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

Dana-Farber Breast Oncology Center

Consensus Statement Regarding First-line Treatment for Patients with Metastatic Triple-Negative Breast Cancer (TNBC)

Consensus: Obtained at Breast Oncology Center meetings on 8/15/2025, 11/21/2025, 12/8/2025, 1/16/2026, 1/23/2026, 04/24/2026, and 05/01/2026.

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Clinical Question	Consensus Statement
Q1. Which patient populations should be considered appropriate candidates for sacituzumab govitecan (SG) plus pembrolizumab?	The Dana-Farber Breast Oncology Center (BOC) group reached consensus to recommend first-line SG plus pembrolizumab for patients who meet the ASCENT-04 eligibility criteria, namely those with PD-L1-positive previously untreated, locally advanced unresectable or metastatic TNBC (mTNBC) who completed prior curative-intent therapy ≥ 6 months earlier or those with *de novo* metastatic disease.
Q2. Should SG plus pembrolizumab be considered for patients with prior exposure to immune checkpoint inhibitors?	Acknowledging the limited data on re-challenge with immune checkpoint inhibitor, the BOC group reached consensus that SG plus pembrolizumab should be considered as first-line treatment for patients with PD-L1-positive recurrent TNBC with a minimum interval of six months since the completion of treatment in the curative setting, including prior immune checkpoint inhibitor.
Q3. If SG plus pembrolizumab is used as first-line therapy, what is the preferred option for second-line treatment?	The BOC group reached consensus to recommend taxane monotherapy as preferred second-line therapy for patients with *de novo* metastatic disease or recurrence > 12 months from prior taxane therapy. For those who recur within 12 months of prior taxane therapy, after first-line SG plus pembrolizumab, the group recommended gemcitabine–carboplatin or non-taxane single-agent chemotherapy. For patients with germline *BRCA1* or *BRCA2* mutations, treatment with a PARP inhibitor is preferred as second-line therapy, regardless of DFI history.
Q4. For patients with *BRCA1/2*-mutated, PD-L1–positive mTNBC, should SG plus pembrolizumab be favored over a PARP inhibitor as first-line therapy?	Among patients with PD-L1–positive mTNBC harboring germline *BRCA1/2* mutations, SG plus pembrolizumab is generally favored over a PARP inhibitor as first-line treatment, while acknowledging the limited evidence in this patient population.
Q5. Should subcutaneous pembrolizumab be considered an alternative route of administration to intravenous pembrolizumab in routine	Subcutaneous pembrolizumab can be considered an alternative route of administration to intravenous pembrolizumab in routine clinical practice for eligible patients with mTNBC, including patients receiving

clinical practice for eligible mTNBC patients, incorporating patient preference?	concurrent intravenous chemotherapy, incorporating patient preference.

Consensus statement regarding first-line treatment for patients with **PD-L1-negative** metastatic triple-negative breast cancer.

Clinical Question	Consensus Statement
Q6. For patients without known g*BRCA1/2* or *PALB2* mutations, what is the preferred regimen for each of the scenarios described in Table 1, assuming no contraindications to any specific regimen?	The BOC group did not identify a single preferred regimen across all scenarios, but instead outlined common clinical scenarios in which SG or Dato-DXd may be favored, or where patient preference should be considered, as summarized in Table 1.
Q7. What is the preferred first-line regimen for patients with g*BRCA1/2* or *PALB2* mutations?	Among patients with PD-L1–negative mTNBC harboring germline *BRCA1/2* mutations, a PARP inhibitor is generally favored over TROP2 ADCs as first-line treatment, while acknowledging the limited supporting evidence in this patient population.
Q8. What regimen is recommended for patients with HR-low/HER2-negative metastatic breast cancer?	The BOC group agreed that a TNBC-aligned approach, including consideration of a TROP2 ADC in the first-line metastatic setting, is appropriate for patients with HR-low/HER2-negative metastatic breast cancer.
Q9. If a TROP2-directed ADC (SG, Dato-DXd) becomes the preferred first-line regimen in PD-L1-negative mTNBC, would you consider using a HER2-directed ADC (T-DXd) in a subsequent line of therapy?	The BOC group agreed that use of a subsequent ADC may be considered following progression on a first-line TROP2-directed ADC, while acknowledging that there are limited data on the role of sequencing of ADCs. The timing of ADC sequencing should be individualized based on factors such as response to the initial TROP2 ADC.
Q10. If a baseline ophthalmologic exam cannot be scheduled immediately, how would you recommend starting Dato-DXd in a patient without ocular symptoms?	The BOC group agreed that initiation of Dato-DXd may be considered in asymptomatic patients if a baseline ophthalmologic exam cannot be completed prior to treatment. A full ophthalmologic exam should be completed when possible, including at initiation of therapy, annually while on treatment, at end of treatment, and as clinically indicated. In addition, visual acuity testing and slit lamp examination should be performed every 3 cycles while on treatment.

