Dana-Farber Cancer Institute | Susan F. Smith Center for Women's Cancers

Dana-Farber Breast Oncology Center

Consensus Statement Regarding Use of Pembrolizumab in Patients With Early-Stage Triple-Negative Breast Cancer

Consensus: Obtained at Breast Oncology Center meetings on: 8/4/2021, 9/3/2021, 10/8/2021, 6/24/2022, 12/5/2025, and 5/1/2026.

Acknowledgement: Ana Garrido-Castro, MD and Rui Kitadai, MD, PhD, for their leadership in the consensus discussions and in writing of the statements. Coordination and editorial support were performed by Mr. Scorzoni, Ms. Bak, and Timothy K. Erick, PhD.

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Q2. What is the optimal neoadjuvant treatment regimen and schedule?	When considering neoadjuvant chemotherapy in combination with pembrolizumab, the optimal regimen and schedule is: pembrolizumab, carboplatin, and paclitaxel for 4 cycles, followed by pembrolizumab with dose-dense doxorubicin and cyclophosphamide (with growth factor support) for 4 cycles. Patients for whom an anthracycline-based regimen is contraindicated may be treated with pembrolizumab, carboplatin, and docetaxel OR paclitaxel for 6 cycles.
Q3. What is the optimal monitoring and management strategy for immune-mediated toxicity?	Routine TSH, fT4 and cortisol assessments should be performed at the time points described in Section 3.
Q4. What are the adjuvant treatment recommendations for patients who receive neoadjuvant pembrolizumab?	For patients who achieve a pathologic complete response (pCR), continuation of pembrolizumab in the adjuvant setting is recommended. For patients with residual invasive disease without a known germline deleterious or suspected deleterious mutation in *BRCA1/BRCA2/PALB2*, continuation of pembrolizumab in the adjuvant setting is recommended. The addition of 6-8 cycles of capecitabine to adjuvant pembrolizumab may also be considered. For patients with residual invasive disease and a germline deleterious or suspected deleterious mutation in *BRCA1/BRCA2/PALB2*, one year of adjuvant olaparib

	is recommended, in addition to continuation of pembrolizumab. Patients who are candidates for endocrine therapy (HR-low/HER2-negative) should not receive pembrolizumab in combination with CDK4/6 inhibition and endocrine therapy due to toxicity concerns.
Q5. Should subcutaneous pembrolizumab be considered as an alternative route of administration to intravenous pembrolizumab for patients with high-risk early-stage TNBC who are eligible for (neo)adjuvant pembrolizumab, incorporating patient preference?	Subcutaneous pembrolizumab can be considered as an alternative route of administration to intravenous pembrolizumab in routine clinical practice for patients with high-risk early-stage TNBC, including patients receiving concurrent intravenous chemotherapy, incorporating patient preference.

Additional considerations:

- For all patients presenting with early-stage TNBC and being considered for neoadjuvant chemotherapy, radiographic assessment of the axilla is recommended to assess for possible nodal involvement.
    - Additionally for patients with T1c tumors with a clinically negative axilla, axillary ultrasound should be considered to assess for potential nodal involvement.
- Potential risks and benefits with pembrolizumab should be considered in an individualized manner and discussed with the patient.
- Guidelines are subject to change with evolution of data from existing and future trials.

Introduction

KEYNOTE-522 (KN522) is a randomized, double-blind, phase 3 trial evaluating the addition of pembrolizumab to neoadjuvant platinum-containing chemotherapy followed by adjuvant pembrolizumab in patients with previously untreated stage II–III triple-negative breast cancer (TNBC).[1] Patients were stratified by nodal status, tumor size, and schedule of carboplatin administration, and were eligible regardless of PD-L1 expression status. Participants were randomized in a 2:1 ratio to receive pembrolizumab plus chemotherapy or placebo plus chemotherapy. In the neoadjuvant phase, patients received pembrolizumab (or placebo) in combination with paclitaxel and carboplatin, followed by pembrolizumab (or placebo) with anthracycline and cyclophosphamide. After surgery, patients continued pembrolizumab or placebo as adjuvant therapy for up to nine cycles. The co-primary endpoints were pathologic complete response (pCR) and event-free survival (EFS); overall survival (OS) was a key secondary endpoint.

A total of 1,174 patients were enrolled. In this trial, pembrolizumab significantly improved pCR (64.8% vs 51.2%; $p < 0.001$)[1] and EFS, with 123 events or deaths (15.7%) versus 93 (23.8%) (hazard ratio [HR] for event or death: 0.63, 95% CI, 0.48–0.82), and an estimated 36-month EFS of 84.5% versus 76.8%.[2] With longer follow-up, the EFS benefit was maintained, with a hazard ratio of 0.65 (95% CI: 0.51–0.83) and an estimated 5-year EFS of 81.2% versus 72.2%.[3] The long-term EFS benefit was generally maintained across prespecified subgroups.

