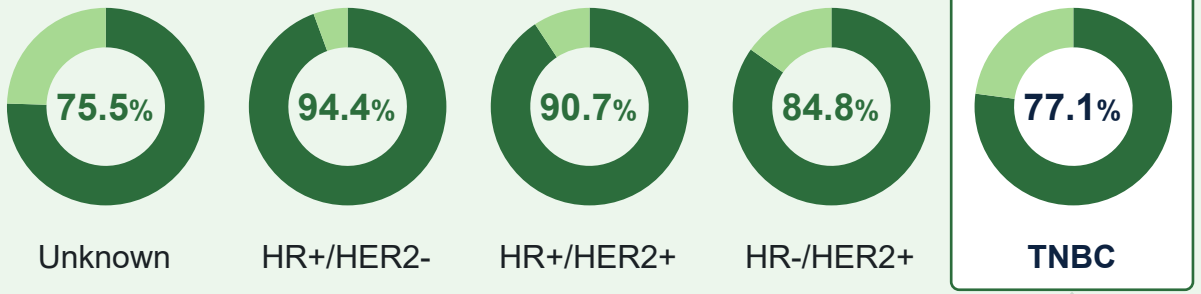
TNBC Has a Lower Relative Survival Rate Compared to Other Breast Cancer Subtypes

Female breast cancer surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated **2.3 million new cases (11.7% of all cancer cases)**[1]

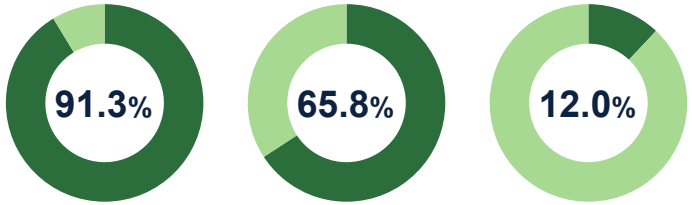


TNBC accounts for about **10%** to **15%** of all breast cancers in the United States[2]

5-year Relative Survival Rates Based on SEER Data, Female Breast Cancer by Cancer Subtypes (2012-2018)[3]



5-year Relative Survival Rates for TNBC Based on SEER Stage for Women Diagnosed With TNBC Between 2012 and 2018[3]



Localized = There is no sign that the cancer has spread outside of the breast[2]
Regional = The cancer has spread outside the breast to nearby structures or lymph nodes[2]
Distant = The cancer has spread to distant parts of the body such as the lungs, liver or bones[2]

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; SEER = Surveillance, Epidemiology, and End Results; TNBC = triple-negative breast cancer.

1. Sung H et al. *CA Cancer J Clin*. 2021;71(3):209–249. 2. American Cancer Society (ACS). Triple-negative Breast Cancer. Accessed June 1, 2020. https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/types-of-breast-cancer/triple-negative.html.
3. NCI SEER Program. Cancer stat facts: female breast cancer subtypes. Accessed May 16, 2022. https://seer.cancer.gov/statfacts/html/breast-subtypes.html.

Even When Diagnosed at Earlier Stages, Patients With TNBC May Have Poorer Outcomes

- The survival curves on the following slide are based on a search of the SEER database for all female breast cancer patients diagnosed from 2010 to 2012
  – **158,358 patients** met the study criteria and were included in the analysis
- The following de-identified information was collected: patient gender, age at diagnosis, ethnicity, overall survival time, tumor grade, HR and HER2 status, and staging based on the TNM and Roman Numeral Staging system from the American Joint Committee on Cancer guidelines (AJCC)
- Number of patients by type

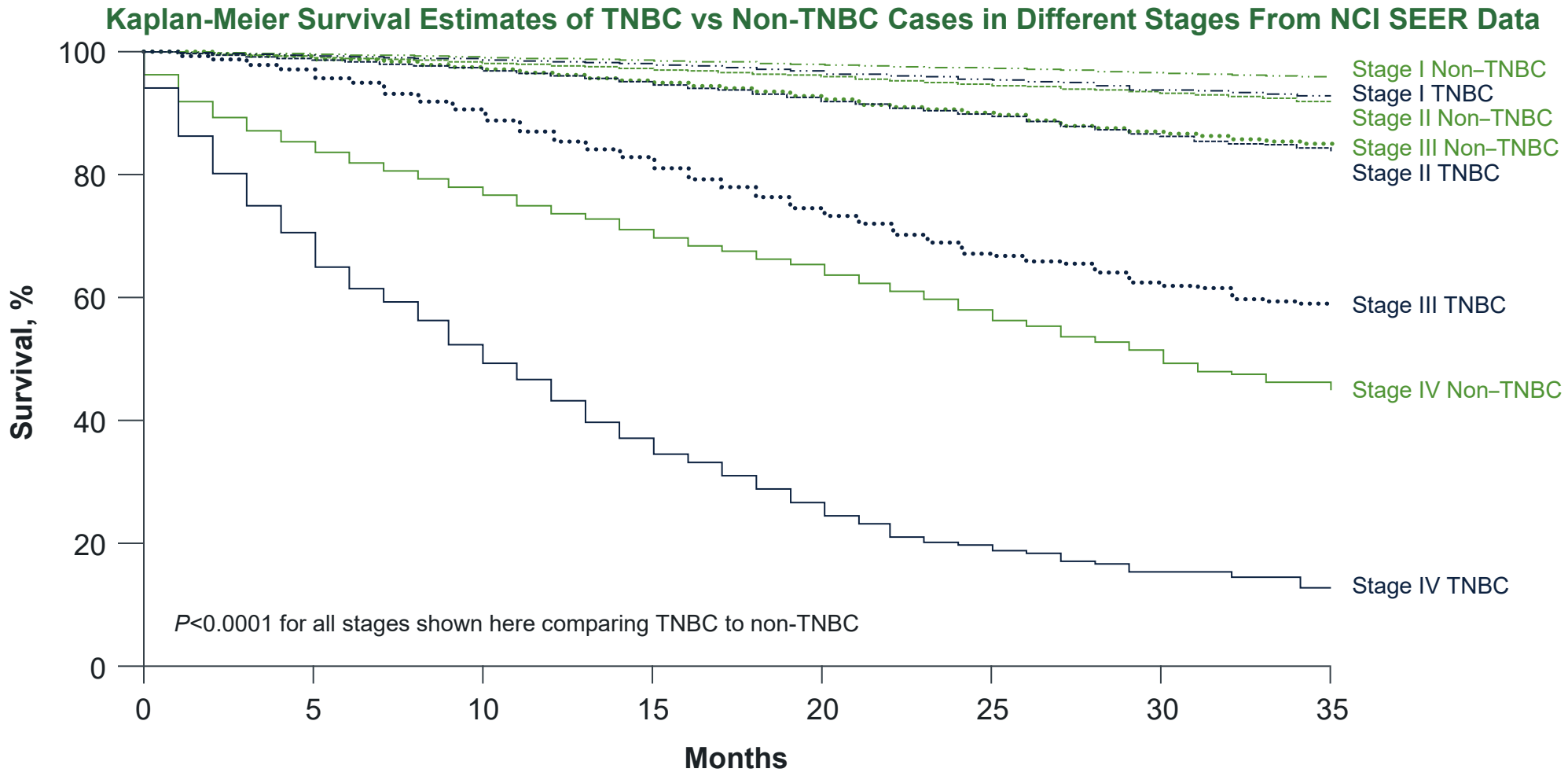
TNBC
- HR-/HER2–: 18,855 (11.9%)

Non-TNBC
- HR+/HER2–: 116,395 (73.5%)
- HR+/HER2+: 16,008 (10.1%)
- HR–/HER2+: 7,100 (4.5%)

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; SEER = Surveillance, Epidemiology, and End Results; TNBC = triple-negative breast cancer; TNM = tumor, node, metastasis staging system.