Q11. For interstitial lung disease (ILD) monitoring during Dato-DXd therapy, how often would you recommend chest computed tomography (CT) scans?	The BOC group agreed that patients receiving Dato-DXd should be monitored for ILD with CT imaging every 6–12 weeks, and as clinically indicated.

3. Additional considerations for all patients receiving first-line treatment for metastatic triple-negative breast cancer (PD-L1-positive or PD-L1-negative).

Clinical Question	Consensus Statement
Q12. If a TNBC patient received a TROP2-directed, topoisomerase I-based ADC in the (neo)adjuvant setting, should a TROP2-directed ADC be offered as first-line treatment for metastatic disease?	The BOC group favored recommending a TROP2-directed, topoisomerase I-based ADC as first-line therapy for patients who previously received a topoisomerase I-based ADC in the (neo)adjuvant setting if the disease-free interval from prior ADC therapy exceeds 12 months.
Q13. Should routine primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) be recommended for mTNBC patients receiving SG (+/- pembrolizumab) in the first-line setting?	The BOC group recommended primary G-CSF prophylaxis for most patients receiving SG (+/- pembrolizumab) in the first-line setting, including all patients at increased risk of febrile neutropenia, such as older patients, patients with previous neutropenia, poor performance status, organ dysfunction, or multiple comorbidities.

PD-L1-Positive Metastatic TNBC

Triple-negative breast cancer (TNBC) accounts for approximately 10–15% of all breast cancers.[1] Among patients with metastatic TNBC (mTNBC), approximately 40% have PD-L1-positive disease, defined as a combined positive score (CPS) ≥ 10 using the 22C3 assay.[2]

KEYNOTE-355 Phase 3 Trial

The randomized phase 3 KEYNOTE-355 trial evaluated pembrolizumab in combination with chemotherapy for the treatment of patients with locally recurrent inoperable or mTNBC who were not previously treated with chemotherapy in the advanced setting (**Figure 1**). Patients with recurrent disease were eligible if treatment in the curative setting had been completed at least six months before first disease recurrence. Participants were randomized to receive pembrolizumab or placebo in combination with chemotherapy of investigator's choice (nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin). The study endpoints included progression-free survival (PFS) and overall survival (OS) in patients whose tumors expressed PD-L1 (CPS ≥1 and CPS ≥10) and in all participants. The other

endpoints were objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and safety.[3]