Pembrolizumab also demonstrated a statistically significant improvement in OS, with an estimated 5-year OS of 86.6% (95% CI: 84.0% to 88.8%) versus 81.7% (95% CI: 77.5% to 85.2%).[3] The OS benefit was observed across clinically relevant subgroups, including those defined by nodal status, tumor size, and PD-L1 expression. In exploratory analyses, a lower risk of death with pembrolizumab was observed regardless of pCR status, with a numerically greater benefit among patients without pCR.[3]

Based on the significant improvement in pCR[1] and EFS[2] observed in the KN522 trial, on July 26, 2021 the U.S. Food and Drug Administration (FDA) approved the use of pembrolizumab for high-risk, early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.[4]

Based on the KN522 findings and regulatory approval, the purpose of the Dana-Farber Breast Oncology Center (BOC) multidisciplinary meetings held on August 4, September 3, and October 8, 2021 was to discuss recommendations for the use of pembrolizumab in patients with early-stage TNBC. Data were reviewed from the following randomized phase 2 and 3 trials that evaluated the addition of PD-1 or PD-L1 inhibition to neoadjuvant chemotherapy for early-stage TNBC: I-SPY2 (paclitaxel +/- pembrolizumab followed by AC)[5], GeparNuevo[6,7], NeoTRIPaPDL1[8], IMpassion031[9], and KN522[1-3]. Use of adjuvant PD-1 or PD-L1 inhibition in the KN522 and IMpassion031 trials, respectively, was reviewed. Data regarding adjuvant capecitabine (CREATE-X)[10] and olaparib (OlympiA)[11-13] for patients with residual disease post-neoadjuvant chemotherapy were also reviewed. Additional relevant data were reviewed to address the questions in this

document as noted below. On June 24, 2022, the BOC updated these recommendations after reviewing data reported from the NeoPACT trial.

A subcutaneous formulation of pembrolizumab was subsequently approved by the U.S. FDA in September 2025. As this formulation does not alter the approved indications for pembrolizumab, subcutaneous pembrolizumab may be used as an alternative route of administration in clinical settings where intravenous pembrolizumab is currently indicated, including as neoadjuvant and adjuvant treatment for high-risk, early-stage TNBC. Accordingly, the BOC reviewed available data and discussed consensus-based recommendations addressing these considerations on December 5, 2025. The overall consensus statement was also updated based on the available data at this time point.

Development of the Consensus Statements

The preparatory materials for the group discussion were developed initially by Ana Garrido-Castro, MD. Coordination and editorial support were performed by Mr. Scorzoni and Ms. Bak. The evidence in support and consensus statements were presented for discussion to a multidisciplinary group, which includes Dana-Farber physicians, nurses, clinical investigators, lab investigators, translational researchers, administrators, and patient advocates, at the BOC weekly staff meeting, on 8/4/2021, 9/3/2021, 10/8/2021 and 6/24/2022. The discussion and suggestions for improvements continued via email exchanges following the meetings. The final consensus statements were consolidated in July 2022.

Subsequently, the statement was updated to address the use of subcutaneous pembrolizumab by Rui Kitadai, MD, PhD, and Dr. Garrido-Castro, with continued editorial support from Mr. Scorzoni, Ms. Bak, and Timothy K. Erick, PhD. These updates were informed by review of newly available data and were discussed at BOC staff meetings in December 2025 and May 2026.

The consensus statements can be subject to future variations and periodic updates, based on emerging evidence and new reports from ongoing clinical studies. Therefore, the information provided in this document should not be considered as being complete or inclusive of all proper assessments, treatments or methods of care or as a statement of the standard of care. This information does not mandate any particular course of medical care and is not intended to be a substitute for the independent professional judgment of a health care provider. The document is based on the opinion of a multidisciplinary team at Dana-Farber but does not represent the official institutional position, and overall must be considered as a consensus based on the positions and ideas of the Dana-Farber providers.

Clinical Questions

This document summarizes the discussions and consensus among the Dana-Farber BOC group regarding the following clinical questions:

- **Q1: Which patients with early-stage triple-negative breast cancer (TNBC) should receive neoadjuvant pembrolizumab?**

- **Q2: What is the optimal neoadjuvant treatment regimen and schedule?**
- **Q3: What is the optimal monitoring and management strategy for immune-mediated toxicity?**
- **Q4: What are the adjuvant treatment recommendations for patients who receive neoadjuvant pembrolizumab?**
- **Q5: Should subcutaneous pembrolizumab be considered as an alternative route of administration to intravenous pembrolizumab for patients with high-risk early-stage TNBC who are eligible for (neo)adjuvant pembrolizumab, incorporating patient preference?**

Additional considerations:

- For all patients presenting with early-stage TNBC and being considered for neoadjuvant chemotherapy, radiographic assessment of the axilla is recommended to assess for possible nodal involvement.
    - Additionally for patients with T1c tumors with a clinically negative axilla, axillary ultrasound should be considered to assess for potential nodal involvement.
- Potential risks and benefits with pembrolizumab should be considered in an individualized manner and discussed with the patient.
- Guidelines are subject to change with evolution of data from existing and future trials.