Li X et al. *Breast Cancer Res Treat*. 2017;161(2):279–287.

Even When Diagnosed at Earlier Stages, Patients With TNBC May Have Poorer Outcomes



NCI = National Cancer Institute; SEER = Surveillance, Epidemiology, and End Results; TNBC = triple-negative breast cancer.

Adapted/Translated by permission from Springer Nature Customer Service Centre GmbH: Springer Nature. Breast Cancer Research and Treatment. Triple-negative breast cancer has worse overall survival and cause-specific survival than non-triple-negative breast cancer, Li X, et al., Copyright © 2017.

Li X et al. *Breast Cancer Res Treat.* 2017;161(2):279–287.

Potential Benefits Associated With Neoadjuvant Systemic Therapy

- May facilitate **breast conservation**
- Can **render inoperable tumors operable**
- Treatment response may provide important **prognostic information at an individual patient level**, particularly in patients with TNBC or HER2-positive breast cancer
- May identify **patients with residual disease at higher risk for relapse** to allow for the addition of supplemental adjuvant regimens, particularly in patients with TNBC or HER2-positive breast cancer
- May allow time for **genetic testing**
- May allow time to plan **breast reconstruction** in patients electing mastectomy
- May allow time for delayed decision-making for definitive surgery

Cautions Associated With Neoadjuvant Systemic Therapy

- Possible overtreatment with systemic therapy if clinical stage is overestimated
- Possible undertreatment locoregionally with radiotherapy if clinical stage is underestimated
- Possibility of disease progression during preoperative systemic therapy

HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer.

National Comprehensive Cancer Network. Breast Cancer (Version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

KEYTRUDA® (pembrolizumab): Approvals in Early-Stage and Advanced TNBC

In the United States:
KEYTRUDA® (pembrolizumab), in combination with chemotherapy, is approved for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

NOV 2020[1]

In the United States:
KEYTRUDA is approved for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

JULY 2021[2]

In the European Union:
KEYTRUDA, in combination with chemotherapy, is approved for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥10 and who have not received prior chemotherapy for metastatic disease

OCT 2021[3]

CPS = combined positive score; FDA = Food and Drug Administration; PD-L1 = programmed death ligand 1; TNBC = triple-negative breast cancer

1. U.S. Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for locally recurrent unresectable or metastatic triple negative breast cancer. Press Release. November 13, 2020. 2. U.S. Food and Drug Administration. FDA approves pembrolizumab for high-risk early-stage triple-negative breast cancer. Press Release. July 26, 2021. 3. KEYTRUDA (pembrolizumab) Summary of Product Characteristics. [Note: Align to local label.]

The Growing Role of KEYTRUDA® (pembrolizumab) Across Tumors

KEYTRUDA® (pembrolizumab) Is Approved to Treat More Than 15 Types of Cancer

Indications in Breast and Gynecologic Cancers

ADVANCED TNBC AND HIGH-RISK EARLY-STAGE TNBC

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (CPS ≥10) as determined by a validated test.

KEYTRUDA is indicated for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.

ADVANCED ENDOMETRIAL CARCINOMA

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

ADVANCED CERVICAL CANCER

KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

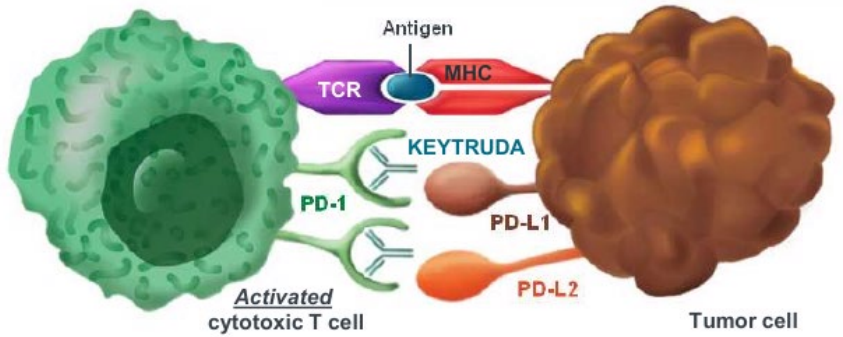
KEYTRUDA, as monotherapy, is indicated for the treatment of patients with recurrent or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by a validated test, with disease progression on or after chemotherapy.

CPS = combined positive score; FDA = Food and Drug Administration; PD-L1 = programmed death ligand 1.

[Insert local label.]

KEYTRUDA® (pembrolizumab): Activates the Antitumor Immune Response

- KEYTRUDA® (pembrolizumab) is a high-affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumor cells[1]
- By inhibiting the PD-1 receptor from binding its ligands, KEYTRUDA reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity[1]
- While having an effect on the tumor cell, this could also affect normal, healthy cells[2]

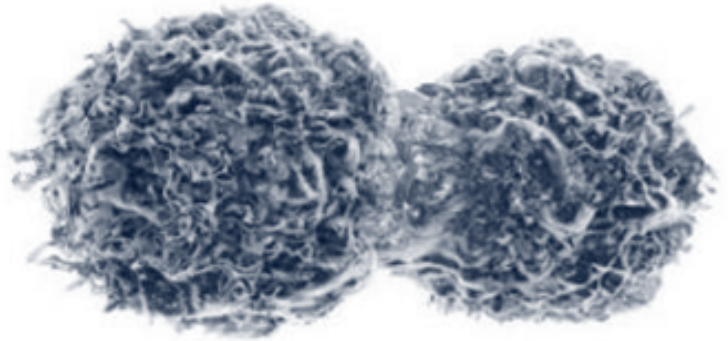


MHC = major histocompatibility complex; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; TCR = T-cell receptor.

1. [Insert local label.] 2. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252–264.

Chemotherapy Targets Proliferating Cells

- Chemotherapy mainly targets cells that are actively proliferating by[1]:
  - Inhibiting cell division
  - Promoting tumor cell killing through deregulation of DNA replication, cellular metabolism, or microtubule assembly
- The mechanism of action varies depending on the type of chemotherapy[1]
- Chemotherapy could also affect normal, healthy cells[2]
- When combined with immunotherapies such as KEYTRUDA® (pembrolizumab), it has been hypothesized that chemotherapy may increase tumor immunogenicity and activate immune response by increasing antigen shedding and presentation and by stimulating T-cell infiltration[1]



DNA = deoxyribonucleic acid.

1. Leonetti A, et al. *Drug Resist Updat.* 2019;46:100644;1–12. 2. American Cancer Society. Chemotherapy side effects. Accessed October 2021. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/chemotherapy-side-effects.html.