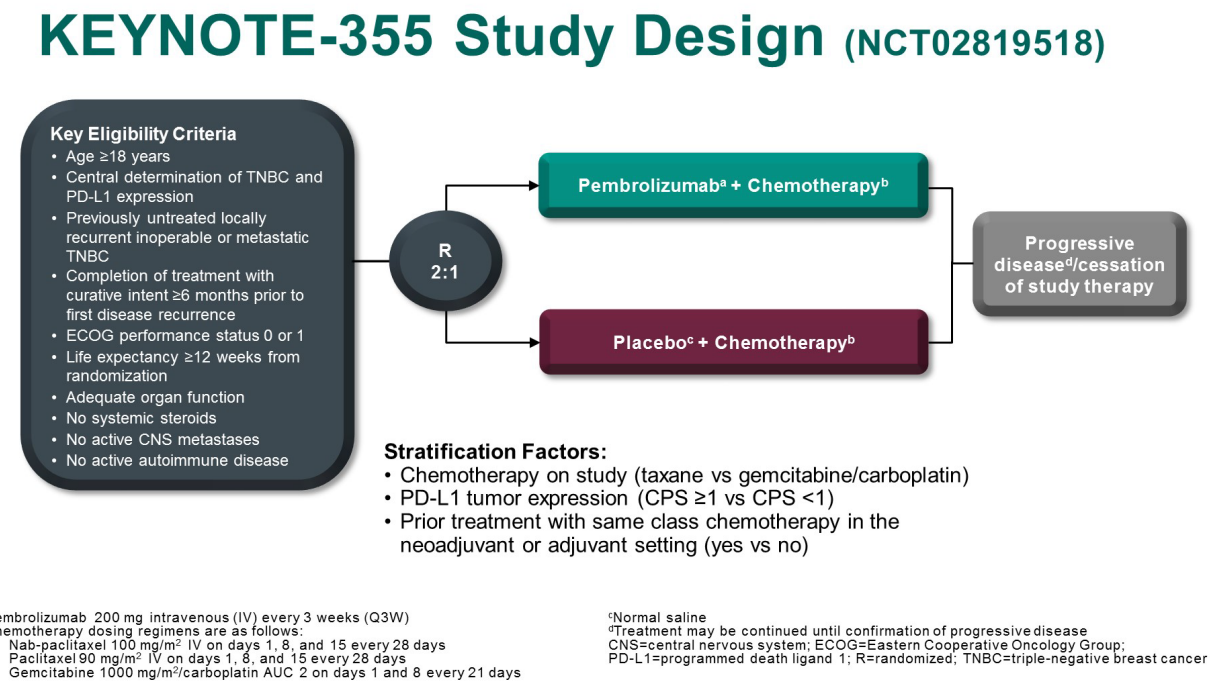

***Figure 1**: KEYNOTE-355 phase 3 trial design*
Source: Rugo 2021. ESMO oral presentation[4]

Among patients with PD-L1 CPS ≥ 10, the median PFS was 9.7 months with pembrolizumab plus chemotherapy versus 5.6 months with chemotherapy along (hazard ratio [HR]: 0.65, 95% CI: 0.49 – 0.86; one-sided p = 0.0012).[3] Moreover, the median OS was 23.0 months with pembrolizumab plus chemotherapy versus 16.1 months with chemotherapy alone (HR: 0.73, 95% CI: 0.55 – 0.95; two-sided p = 0.0185).[2] Based on these results, the combination of pembrolizumab plus chemotherapy was established as the standard first-line treatment for patients with PD-L1–positive mTNBC.

ASCENT-04 Phase 3 Trial
ASCENT-04/KEYNOTE-D19 was a randomized phase 3 trial evaluating sacituzumab govitecan (SG) plus pembrolizumab versus chemotherapy plus pembrolizumab in patients with previously untreated PD-L1–positive (CPS ≥ 10) mTNBC.[5] Patients were stratified by curative treatment-free interval (*de novo* metastatic disease, recurrence within 6-12 months, or recurrence after more than 12 months); geographic location (US/Canada/Western Europe versus the rest of the world); and prior exposure to PD-1/PD-L1 inhibition (yes versus no) (**Figure 2**).[6]

Participants were randomized 1:1 to receive SG plus pembrolizumab or chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin) plus pembrolizumab. Patients in

the chemotherapy arm who experienced disease progression were offered the option to cross over to receive second-line SG monotherapy, which was provided on trial. The primary endpoint was PFS by blinded independent central review (BICR). Secondary endpoints included OS, ORR, and DOR (all by BICR); safety; and quality of life.[5]

A total of 443 patients were included. Most patients had developed recurrence more than 12 months after curative treatment (48% in both the SG and chemotherapy arms), followed by *de novo* metastatic disease (34% in each arm), and recurrence within 6 to 12 months (18% in each arm). Among patients randomized to receive chemotherapy plus pembrolizumab, the investigator-selected chemotherapy prior to randomization was a taxane in 51% of patients and gemcitabine/carboplatin in 49% of patients. Nine patients (4%) in the SG arm and 11 patients (5%) in the chemotherapy arm had prior exposure to PD-1/PD-L1 inhibitors.[5]

Figure 2: *ASCENT-04 phase 3 trial design*
Source: Tolaney et al. 2025. ASCO oral presentation[6]

After a median follow-up of 14.0 months, the median PFS was 11.2 months in the SG plus pembrolizumab arm versus 7.8 months in the chemotherapy plus pembrolizumab arm (HR: 0.65, 95% CI: 0.51 – 0.84; p = 0.0009). In subgroup analyses, the PFS benefit appeared consistent across prespecified subgroups. The ORR was 60% in the SG plus pembrolizumab arm versus 53% in the chemotherapy plus pembrolizumab arm. The median DOR was 16.5 months in the SG plus pembrolizumab arm versus 9.2 months in the chemotherapy plus pembrolizumab arm. OS data were immature (26% of events), but a positive early trend for improved OS with SG plus pembrolizumab was observed (HR 0.89, 95% CI: 0.62 - 1.29). Notably, at data cutoff, among 119 patients in the chemotherapy arm who received any subsequent anti-cancer therapy after discontinuation of protocol therapy, 96 (81%) received SG monotherapy as second-line therapy.[5]