Q1. Which patients with early-stage triple-negative breast cancer (TNBC) should receive neoadjuvant pembrolizumab?

The following considerations, including a) clinical stage at diagnosis and b) hormone receptor expression, for recommendations on the use of neoadjuvant pembrolizumab are detailed below.

A) Clinical anatomic stage at diagnosis:
After review of the data noted above, the consensus among the group was to consider neoadjuvant pembrolizumab for patients with anatomic stage II or III TNBC per the eligibility criteria of the KN522 trial[1], recognizing that the potential risks and benefits of the addition of pembrolizumab to neoadjuvant chemotherapy should be carefully considered and that the absolute benefits may vary within each stage category. The potential absolute improvement in EFS and OS with the addition of pembrolizumab will likely be greater for patients at higher risk of recurrence (e.g., larger tumor size, node-positive status).

B) Hormone receptor expression:
Patients with centrally confirmed TNBC in all foci (as defined by ASCO/CAP guidelines[14,15]) were eligible for KN522. Retrospective studies suggest that hormone receptor (HR)-low/HER2-negative tumors (ER/PR 1% to <10%) may have similar clinicopathologic and molecular features compared to HR-negative/HER2-negative tumors, including similar distribution of histologic grade, prevalence of basal PAM50

subtype, response to neoadjuvant chemotherapy, and survival outcomes in patients with residual disease.[16-19]

In patients with HR-low/HER2-negative tumors who are considered candidates for neoadjuvant chemotherapy, use of neo-/adjuvant pembrolizumab may be considered.

Consensus Statement

Neoadjuvant pembrolizumab should be considered for patients with previously untreated high-risk early-stage (anatomic clinical stage II-III) TNBC or HR-low/HER2-negative breast cancer who are considered candidates for neoadjuvant chemotherapy.

Q2. What is the optimal neoadjuvant treatment regimen and schedule?

The schedule of administration of neoadjuvant chemotherapy and pembrolizumab in KN522 was as follows:

- First neoadjuvant treatment: 4 cycles of pembrolizumab 200 mg Q3W plus paclitaxel (80 mg/m^2 once weekly) plus carboplatin (at AUC 5 mg/mL/min once every 3 weeks or 1.5 mg/mL/min once weekly) in the first 12 weeks, followed by:
- Second neoadjuvant treatment: 4 cycles of pembrolizumab 200 mg Q3W plus doxorubicin (60 mg/m^2) or epirubicin (90 mg/m^2) plus cyclophosphamide (600 mg/m^2) once every 3 weeks in the subsequent 12 weeks

Considerations regarding the optimal neoadjuvant regimen, including dosing and schedule, are detailed below.

A) Addition of carboplatin to the neoadjuvant chemotherapy backbone:
The impact on long-term outcomes of the addition of carboplatin to an anthracycline- and taxane-based regimen in the neoadjuvant TNBC setting has been investigated in several randomized clinical trials, including the CALGB 40603, GeparSixto, and BrighTNess trials. Differences in survival results with the addition of carboplatin have been observed across these studies. Importantly, these trials were not powered to detect differences in long-term outcomes.

- In CALGB 40603, patients with TNBC were randomized in a 2x2 factorial design to receive the addition of carboplatin (Q3W) and/or bevacizumab to weekly paclitaxel followed by dose-dense doxorubicin and cyclophosphamide (ddAC). While carboplatin was associated with a significant increase in pCR[20], long-term follow-up analyses did not demonstrate a significant difference in EFS or OS between patients treated with or without carboplatin. Patients who experienced pCR had substantially improved long-term outcomes compared to those with residual disease.[21]

- GeparSixto explored the addition of platinum to a non-standard concurrent anthracycline-, taxane-, and bevacizumab-containing regimen. Patients with TNBC received 18 weeks of weekly non-pegylated liposomal doxorubicin and paclitaxel plus every 3-week bevacizumab, with or without weekly carboplatin. The addition of carboplatin significantly improved pCR and disease-free survival, but not OS.[22,23]
- The BrighTNess trial compared the addition of carboplatin (Q3W) plus veliparib to weekly paclitaxel, and the addition of veliparib to carboplatin (Q3W) plus weekly paclitaxel, followed by AC (dose-dense or Q3W) as neoadjuvant therapy for stage II-III TNBC. A significant increase in pCR was observed with the addition of carboplatin and veliparib to paclitaxel followed by AC, but not with the addition of veliparib to carboplatin and paclitaxel.[24] Given that both co-primary pCR endpoints were required to be statistically significant to continue formally testing secondary endpoints (EFS and OS), secondary analyses were descriptive. At a median follow-up of 4.5 years, improved EFS was reported in each of the carboplatin-containing arms compared to paclitaxel (including a post-hoc analysis comparing carboplatin plus paclitaxel vs. paclitaxel). Notably, the rates of distant recurrence were numerically similar across the three treatment arms. No significant differences in OS were reported between treatment arms.[25]
- A pooled analysis of the BrighTNess, CALGB 40603, and GeparSixto trials demonstrated that the addition of carboplatin significantly increased pCR rates and was associated with improved EFS, although no significant improvement in OS was observed.[26]