KEYNOTE-522: Eligibility Criteria

KEY Inclusion Criteria

- Newly diagnosed, not previously treated high-risk, early-stage TNBC
- Tumor size >1 cm but ≤2 cm in diameter with nodal involvement or tumor size >2 cm in diameter regardless of nodal involvement
- Enrolled regardless of tumor PD-L1 expression

KEY Exclusion Criteria

- Active autoimmune disease that required systemic therapy within 2 years of treatment
- Medical condition that required immunosuppression

Stratification Factors

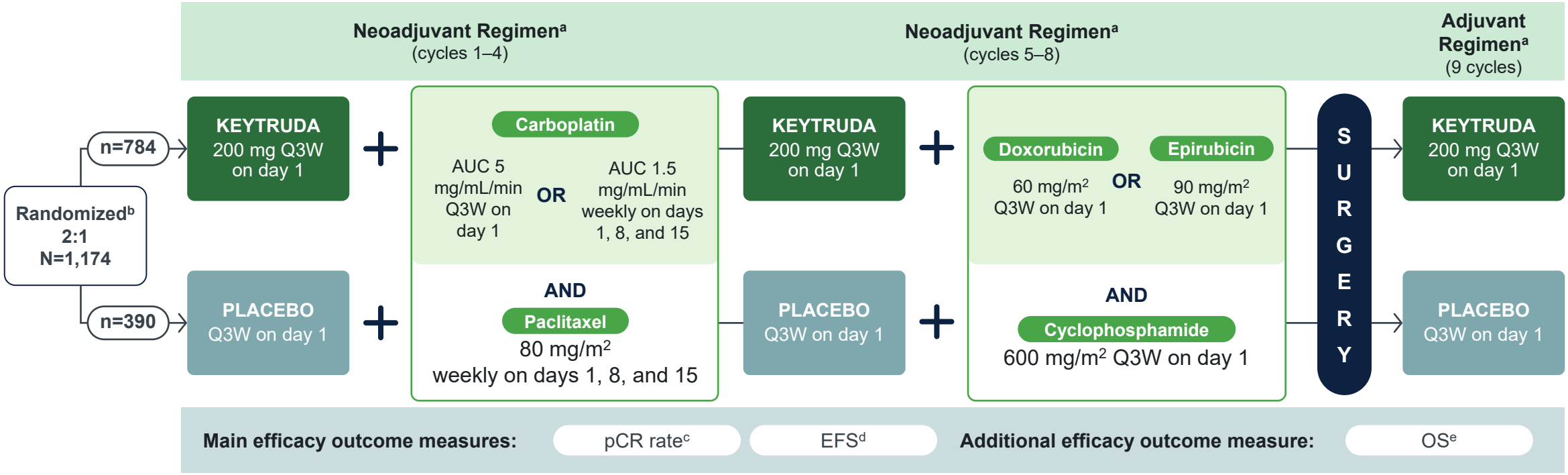
- Nodal status (positive vs negative)
- Tumor size (T1/T2 vs T3/T4)
- Choice of carboplatin (Q3W vs weekly)

PD-L1 = programmed death ligand 1; Q3W = every 3 weeks; TNBC = triple-negative breast cancer.

[Insert local label.]

KEYNOTE-522: Study Design

This was a randomized (2:1), double-blind, multicenter, placebo-controlled study evaluating the efficacy and safety of KEYTRUDA® (pembrolizumab) in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin and cyclophosphamide [AC] or epirubicin and cyclophosphamide [EC]) given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment after surgery, in newly diagnosed, previously untreated, high-risk early-stage TNBC patients (N=1,174)

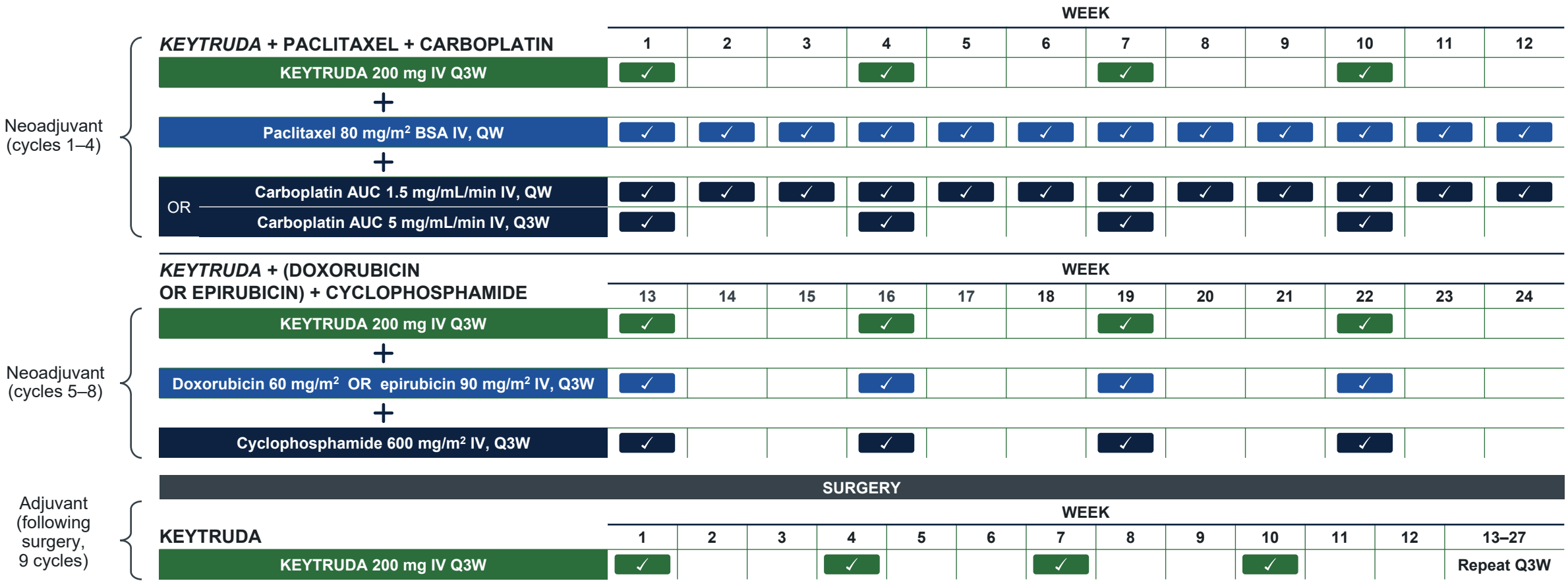


[a]All study medications were administered intravenously. [b]Treatment with KEYTRUDA or placebo continued until completion of the treatment (17 cycles), disease progression that precludes definitive surgery, disease recurrence in the adjuvant phase, or unacceptable toxicity. [c]pCR (ypT0/Tis ypN0) was defined as absence of invasive cancer in the breast and lymph nodes and was assessed by the blinded local pathologist at the time of definitive surgery. [d]EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. [e]At the time of EFS analysis, OS results were not yet mature (45% of the required events for final analysis).

AUC = area under the curve; EFS = event-free survival; OS = overall survival; pCR = pathologic complete response; Q3W = every 3 weeks; TNBC = triple-negative breast cancer; ypT0/Tis ypN0 = absence of invasive cancer in the breast and lymph nodes.

[Insert local label.]

KEYNOTE-522: Dosing Regimen[a]



The recommended dose of KEYTRUDA® (pembrolizumab) in adults is either 200 mg IV Q3W or 400 mg IV Q6W.