Safety findings were consistent with the known toxicity profiles of each agent, and no new safety signals were identified. The most frequent treatment-emergent adverse events (TEAEs) of grade ≥ 3 were neutropenia (43%) and diarrhea (10%) with SG plus

pembrolizumab, and neutropenia (45%), anemia (16%), and thrombocytopenia (14%) with chemotherapy plus pembrolizumab.[5]

Overall, data from the ASCENT-04 trial support the use of SG with pembrolizumab as a first-line treatment for patients with PD-L1-positive mTNBC. Given the positive results from this trial, the combination of SG plus pembrolizumab is included in the National Comprehensive Cancer Network (NCCN) Invasive Breast Cancer Guideline (version 2.2026)[7] as a category 1 preferred first-line treatment option for patients with PD-L1-positive (CPS $\geq$ 10) metastatic TNBC, irrespective of germline *BRCA1/2* status.

PD-L1-Negative Metastatic TNBC

Approximately 60% of patients with treatment-naive mTNBC are not candidates for immunotherapy, mostly due to PD-L1-negative disease.[8,9] Olaparib or talazoparib monotherapy may be considered in the first line for patients with germline *BRCA1/2* (g*BRCA1/2*) mutations. For the remaining patients, chemotherapy has been the standard first-line treatment.[10] However, the median PFS of first-line chemotherapy in patients with PD-L1-negative mTNBC is less than six months[8,11], highlighting a substantial unmet clinical need for more effective therapeutic strategies.

ASCENT-03 Phase 3 Trial

The randomized phase 3 ASCENT-03 trial evaluated SG versus chemotherapy in patients with locally advanced inoperable or mTNBC who were not previously treated with chemotherapy in the advanced setting and were not candidates for PD-1/PD-L1 inhibitor (**Figure 3**). Patients with recurrent disease were eligible if they had completed treatment in the curative setting at least six months before recurrence. Patients were stratified by geographic location (US/Canada/Western Europe versus the rest of the world) and curative treatment-free interval (*de novo* metastatic disease; recurrence within 6-12 months; or recurrence after more than 12 months).[12]

Participants were randomized 1:1 to receive SG (10 mg/kg IV on days 1, 8 of 21-day cycles) or chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin). Patients in the chemotherapy arm were offered to cross over to second-line SG at the time of disease progression, which was provided on trial. The primary endpoint was PFS by BICR. Secondary endpoints included OS; ORR, DOR, and TTR (all by BICR); safety; and quality of life.[12]

A total of 558 patients were included, among whom 555 (99.5%) had PD-L1-negative disease. Most patients had developed recurrence more than 12 months after treatment in the curative setting (48% in both the SG and chemotherapy arms), followed by *de novo* metastatic disease (31% in the SG arm and 32% in the chemotherapy arm), and recurrence within 6 to 12 months (21% in SG arm and 20% in chemotherapy arm). Among patients randomized to receive chemotherapy, the investigator-selected chemotherapy prior to randomization was a taxane in 56% of patients and gemcitabine-carboplatin in 44% of patients. In total, 59% of the patients in the SG arm and 61% in the chemotherapy

arm had lung metastasis, 29% in the SG arm and 26% in the chemotherapy arm had liver metastasis, and 5% of the patients in each arm had brain metastasis.[12]