Data from the CALGB 40603 trial suggest that addition of carboplatin (AUC 6 mg/mL/min Q3W) increases the need for dose reductions of both weekly paclitaxel and ddAC, and increases the likelihood of missing two or more doses of paclitaxel.[20] Similarly, treatment discontinuations were higher and the mean relative total dose intensity for all treatments was lower in patients randomized to receive carboplatin (AUC 2 mg/mL/min [or 1.5 mg/mL/min after study amendment due to safety interim analysis] weekly) in GeparSixto.[22]

Given the demonstrated pCR[1], EFS[2], and OS benefit[3] with treatment following the KN522 regimen, at the time of the updated statement in December 2025, the consensus within the group was to consider inclusion of carboplatin in the neoadjuvant regimen for all patients who are candidates for the KN522 regimen and do not otherwise have a contraindication to platinum therapy.

B) Dose intensity of chemotherapy:
Considering the benefit of dose-dense administration of chemotherapy in early-stage ER-negative breast cancer[27], the group favored dose-dense scheduling of AC in combination with pembrolizumab, recognizing that this differs from the schedule of administration of chemotherapy in KN522.[1] Prophylactic growth factor support should be administered with dose-dense AC and as needed during neoadjuvant chemotherapy to prevent re-occurrence of severe neutropenia or febrile neutropenia.

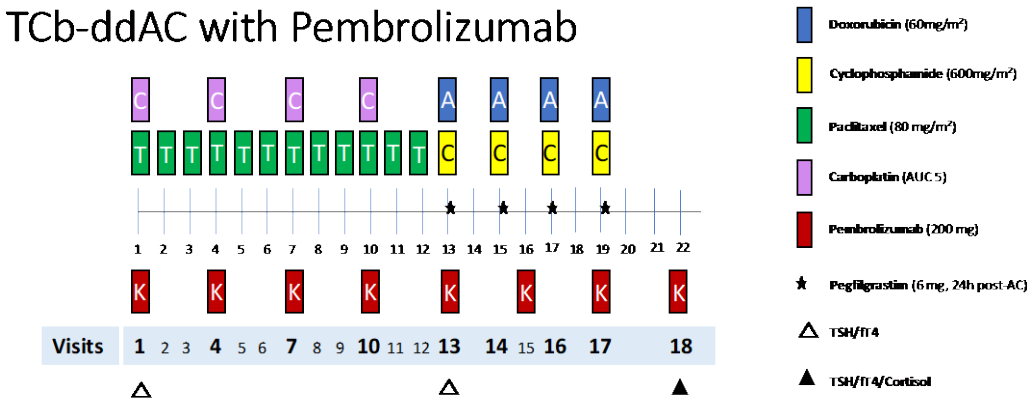
C) Dosing of neoadjuvant chemotherapy with pembrolizumab:

- **Carboplatin** (Q3W or weekly) **+ paclitaxel** (weekly) + **pembrolizumab** (Q3W) followed by **AC** (Q2W) **+ pembrolizumab** (Q3W): TCb-ddAC with pembrolizumab

Both weekly and Q3W versions of carboplatin may be administered in combination with paclitaxel. The risk of hypersensitivity reactions has been shown to increase with cumulative dose and number of cycles of carboplatin. Deleterious mutations in *BRCA1* and *BRCA2* are also an independent risk factor for hypersensitivity to platinum salts, with potential earlier onset of reactions.[28-30]

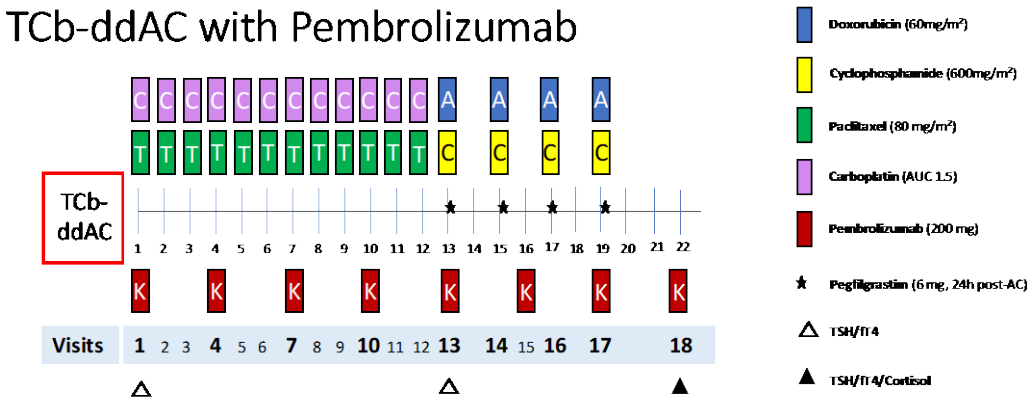
Pembrolizumab is approved with 200 mg Q3W or 400 mg Q6W intravenous (IV) dosing. The group preferred Q3W IV dosing during the neoadjuvant portion of therapy (when the risk of immune-mediated toxicity is higher) to allow dose delays and/or discontinuation of pembrolizumab, if needed.