[a]When administering KEYTRUDA as part of a combination with IV chemotherapy, KEYTRUDA should be administered first as an IV infusion over 30 minutes. For the neoadjuvant and adjuvant treatment of high-risk early-stage TNBC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 8 doses of 200 mg Q3W or 4 doses of 400 mg Q6W or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 200 mg Q3W or 5 doses of 400 mg Q6W or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment. No dose reductions of KEYTRUDA are recommended. Withhold or discontinue KEYTRUDA to manage moderate to severe adverse reactions per recommendations in the product labeling.

AUC = area under the curve; BSA = body surface area; IV = intravenous; Q3W = every 3 weeks; Q6W = every 6 weeks; QW = weekly; TNBC = triple-negative breast cancer.

[Insert local label.]

MSD | KEYTRUDA® (pembrolizumab) injection 100 mg

KEYNOTE-522: Baseline Patient Characteristics (N=1,174)

Baseline Characteristics	KEYNOTE-522 (N=1,174)
Median age, years (range)	**49 (22–80)**
Aged ≥65 years	**11%**
Female	**99.9%**
Ethnicity/race	
White	**64%**
Asian	**20%**
Black	**5%**
American Indian or Alaska Native	**2%**
ECOG PS	
0	**87%**
1	**13%**
Menopausal status	
Pre-menopausal	**56%**
Post-menopausal	**44%**

Baseline Characteristics (*continued*)	KEYNOTE-522 (N=1,174)
Primary tumor classification	
T1	**7%**
T2	**68%**
T3	**19%**
T4	**7%**
Nodal involvement	
N0	**49%**
N1	**40%**
N2	**11%**
N3	**0.2%**
Overall disease stage	
II	**75%**
III	**25%**

ECOG PS = Eastern Cooperative Oncology Group performance status.

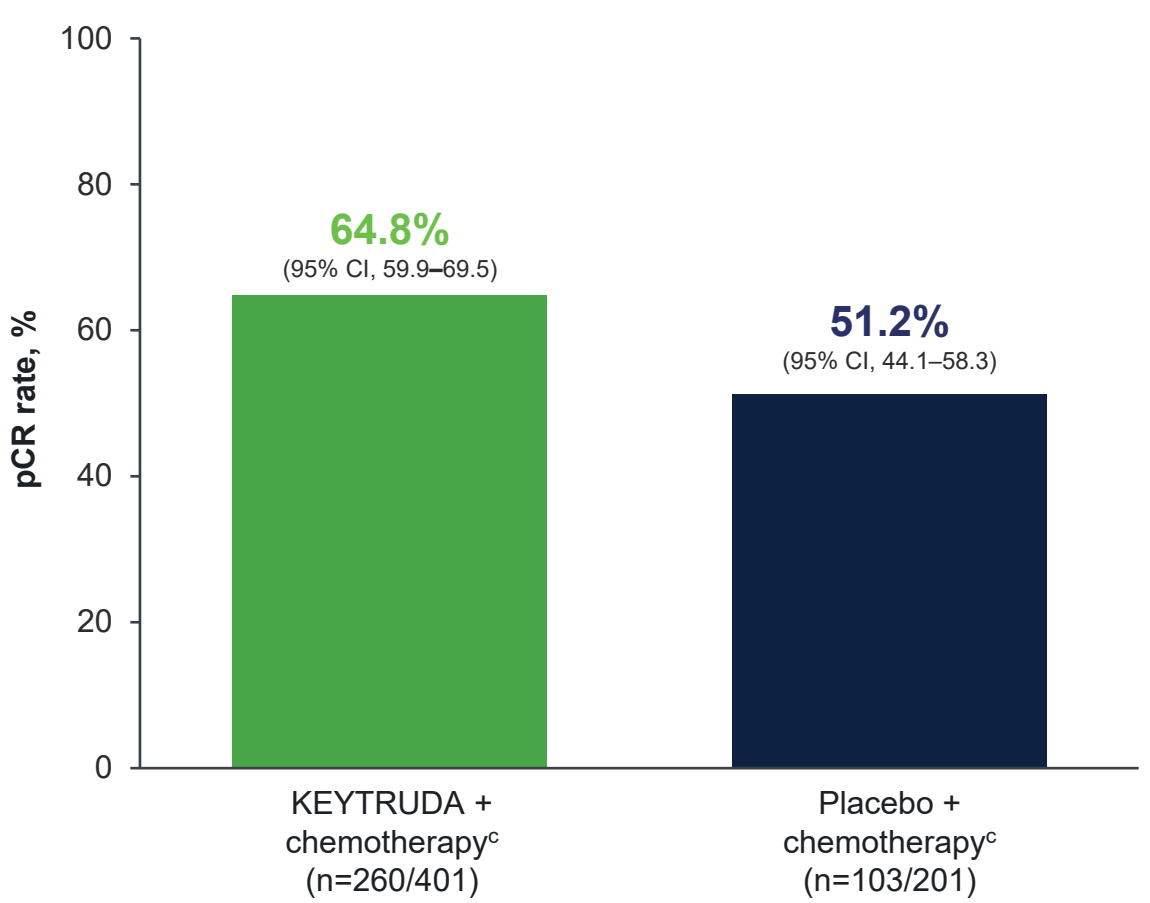
[Insert local label.]

MSD | KEYTRUDA® (pembrolizumab) injection 100 mg

KEYNOTE-522: Pathological Complete Response (pCR) Rate in the ITT Population (N=1,174)

13.6% (95% CI[a], 5.4–21.8; *P*=0.00055)[b] more patients had a pCR with KEYTRUDA® (pembrolizumab) + chemotherapy regimen[c] vs placebo + chemotherapy regimen[c]

The **pCR rate** was **64.8% (260/401)** with KEYTRUDA + chemotherapy regimen[c] vs **51.2% (103/201)** with placebo + chemotherapy regimen[c]