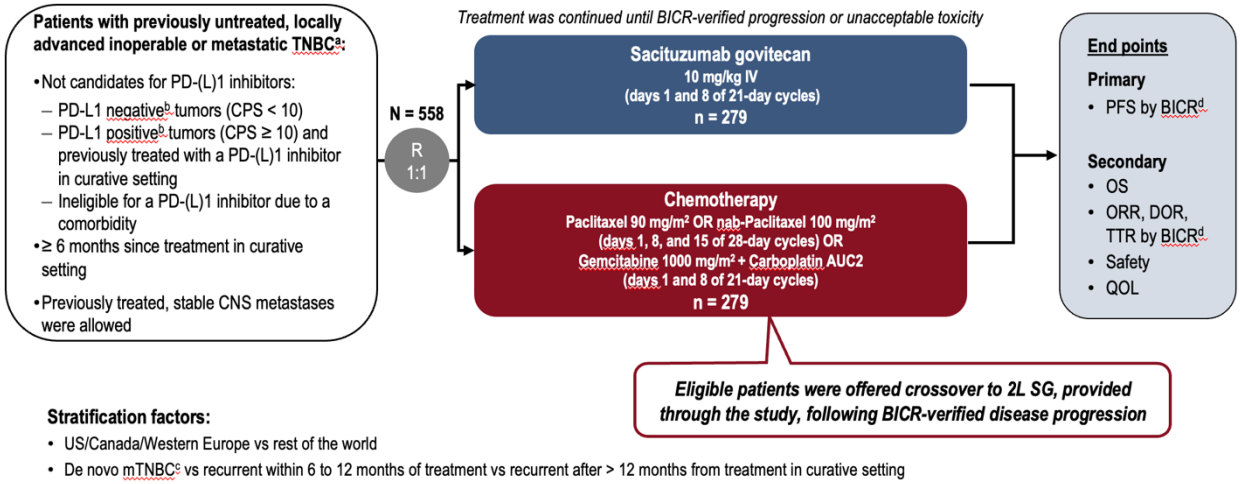

Figure 3: *ASCENT-03 phase 3 trial design*
Source: Cortés 2025. ESMO oral presentation[13]

After a median follow-up of 13.2 months, the median PFS was 9.7 months in the SG arm versus 6.9 months in the chemotherapy arm (HR: 0.62, 95% CI: 0.50 – 0.77; $p < 0.0001$). In subgroup analyses, the PFS benefit appeared consistent across prespecified subgroups, including patients with *de novo* disease and those with early relapse. The ORR was 48% in the SG arm versus 46% in the chemotherapy arm. The median DOR was 12.2 months in the SG arm versus 7.2 months in the chemotherapy arm. OS data were immature (37% of events). At the time of the primary analysis, the median OS was 21.5 months in the SG arm versus 20.2 months in the chemotherapy arm. Notably, at data cutoff, among 179 patients in the chemotherapy group who received any subsequent anti-cancer therapy after discontinuing trial treatment, 147 (82%) received SG as second-line therapy.[12]

Safety findings were consistent with the known toxicity profiles of each agent, and no new safety signals were identified. The most frequent adverse events (AEs) of grade ≥ 3 were neutropenia (43%) and diarrhea (9%) with SG, and neutropenia (41%), anemia (16%), and leukopenia (13%) with chemotherapy. There were 6 (2%) treatment-related adverse events (TRAEs) leading to death in the SG arm; all were due to infections, five of which were secondary to neutropenia in the absence of primary G-CSF prophylaxis in patients at high risk of febrile neutropenia.[12]

Overall, data from the ASCENT-03 trial support the use of SG as a first-line treatment for patients with PD-L1-negative mTNBC. Given the positive results from this trial, SG is included in the National Comprehensive Cancer Network (NCCN) Invasive Breast Cancer Guideline (version 2.2026)[7] as a category 1 preferred first-line treatment option for patients with PD-L1-negative (CPS < 10), *BRCA1/2*-wild type metastatic TNBC.

TROPION-Breast02 Phase 3 Trial

TROPION-Breast02 was a randomized phase 3 trial that evaluated datopotamab deruxutecan (Dato-DXd) versus chemotherapy in patients with locally advanced inoperable or mTNBC who were not previously treated with chemotherapy in the advanced setting and were not candidates for PD-1/PD-L1 inhibitor (**Figure 4**).[14] Patients with recurrent disease were eligible with any disease-free interval (DFI) following curative treatment (20% cap for DFI 0-12 months). Patients were stratified by geographic location (US/Canada/Western Europe versus the rest of the world); DFI history (*de novo* metastatic disease; recurrence within 0-12 months; or recurrence after more than 12 months); and PD-L1 status (high [CPS $\geq$10] versus low [CPS < 10]).