Option A: TCb (Q3W carboplatin/weekly paclitaxel) followed by ddAC



- Carboplatin (starting dose of AUC 5 mg/mL/min) IV Q3W x 4 doses.
- Paclitaxel (80 mg/m^2) weekly IV x 12 doses.
- Doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) IV Q2W x 4 doses, with growth factor support.
- Pembrolizumab 200 mg IV Q3W x 8 doses in the neoadjuvant portion of treatment.

Option B: TCb (weekly carboplatin/paclitaxel) followed by ddAC



- Carboplatin (starting dose of AUC 1.5 mg/mL/min) IV weekly x 12 doses.
- Paclitaxel (80 mg/m^2) weekly IV x 12 doses.
- Doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) IV Q2W x 4 doses, with growth factor support.
- Pembrolizumab 200 mg IV Q3W x 8 doses in the neoadjuvant portion of treatment.

- **If anthracyclines are contraindicated: Carboplatin** (Q3W) **+ docetaxel** (Q3W) + **pembrolizumab** (Q3W):

  In patients in whom an anthracycline-based regimen is contraindicated, data from the NeoPACT trial[31] support the use of an anthracycline-sparing regimen with carboplatin, docetaxel, and pembrolizumab as neoadjuvant therapy. Among all patients enrolled on the trial (stage I-III with tumor size >1.0 cm or node-positive; ER and PR up to 10%), the pCR rate was 58%. Among patients with stage II-III TNBC (defined as ER and PR <1%, similar to the eligibility in KN522), the pCR rate was 58%. In this phase 2 trial, patients received a total of 6 cycles of combination therapy prior to surgery:

  - Carboplatin (starting dose of AUC 6 mg/mL/min) IV Q3W x 6 doses
  - Docetaxel (starting dose of 75 mg/m^2) IV Q3W x 6 doses
  - Pembrolizumab 200 mg IV Q3W x 6 doses

  Alternatively, if paclitaxel-based treatment is preferred (e.g., due to toxicity concerns with docetaxel), weekly paclitaxel may be considered in combination with carboplatin and pembrolizumab:

  - Carboplatin (starting dose of AUC 6 mg/mL/min) IV Q3W x 6 doses
  - Paclitaxel (starting dose of 80 mg/m^2) IV weekly x 18 doses
  - Pembrolizumab 200 mg IV Q3W x 6 doses

Consensus Statement

When considering neoadjuvant chemotherapy in combination with pembrolizumab, the optimal regimen and schedule is: pembrolizumab, carboplatin, and paclitaxel for 4 cycles, followed by pembrolizumab with dose-dense doxorubicin and cyclophosphamide (with growth factor support) for 4 cycles.

Patients for whom an anthracycline-based regimen is contraindicated may be treated with pembrolizumab, carboplatin, and docetaxel OR paclitaxel for 6 cycles.

Q3. What is the optimal monitoring and management strategy for immune-mediated toxicity?

Toxicity monitoring assessment time points from the KN522 trial were reviewed. In KN522[1], most treatment-related adverse events (TRAEs) occurred during the neoadjuvant phase. TRAEs of grade 3 or higher occurred in 76.8% of patients in the pembrolizumab–chemotherapy group and 72.2% of those in the placebo–chemotherapy group. Serious TRAEs occurred in 32.5% and 19.5% of patients, respectively; febrile neutropenia was the most common serious TRAE (14.6% vs 12.1%). TRAEs led to discontinuation of any trial drug in 23.3% of patients in the pembrolizumab–chemotherapy group and 12.3% in the placebo–chemotherapy group. In the KN522 protocol, thyroid function testing (T3, free T4, and TSH) was specified at screening, at Treatment 2 (AC or EC) Cycle 1 Day 1, at the 30-day safety follow-up after the neoadjuvant phase, at the 30-day safety follow-up after definitive surgery, at the 30-day safety follow-up after the adjuvant phase, and at early discontinuation and long-term follow-up visits. During long-term follow-up, assessments were scheduled every 3 months for the first 2 years after adjuvant treatment, every 6 months in years 3–4, and annually thereafter. Cortisol assessment was specified at screening and at the definitive surgery time point.