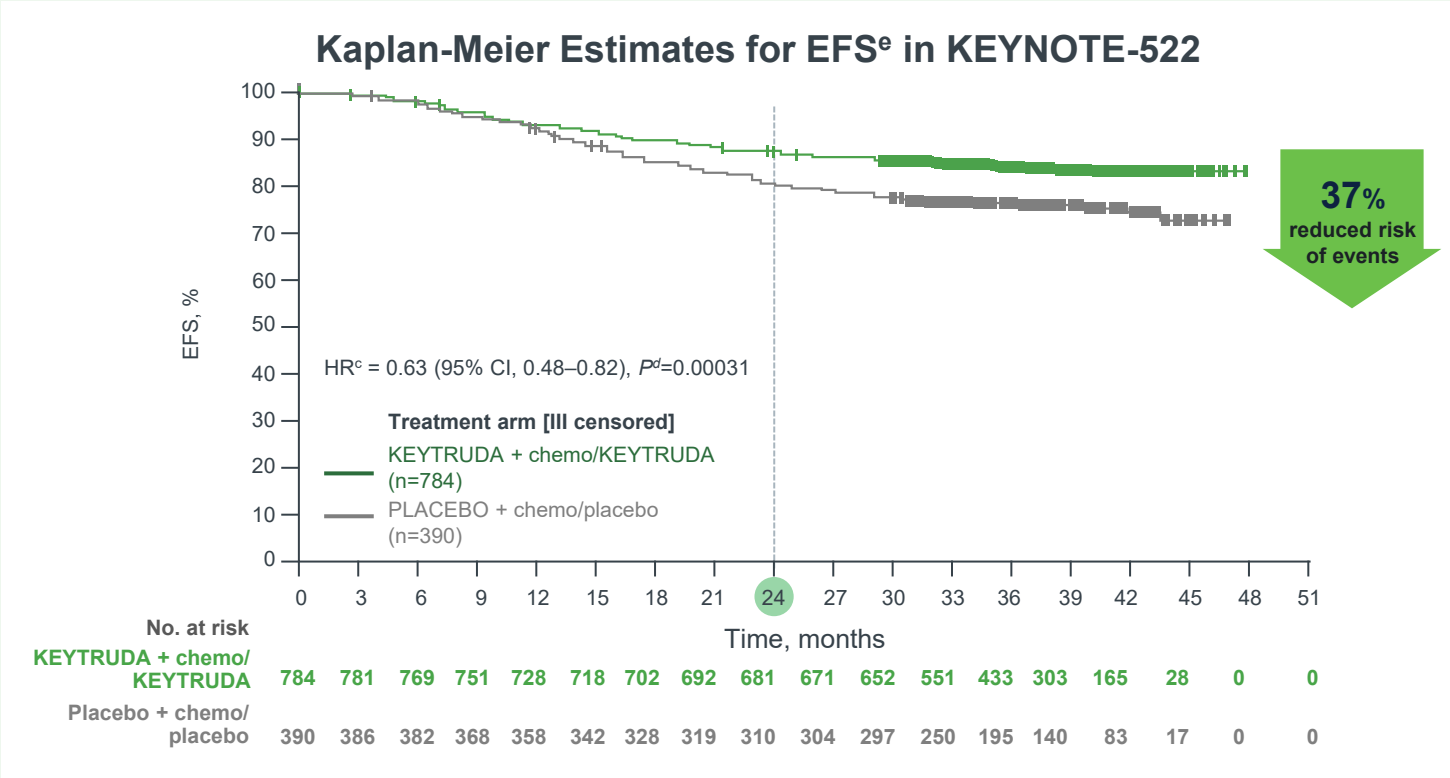
[a]Based on Miettinen and Nurminen method stratified by nodal status, tumor size, and choice of carboplatin. [b]Based on a pre-specified pCR interim analysis (compared to a significance level of 0.003). [c]Carboplatin and paclitaxel followed by (doxorubicin or epirubicin) and cyclophosphamide.
CI = confidence interval; ITT = intent to treat; ypT0/Tis ypN0 = absence of invasive cancer in the breast and lymph nodes.
[Insert local label.]

KEYNOTE-522: Event-free Survival (EFS) in the ITT Population (N=1,174) – at 24-months

Superior EFS with KEYTRUDA® (pembrolizumab) + chemotherapy regimen (carboplatin/paclitaxel followed by AC or EC) vs placebo + the same chemotherapy[a] regimen in the neoadjuvant setting and then KEYTRUDA alone vs placebo alone in the adjuvant setting after surgery

The number of patients with an event[b] was 123/784 (16%) with KEYTRUDA + chemotherapy[a]/KEYTRUDA alone vs **93/390 (24%)** with placebo + chemotherapy[a]/placebo alone

Neoadjuvant treatment with KEYTRUDA + chemotherapy[a] followed by adjuvant treatment with KEYTRUDA vs placebo + chemotherapy[a] followed by placebo alone was associated with a **37% reduction in the risk of an event[b]** (HR[c]=0.63; 95% CI, 0.48–0.82; *P*[d]=0.00031)



[a]Carboplatin and paclitaxel followed by (doxorubicin or epirubicin) and cyclophosphamide. [b]EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. [c]Based on stratified Cox regression model with Efron's method of the handling with treatment as a covariate stratified by nodal status, tumor size, and choice of carboplatin. [d]Based on log-rank test stratified by nodal status, tumor size, and choice of carboplatin. [e]Based on a prespecified EFS interim analysis (compared with a significance level of 0.0052).

AC = doxorubicin and cyclophosphamide; chemo = chemotherapy; CI = confidence interval; EC = epirubicin and cyclophosphamide; HR = hazard ratio; ITT = intent to treat.

[Insert local label.]

KEYNOTE-522: Event-free Survival (EFS) in the ITT Population (N=1,174) – at 36-months

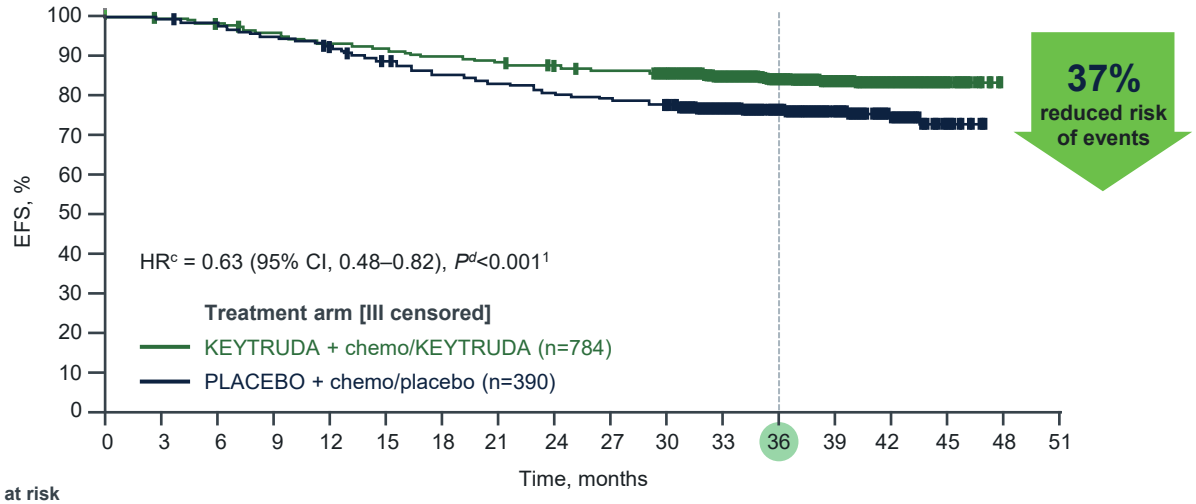
Superior EFS with KEYTRUDA® (pembrolizumab) + chemotherapy regimen (carboplatin/paclitaxel followed by AC or EC) vs placebo + the same chemotherapy[a] regimen in the neoadjuvant setting and then KEYTRUDA alone vs placebo alone in the adjuvant setting after surgery[1,2]

The estimated EFS at **36 months** was **84.5%** (95% CI, 81.7–86.9) in the KEYTRUDA + chemotherapy[a]/KEYTRUDA alone group and **76.8%** (95% CI, 72.2–80.7) in the placebo + chemotherapy[a]/placebo alone group; the median EFS was not reached in either group[1]

The number of patients with an event[b] was **123/784 (15.7%)** with KEYTRUDA + chemotherapy[a]/KEYTRUDA alone vs **93/390 (23.8%)** with placebo + chemotherapy[a]/placebo alone[1]

Neoadjuvant treatment with KEYTRUDA + chemotherapy[a] followed by adjuvant treatment with KEYTRUDA vs placebo + chemotherapy[a] followed by placebo alone was associated with a **37% reduction in the risk of an event[b]** (HR[c]=0.63; 95% CI, 0.48–0.82; *P*[d]<0.001)[1]

Kaplan-Meier Estimates of EFS[e] in KEYNOTE-522[2]



No. at risk																		
KEYTRUDA + chemo/ KEYTRUDA	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo + chemo/placebo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

[a]Carboplatin and paclitaxel followed by (doxorubicin or epirubicin) and cyclophosphamide. [b]EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. [c]Based on stratified Cox regression model with Efron's method of the handling with treatment as a covariate stratified by nodal status, tumor size, and choice of carboplatin. [d]Based on log-rank test stratified by nodal status, tumor size, and choice of carboplatin. [e]Based on a prespecified EFS interim analysis (compared with a significance level of 0.0052).