The consensus among the group was to perform the following routine assessments (regardless of whether pembrolizumab is held, delayed or discontinued, and regardless of whether pembrolizumab is continued in the adjuvant setting):

- Baseline: TSH, fT4
- Between anthracycline- and taxane-based portions of neoadjuvant therapy: TSH, fT4
- On day of last dose of neoadjuvant chemotherapy/prior to surgery: Cortisol (am), TSH, fT4
- First postoperative appointment: TSH, fT4
- Every 12 weeks while receiving adjuvant systemic therapy (with or without pembrolizumab): TSH, fT4
- At follow-up visits (e.g. 3-6 months): TSH, fT4 (for at least 12 months post-discontinuation of pembrolizumab)

These recommendations are also consistent with SITC guidance[32] emphasizing ongoing monitoring for immune-related toxicities, including endocrine toxicities such as thyroid dysfunction and adrenal insufficiency, and referral to appropriate specialists when indicated, recognizing that immune-related adverse events may occur not only during treatment but also after treatment discontinuation.

There are no contraindications for intravenous (IV) pembrolizumab per FDA label. However, in patients who meet KN522 exclusion criteria, the risks of immune-mediated toxicity should be carefully considered and discussed with the corresponding specialist and patient. KN522 exclusion criteria included (but were not limited to):

- Active autoimmune disease for which the patient had received systemic treatment within the previous 2 years
- Diagnosis of immunodeficiency or use of immunosuppressive therapy within the previous week
- History of HIV infection
- History of noninfectious pneumonitis for which the patient had received glucocorticoids or current pneumonitis
- Active tuberculosis
- Active HBV or HCV infection
- Any active infection for which the patient was receiving systemic therapy

Consensus Statement

Routine TSH, fT4 and cortisol assessments should be performed at the time points described in Section 3.

Q4. What are the adjuvant treatment recommendations for patients who receive neoadjuvant pembrolizumab?

It remains unclear if/how continuation of pembrolizumab in the adjuvant setting, after prior pembrolizumab in the neoadjuvant setting, contributed to the EFS[2] and OS[3] benefit observed in KN522 in patients randomized to the pembrolizumab arm. Long-term outcome results from the GeparNuevo trial[7], albeit not powered to detect significant differences in survival, showed higher rates of 7-year invasive disease-free, distant disease-free, and overall survival in patients who received neoadjuvant durvalumab (vs. placebo) in combination with an anthracycline- and taxane-based (non-platinum containing) regimen, without receipt of additional immune checkpoint inhibition in the adjuvant setting. However, given the significant EFS[2] and OS[3] benefit demonstrated with the schedule of administration of pembrolizumab in KN522 (8 doses Q3W in the neoadjuvant setting followed by 9 doses Q3W in the adjuvant setting to complete a total duration of one year of PD-1 inhibitor therapy), the consensus among the group was that pembrolizumab should be continued in the adjuvant setting in patients who have not experienced significant immune-related toxicity. Ongoing clinical trials are evaluating optimal use of immune checkpoint inhibitors in the adjuvant setting. The

phase 3 OptimICE-pCR trial (NCT05812807) is evaluating whether pembrolizumab continuation can be safely omitted in patients who experience pCR after neoadjuvant chemoimmunotherapy.[33]

Improvements in long-term outcomes with other systemic therapies in patients with residual disease post-neoadjuvant chemotherapy have also been reported (e.g., capecitabine, CREATE-X trial[10]; olaparib in patients with germline *BRCA1* or *BRCA2* mutation, OlympiA trial[11-13]). Relatively consistent benefits have been observed in long-term outcomes across these trials for patients with TNBC with residual disease post neoadjuvant chemotherapy. Given the benefits observed with olaparib in the metastatic setting in patients with germline *PALB2* mutations[34], adjuvant olaparib may also be considered for patients with germline *PALB2* mutations with TNBC who meet eligibility criteria for the OlympiA trial, including those with residual disease after neoadjuvant chemotherapy.

To our knowledge, data have not been reported to date on the efficacy of adjuvant pembrolizumab combined with capecitabine or with olaparib (concurrent or sequential administration) in patients with early-stage TNBC. Safety data have been reported for these combinations (capecitabine plus pembrolizumab[35,36]; olaparib plus pembrolizumab[37]) in the metastatic setting.

A) Adjuvant systemic treatment post neoadjuvant chemotherapy plus pembrolizumab:

Type of neoadjuvant chemotherapy, residual cancer burden, germline *BRCA1/BRCA2/PALB2* status, and individualized risk assessment should be considered when making decisions about systemic therapy in the adjuvant setting.

- In patients with **pCR at surgery** after neoadjuvant pembrolizumab + chemotherapy, **continuation of pembrolizumab** in the adjuvant setting is recommended for patients who have not experienced significant immune-related toxicity.

- In patients with **residual disease at surgery** after neoadjuvant pembrolizumab + chemotherapy:
  - **For non-germline *BRCA1/ BRCA2/ PALB2* carriers:**
    - **Continuation of pembrolizumab** in the adjuvant setting is recommended for patients who have not experienced significant immune-related toxicity.
    - **Addition of capecitabine** (6-8 cycles; 1000 mg/m^2 twice daily on days 1-14 every 3 weeks) is recommended. Decisions regarding the addition of capecitabine to adjuvant pembrolizumab should be made in an individualized manner, with careful consideration of potential residual toxicities from the neoadjuvant regimen.
    - When considering administration of both pembrolizumab and capecitabine, the group favored concurrent administration of both agents, if adequately tolerated.
  - **For germline *BRCA1/ BRCA2/ PALB2* carriers:**

- **Adjuvant olaparib** (300 mg twice daily for 52 weeks) is recommended.
- Addition of pembrolizumab is recommended for patients who have not experienced significant immune-related toxicity.
- When considering administration of both olaparib and pembrolizumab, the group favored concurrent administration of both agents, if adequately tolerated.