AC = doxorubicin and cyclophosphamide; chemo = chemotherapy; CI = confidence interval; EC = epirubicin and cyclophosphamide; HR = hazard ratio; ITT = intent to treat.

1. Schmid P, et al. *N Engl J Med*. 2022;386(6):556-567. 2. [Insert local label.]

KEYNOTE-522: Exploratory Analysis of EFS Based on pCR Status (ypT0/Tis ypN0)

LIMITATION: This was an exploratory subgroup analysis from the KEYNOTE-522 trial. KEYNOTE-522 was not powered to detect differences between subgroups. No formal statistical testing was planned for this exploratory analysis and, therefore, results should be interpreted with caution.

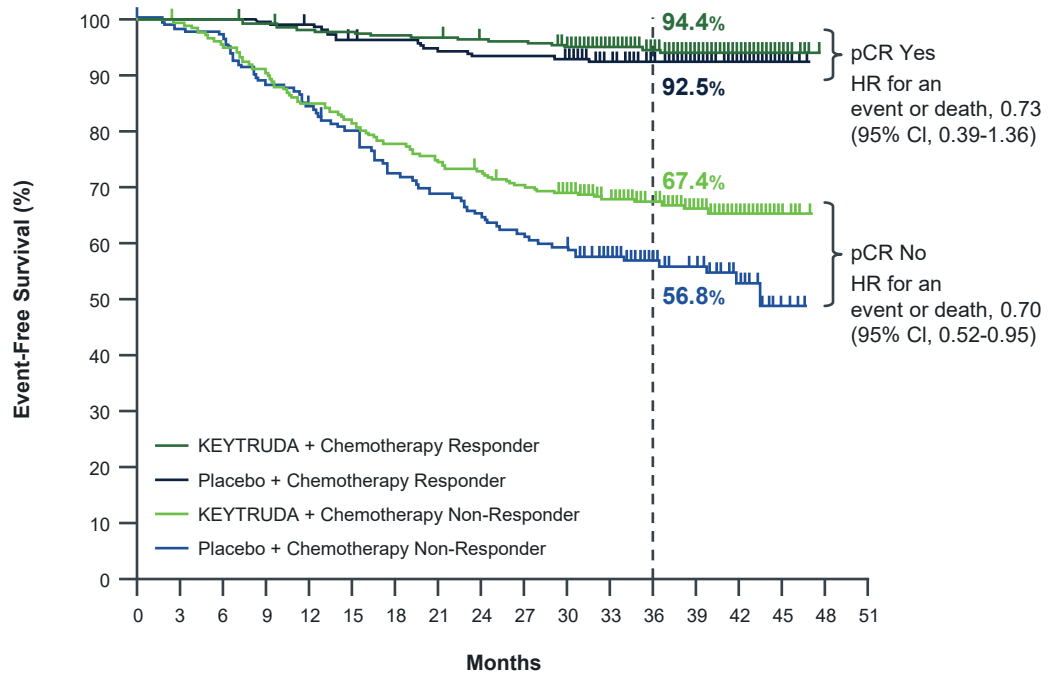
Among patients **with a pCR**, **27/494** (**5.5%**) in the KEYTRUDA® (pembrolizumab) + chemotherapy[a]/ KEYTRUDA alone group and **16/217** (**7.4%**) in placebo + chemotherapy[a]/placebo alone group had an event or died

HR[b]=0.73; 95% CI,[b] 0.39–1.36

Among patients **without a pCR**, **96/290** (**33.1%**) in the KEYTRUDA + chemotherapy[a]/ KEYTRUDA alone group **and** **77/173** (**44.5%**) in the placebo + chemotherapy[a]/placebo alone group had an event or died

HR[b]=0.70; 95% CI,[b] 0.52–0.95

Kaplan-Meier Estimates of EFS By pCR (ypT0/Tis ypN0) By Treatment Group in the ITT Population[b,c]



No. at Risk																		
KEYTRUDA + Chemotherapy Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Placebo + Chemotherapy Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
KEYTRUDA + Chemotherapy Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Placebo + Chemotherapy Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

[a]Carboplatin and paclitaxel followed by (doxorubicin or epirubicin) and cyclophosphamide. [b]The HR and CI were analyzed based on a Cox regression model with treatment as a covariate. [c]Tick marks represent data censored at the last time the patient was known to be alive and without an event (disease progression that precludes definitive surgery; local or distant recurrence or a second primary tumor; or death from any cause) for patients who did not experience an event.

CI = confidence interval; EFS = event-free survival; HR = hazard ratio; ITT = intent to treat; pCR = pathological complete response; ypT0/Tis ypN0 = absence of invasive cancer in the breast and lymph nodes.

Schmid P, et al. *N Engl J Med.* 2022;386(6):556-567.

KEYNOTE-522: Selected Safety Data

In patients with high-risk early-stage TNBC receiving KEYTRUDA® (pembrolizumab) in combination with chemotherapy (carboplatin and paclitaxel followed by AC or EC) given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment, adverse reactions occurring in at least **20%** of the patients and at a higher incidence (**≥5%** difference) compared to patients with TNBC receiving placebo in combination with chemotherapy (carboplatin and paclitaxel followed by AC or EC) given as a neoadjuvant treatment and continued alone as adjuvant treatment were:

Adverse Reaction	KEYTRUDA + Chemotherapy/KEYTRUDA		Placebo + Chemotherapy/Placebo	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Diarrhea	41%	3.2%	34%	1.8%
Rash	30%	1.8%	24%	0.3%
Pyrexia	28%	1.3%	19%	0.3%
Decreased appetite	23%	0.9%	17%	0.3%

AC = doxorubicin and cyclophosphamide; EC = epirubicin and cyclophosphamide; TNBC = triple-negative breast cancer.

[Insert local label.]

Monitoring and Management of Adverse Reactions Associated With KEYTRUDA® (pembrolizumab)

- No dose reductions for KEYTRUDA® (pembrolizumab) are recommended
- Withhold or discontinue KEYTRUDA to manage adverse reactions (as described in the tables below)

Adverse Reactions	Monitoring and Management	Severity	Dose Modification
Immune-mediated pneumonitis	Monitor patients for signs and symptoms of pneumonitis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grades 0–1[a]
	If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes	Severe or life-threatening (Grades 3 or 4) or recurrent moderate (Grade 2)	Permanently discontinue
	Administer corticosteroids for Grade 2 or greater events (initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper)		
Immune-mediated colitis	Monitor patients for signs and symptoms of colitis and exclude other causes	Moderate or severe (Grades 2 or 3)	Withhold until adverse reactions recover to Grades 0–1[a]
	Administer corticosteroids for Grade 2 or greater events (initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper)	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Immune-mediated nephritis	Monitor patients for changes in renal function and exclude other causes	Moderate (Grade 2)	Withhold until adverse reactions recover to Grades 0–1[a]
	Administer corticosteroids for Grade 2 or greater events (initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper)	Severe or life-threatening (Grades 3 or 4)	Permanently discontinue

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v.4).

[a]If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after last dose of KEYTRUDA, then KEYTRUDA should be permanently discontinued. [Insert local label.]

Monitoring and Management of Adverse Reactions Associated With KEYTRUDA® (pembrolizumab)

Adverse Reactions	Monitoring and Management	Severity	Dose Modification
Immune-mediated endocrinopathies	Monitor patients for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and exclude other causes Administer corticosteroids to treat adrenal insufficiency and other hormone replacement as clinically indicated Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids Hyperthyroidism may be managed symptomatically	Moderate (Grade 2) Severe or life-threatening (Grades 3 or 4)	Withhold KEYTRUDA® (pembrolizumab) Withhold until adverse reactions recover to Grades 0–1[a] For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered Withhold KEYTRUDA in cases of severe hyperglycemia until metabolic control is achieved Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency or hypophysitis

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v.4).

[a]If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after last dose of KEYTRUDA, then KEYTRUDA should be permanently discontinued. [Insert local label.]

Monitoring and Management of Adverse Reactions Associated With KEYTRUDA® (pembrolizumab)

Adverse Reactions	Monitoring and Management	Severity	Dose Modification
Immune-mediated hepatitis/non-HCC	Monitor patients for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis and exclude other causes Administer corticosteroids (initial dose of 0.5-1 mg/kg/day [for Grade 2 events] and 1–2 mg/kg/day [for Grade 3 or greater events] prednisone or equivalent followed by a taper)	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 to 5 times upper limit of normal (ULN) or total bilirubin >1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0–1[a]
		AST or ALT >5 times ULN or total bilirubin >3 times ULN	Permanently discontinue
		For patients with liver metastases who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases ≥50% relative to baseline and lasts ≥1 week	Permanently discontinue
Immune-mediated hepatitis/HCC	Monitor patients for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis and exclude other causes. Administer corticosteroids (initial dose of 0.5–1 mg/kg/day [for Grade 2 events] and 1–2 mg/kg/day [for Grade 3 or greater events] prednisone or equivalent followed by a taper)	AST or ALT with baseline <2 times ULN and increases to ≥5 times ULN; AST or ALT with baseline ≥2 times ULN and increases to >3 times baseline; or AST or ALT >500 U/L regardless of baseline levels Total bilirubin with baseline levels <1.5 mg/dL and increases to >2 mg/dL; total bilirubin with baseline levels ≥1.5 mg/dL and increases to ≥2 times baseline; or total bilirubin >3.0 mg/dL regardless of baseline levels	Withhold until adverse reactions recover to Grades 0–1[a]
		ALT >20 times ULN; Child Pugh score ≥9 points; gastrointestinal bleeding suggestive of portal hypertension; ascites; or encephalopathy	Permanently discontinue

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v.4).

[a]If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after last dose of KEYTRUDA, then KEYTRUDA should be permanently discontinued.

HCC = hepatocellular carcinoma.

[Insert local label.]

Monitoring and Management of Adverse Reactions Associated With KEYTRUDA® (pembrolizumab)

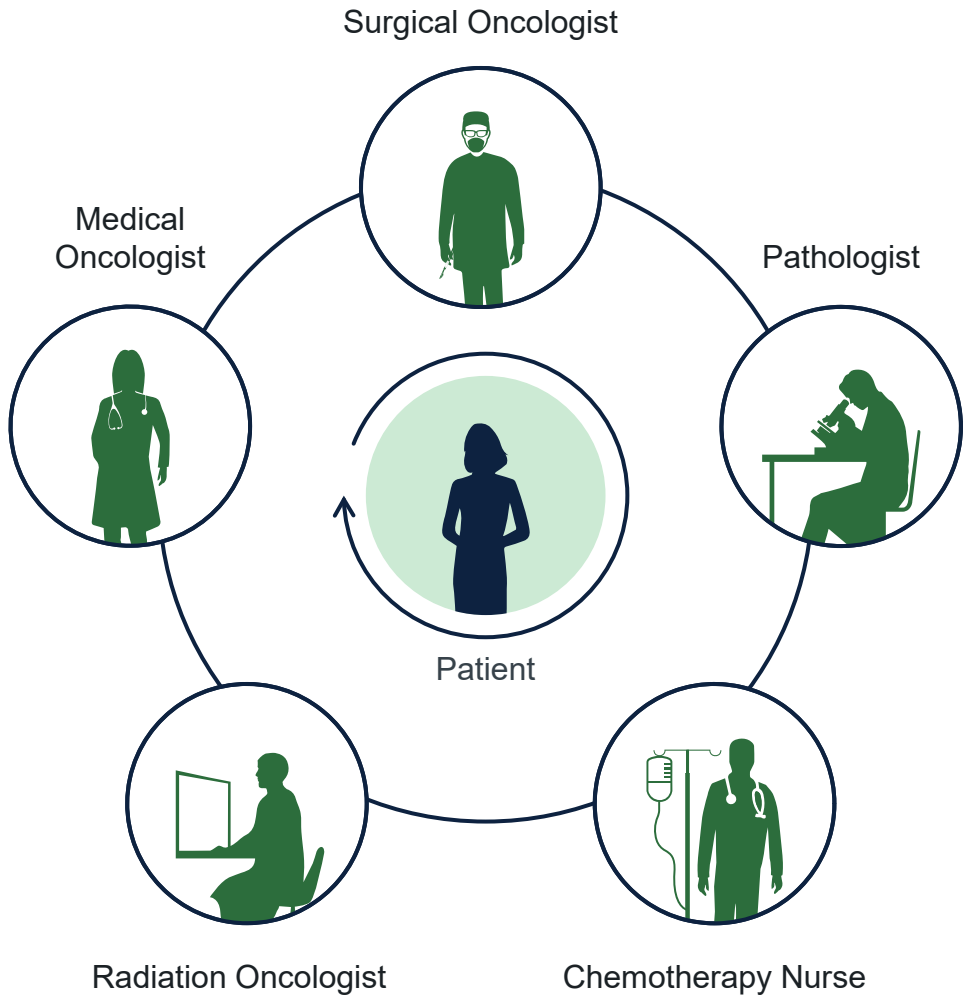
Adverse Reactions	Monitoring and Management	Severity	Dose Modification
Immune-mediated skin reactions or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Monitor patients for suspected severe skin reactions and exclude other causes Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment	Severe skin reactions (Grade 3) or suspected SJS or TEN	Withhold until adverse reactions recover to Grades 0–1[a]
		Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue
Other immune-mediated adverse reactions		Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0–1[a]
		Severe or life-threatening (Grades 3 or 4) myocarditis, encephalitis, or Guillain-Barré syndrome	Permanently discontinue
		Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Infusion-related reactions	Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring Premedication with antipyretic and antihistamine may be considered	Severe or life-threatening (Grades 3 or 4)	Stop infusion and permanently discontinue

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v.4).