B) Additional considerations regarding pembrolizumab use in the adjuvant setting:

Dosing and schedule: The preference among the group was to consider pembrolizumab 400 mg Q6W dosing when administered in the adjuvant setting. To complete a total duration of one year of pembrolizumab, after 24 weeks of neoadjuvant pembrolizumab (200 mg Q3W x 8 doses), adjuvant pembrolizumab may be administered 400 mg Q6W x 4 doses followed by 200 mg Q3W x 1 dose. When possible, immune-mediated toxicity monitoring assessments should be aligned with pembrolizumab treatment visits in the adjuvant setting.

Radiation therapy: Concurrent administration of adjuvant radiation therapy with pembrolizumab was allowed in KN522. Per KN522, if postoperative radiation therapy is indicated, adjuvant pembrolizumab may be started either concurrently with radiation therapy or post radiation therapy. Concurrent administration of other systemic therapies (e.g. capecitabine, olaparib) with adjuvant pembrolizumab was not allowed.[1]

When considering adjuvant radiation therapy and pembrolizumab with or without capecitabine or olaparib:
- If pCR: patients may receive concurrent radiation therapy and pembrolizumab, followed by pembrolizumab alone.
- If residual disease: patients may receive concurrent radiation therapy and pembrolizumab, followed by pembrolizumab with capecitabine or olaparib.

No prior neoadjuvant IO: Considering the lack of data supporting the use of adjuvant pembrolizumab in patients who have not received neoadjuvant pembrolizumab, for patients with early-stage TNBC who have undergone surgery (without neoadjuvant chemotherapy or with neoadjuvant chemotherapy that did not include pembrolizumab), the group would **not** routinely recommend treatment with pembrolizumab in the adjuvant setting.

There are adjuvant-only immunotherapy trials that may support this consideration. The phase 3 A-BRAVE trial evaluated one year of adjuvant avelumab versus observation in patients with high-risk early TNBC who had completed standard surgery and anthracycline- and taxane-based (neo)adjuvant chemotherapy. High-risk disease was defined as either ≥pN2/any pT, pN1/pT2, or pN0/pT3 after primary surgery (stratum A), or residual invasive disease after neoadjuvant chemotherapy (stratum B). This trial did not demonstrate a significant DFS benefit in the intent-to-treat population or in stratum B, although a descriptive analysis suggested a potential OS benefit favoring avelumab.[38] The phase 3 ALEXANDRA/IMpassion030 trial evaluated the addition of one year of adjuvant atezolizumab to anthracycline- and taxane-based chemotherapy in patients

with stage II–III TNBC who underwent primary surgery without prior neoadjuvant therapy. The addition of atezolizumab did not improve iDFS compared with chemotherapy alone. Enrollment was halted early and atezolizumab was discontinued in all patients following a planned interim futility analysis.[39]

Hormone Receptor Status: Patients with HR-low/HER2-negative tumors are considered candidates for adjuvant endocrine therapy. Endocrine therapy plus CDK4/6 inhibition (e.g., abemaciclib, ribociclib) plus PD-1 inhibition should not be given in combination due to toxicity concerns.[40-42]

Consensus Statement

For patients who achieve a pathologic complete response (pCR), continuation of pembrolizumab in the adjuvant setting is recommended.

For patients with residual invasive disease without a known germline deleterious or suspected deleterious mutation in *BRCA1/BRCA2/PALB2*, continuation of pembrolizumab in the adjuvant setting is recommended. The addition of 6-8 cycles of capecitabine to adjuvant pembrolizumab may also be considered.

For patients with residual invasive disease and a germline deleterious or suspected deleterious mutation in *BRCA1/BRCA2/PALB2*, one year of adjuvant olaparib is recommended, in addition to continuation of pembrolizumab.

Patients who are candidates for endocrine therapy (HR-low/HER2-negative) should not receive pembrolizumab in combination with CDK4/6 inhibition and endocrine therapy due to toxicity concerns.

Q5. Should subcutaneous pembrolizumab be considered as an alternative route of administration to intravenous pembrolizumab for patients with high-risk early-stage TNBC who are eligible for (neo)adjuvant pembrolizumab, incorporating patient preference?

Subcutaneous (SC) pembrolizumab has been developed as an alternative route of administration to intravenous (IV) pembrolizumab. In the randomized phase 3 MK-3475A-D77 trial, patients with metastatic non–small cell lung cancer (NSCLC) were randomized 2:1 to receive SC (n = 251) or IV pembrolizumab plus chemotherapy (n = 126). Pembrolizumab was administered as SC pembrolizumab 790 mg every 6 weeks (q6w) or IV pembrolizumab 400 mg q6w, each in combination with chemotherapy, for up to 18 cycles. The primary objective was to demonstrate noninferiority of pembrolizumab exposure with SC versus IV administration, assessed by cycle 1 AUC_0–6weeks and cycle 3 steady-state trough concentration ($C_t$rough). SC pembrolizumab met the prespecified noninferiority criteria, with geometric mean ratios of 1.14 (96% CI: 1.06–1.22) for AUC_0–6weeks and 1.67 (94% CI: 1.52–1.84) for $C_t$rough compared with IV administration. Descriptive efficacy outcomes were similar between arms, with an objective response rate (ORR) of 45% in the SC group and 42% in the IV group (ORR ratio 1.08, 95% CI: 0.85-1.37), and a median progression-free survival (PFS) of 8.1

months versus 7.8 months, respectively (HR: 1.05, 95% CI, 0.78–1.43). Although the median OS was not reached in either treatment arm (HR: 0.81, 95% CI: 0.53-1.22), the OS event rate was comparable between the pembrolizumab SC and IV arms (24.3% versus 29.4%). The safety profile was consistent between the two arms. Injection-site reactions occurred in 2.4% of patients in the SC arm, all grade 1, and without treatment discontinuation.[43]

An additional study, the randomized, phase 2, two-arm crossover MK-3475A-F11 trial, evaluated participant preferences for SC versus IV pembrolizumab across multiple tumor types, including melanoma, renal cell carcinoma, and NSCLC. Overall, 71 participants were randomized to Arm A (3 cycles of pembrolizumab SC 395 mg Q3W followed by 3 cycles of pembrolizumab IV 200 mg Q3W) and 76 were randomized to Arm B (3 cycles of pembrolizumab IV 200 mg Q3W followed by 3 cycles of pembrolizumab SC 395 mg Q3W). After completion of the crossover period, following all 6 cycles of treatment, the participant preference rate for SC pembrolizumab was 65% (95% CI: 56%–74%). Following completion of the crossover period, a greater proportion of participants elected to continue treatment with SC rather than IV pembrolizumab (68% vs 32%). Health care professional (HCP) preference was assessed as a secondary endpoint, with 66% of HCPs favoring SC administration. Among participants, the preference for SC administration was primarily driven by shorter time required for administration and greater comfort during administration, whereas preference for IV administration was primarily related to greater comfort during administration and lower emotional distress. Among HCPs, preference for SC administration was largely driven by shorter administration time and ease of administration. Compared with SC preference, IV preference was more specifically characterized by considerations related to participant body type and skin integrity. Safety findings were comparable within and between arms, supporting the safety of switching between routes of administration.[44]

The SC formulation does not alter the approved indications for pembrolizumab and is intended to provide an alternative route of administration in clinical settings where IV pembrolizumab is currently indicated, including early-stage TNBC. SC pembrolizumab is contraindicated in patients with known hypersensitivity to berahyaluronidase alfa, hyaluronidase, or any of its excipients.[45] From a practical perspective, SC pembrolizumab offers meaningful advantages in routine clinical practice, including substantially shorter administration times compared with IV infusion (approximately 1 minute for Q3W dosing and 2 minutes for Q6W dosing with SC administration, versus approximately 30 minutes for IV infusion for both 200 mg and 400 mg dosing).

For patients with early-stage TNBC receiving pembrolizumab in combination with IV chemotherapy, an important practical consideration is whether SC pembrolizumab should be preferred over IV pembrolizumab given that IV access is routinely required for chemotherapy administration. As reviewed above, SC pembrolizumab has demonstrated comparable pharmacokinetic exposure, efficacy, and safety to IV administration across different solid tumor types, while offering substantially shorter administration times and potential improvements in clinic workflow and patient experience. During discussions within the BOC group, the majority of providers indicated that they would prefer SC pembrolizumab regardless of concurrent administration of IV chemotherapy, assuming patient preference is incorporated,

whereas some providers did not prefer SC administration in this setting. The primary reasons for preferring SC administration included the substantially shorter administration time and reduced infusion chair utilization.

Based on available clinical trial data and considerations related to real-world clinical implementation, the BOC group reached consensus that subcutaneous pembrolizumab should be considered an alternative route of administration to intravenous pembrolizumab in routine clinical practice for patients with early-stage TNBC, including patients receiving concurrent intravenous chemotherapy, incorporating patient preference. The BOC group acknowledges that breast cancer-specific prospective efficacy data for SC pembrolizumab remain limited. However, the totality of available evidence supports SC pembrolizumab as a reasonable and evidence-based alternative to IV administration in appropriate clinical settings.

Consensus Statement

Subcutaneous pembrolizumab can be considered as an alternative route of administration to intravenous pembrolizumab in routine clinical practice for patients with high-risk early-stage TNBC, including patients receiving concurrent intravenous chemotherapy, incorporating patient preference.

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