[a]If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grades 0–1 within 12 weeks after last dose of KEYTRUDA, then KEYTRUDA should be permanently discontinued. [Insert local label.]

Multidisciplinary Team (MDT): Management of High-Risk Early-Stage TNBC

- An MDT is an important component to providing consistent, continuous, and coordinated care for patients[1]
- Collaboration among specialists can help:
  - Identify the most appropriate treatment options[2]
  - Facilitate the development of a treatment plan[2]



TNBC = triple-negative breast cancer.

1. Saini KS, et al. *Ann Oncol.* 2012;23(4):853–859. 2. Shao J, et al. *Curr Oncol*. 2019;26(3):e385–e397.

Improving Breast Cancer Treatment With Multidisciplinary Care

Improved decision making[1,2]

- Evidence-based treatment decisions
- Adherence to national and local guidelines

More coordination and continuity in patient care[1–3]

- Awareness of services available[3]
- Efficient referrals[3]
- Optimization of resources and more efficient use of time[2]

Improved overall quality of treatment[1]

According to an observational retrospective cohort study, patients discussed by a well-organized MDT showed **15.6%** higher survival at **5 years** vs those not discussed by an MDT[4]

1. Saini KS, et al. *Ann Oncol*. 2012;23(4);853-859. 2. Selby P, et al. *Am Soc Clin Oncol Educ Book*. 2019;39:332-340. 3. Chirgwin J, et al. *J Oncol Pract*. 2010;6(6):294-300. 4. Lu J, et al. *Int J Environ Public Health*. 2020;17:277.

49-year-old Female With No Previous Personal or Family History of Breast Cancer

Hypothetical patient case.

Initial Presentation

- Complains of painless lump in left breast
- BMI: 29 kg/m^2
- Pre-menopausal; no family history of breast cancer

Evaluation

- Physical exam: palpable mass in the left breast
- Diagnostic bilateral mammogram: 2.1-cm spiculated mass lesion in the upper outer quadrant of the left breast corresponding to palpable mass lesion
- Ultrasound: 2.1-cm, irregularly shaped solid mass lesion corresponding to mammographic abnormality without nodal involvement
- Core needle biopsy of the tumor: Grade 3 invasive ductal carcinoma
- Biomarker results: ER/PR-negative, HER2-negative
- Positron emission tomography/computed tomography (PET/CT) scan: negative for distant metastases
- ECOG PS: 0

Diagnosis Clinical prognostic stage IIB TNBC

How would you approach treatment of a patient like this in your own clinic?

BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor; TNBC = triple-negative breast cancer.

MSD | KEYTRUDA (pembrolizumab) injection 100 mg

49-year-old Female With No Previous Personal or Family History of Breast Cancer

Hypothetical patient case.

Treatment Plan

The MDT recommended the patient receive KEYTRUDA® (pembrolizumab) as part of her overall treatment plan, which includes neoadjuvant and adjuvant treatment

Neoadjuvant Treatment

Treatment regimen[a]:

- 4 cycles of KEYTRUDA 200 mg Q3W + carboplatin[b] + paclitaxel[c]
- 4 cycles of KEYTRUDA 200 mg Q3W + doxorubicin + cyclophosphamide (AC)[d]

Follow-up and Management of Adverse Events

- Blood cortisol, along with other screening labwork, were measured before treatment initiation and monitored regularly
- After 12 weeks of neoadjuvant treatment: symptoms of abdominal pain and diarrhea
- Diagnosis: Grade 2 immune-mediated colitis (after other causes were excluded)
- Management:
  - KEYTRUDA was withheld and she was placed on corticosteroids
  - Symptoms subsided and improved to Grade 1; corticosteroids were then successfully tapered over 1 month
  - Treatment with KEYTRUDA was then resumed

[a]All medications were given as an intravenous infusion. [b]carboplatin (AUC 1.5 mg/mL/min QW on days 1, 8, and 15 of cycles 1–4). [c]paclitaxel (80 mg/m^2 QW on days 1, 8, and 15 of cycles 1–4). [d]doxorubicin (60 mg/m^2 Q3W) and cyclophosphamide (600 mg/m^2 Q3W).
AC = doxorubicin and cyclophosphamide; AUC = area under the curve; MDT = multidisciplinary team; Q3W = every 3 weeks; QW = weekly.

49-year-old Female With No Previous Personal or Family History of Breast Cancer

Hypothetical patient case.

Definitive Surgery

- Blood cortisol levels were measured again before surgery
- 5 weeks after last neoadjuvant treatment: Lumpectomy with surgical axillary staging
- Histological analysis showed pCR (ypT0/Tis ypN0)

Adjuvant Treatment

- 4 weeks after surgery: Started treatment with adjuvant KEYTRUDA® (pembrolizumab) 200 mg IV Q3W
- 3 months into adjuvant treatment, she experienced symptoms of fatigue, lethargy, and cold sensitivity
- Thyroid function tests revealed elevated levels of thyroid-stimulating hormone and low free-T4 levels
- Diagnosis: Grade 2 immune-mediated hypothyroidism
- Management: started on thyroid hormone replacement treatment
- Patient continued on adjuvant KEYTRUDA 200 mg IV Q3W for a total of 9 cycles

IV = intravenous; pCR = pathologic complete response; Q3W = every 3 weeks; ypT0/Tis ypN0 = absence of invasive cancer in the breast and lymph nodes.

KEYTRUDA® (pembrolizumab) Is Part of an Effective Treatment Option for Both High-Risk Early-Stage and Advanced TNBC[1,2]

TNBC has poorer outcomes compared to breast cancers of other subtypes, **demonstrating an unmet medical need** in this setting[3,4]

KEYTRUDA® (pembrolizumab) is approved as part of a regimen in **both high-risk early-stage and advanced TNBC**[1,2]

Patients with high-risk early-stage TNBC receiving neoadjuvant KEYTRUDA plus chemotherapy, followed by adjuvant KEYTRUDA in the KEYNOTE-522 study **achieved better outcomes with positive pCR and EFS** compared to neoadjuvant placebo plus chemotherapy, followed by adjuvant placebo[1]

Surgeons and medical oncologists, along with their MDT partners, play an **important role in improving TNBC patient outcomes**[5,6]

EFS = event-free survival; MDT = multidisciplinary team; pCR = pathologic complete response; TNBC = triple-negative breast cancer.

1. [Insert local label.] 2. Cancer Research Institute (CRI). Immunotherapy for Breast Cancer. Accessed March 24, 2022. https://www.cancerresearch.org/en-us/immunotherapy/cancer-types/breast-cancer. 3. NCI SEER Program. Cancer stat facts: female breast cancer subtypes. Accessed May 13, 2022. https://seer.cancer.gov/statfacts/html/breast-subtypes.html. 4. Li X et al. *Breast Cancer Res Treat*. 2017;161(2):279–287. 5. Shao J, et al. *Curr Oncol*. 2019;26(3):e385–e397. 6. Lu J, et al. *Int J Environ Public Health*. 2020;17:277.

Thank You!