Participants were randomized 1:1 to receive Dato-DXd (6 mg/kg IV on day 1 of 21-day cycle) or chemotherapy (paclitaxel or nab-paclitaxel if no prior taxane, or if prior taxane was given in the (neo)adjuvant setting with a DFI >12 months; or capecitabine, eribulin, or carboplatin if prior taxane was given with a DFI of 0–12 months). There was no cross over to Dato-DXd in the chemotherapy arm at the time of progression as part of the study. The co-primary endpoints were PFS by BICR and OS. Secondary endpoints included PFS by investigator assessment, ORR, DOR, and safety.[14]

A total of 644 patients were included (Dato-DXd arm, n = 323; chemotherapy arm, n = 321), of whom 578 had PD-L1 CPS <10 (287 in the Dato-DXd arm and 291 in the chemotherapy arm). Most patients had developed recurrence more than 12 months after treatment in the curative setting (46% in the Dato-DXd arm and 45% in the chemotherapy arm), followed by *de novo* metastatic disease (34% in each arm). Patients with recurrence within 0–12 months accounted for 21% of patients in each arm, including recurrence within 0–6 months in 15% of patients in the Dato-DXd arm and 16% of patients in the chemotherapy arm. Among patients randomized to receive chemotherapy, the pre-selected chemotherapy was nab-paclitaxel in 54%, paclitaxel in 29%, eribulin in 11%, carboplatin in 4% and capecitabine in 2% of patients.[14]

Visceral metastases were observed in 78% of patients in the Dato-DXd arm and 73% in the chemotherapy arm. Liver metastases were observed in 29% of patients in the Dato-DXd arm and 31% in the chemotherapy arm. Brain metastases were observed in 11% of patients in the Dato-DXd arm and 9% in the chemotherapy arm.[14]

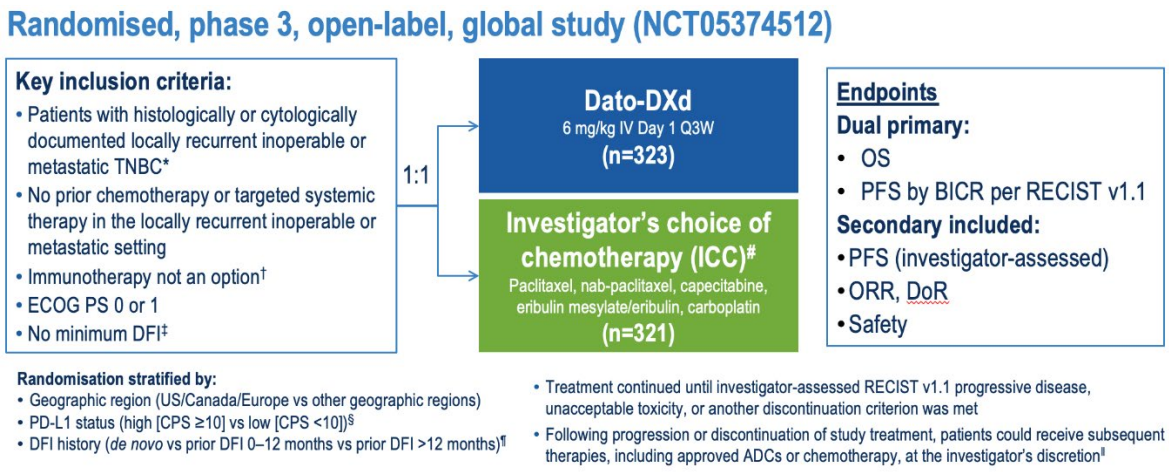

Figure 4: *TROPION-Breast02 phase 3 trial design*
Source: Dent et al. 2025. ESMO oral presentation[14]

After a median follow-up of 27.5 months, the median PFS was 10.8 months in the Dato-DXd arm versus 5.6 months in the chemotherapy arm (HR: 0.57, 95% CI: 0.47 – 0.69; p < 0.0001) (**Figure 5**). In subgroup analyses, the PFS benefit appeared consistent across prespecified subgroups. The ORR was 63% in the Dato-DXd arm versus 29% in the chemotherapy arm. The median DOR was 12.3 months in the Dato-DXd arm versus 7.1 months in the chemotherapy arm. The median OS was 23.7 months in the Dato-DXd arm versus 18.7 months in the chemotherapy arm (HR: 0.79, 95% CI: 0.64 – 0.98; p = 0.0291) (**Figure 6**). The OS benefit was largely consistent across most subgroups, except for geographic region and DFI.[14] Notably, subsequent ADC therapy in any treatment line was received by 14% of patients in the Dato-DXd arm and 30% in the chemotherapy arm (SG, sacituzumab tirumotecan, T-DXd).

Safety findings were consistent with the known toxicity profiles of each agent, and no new safety signals were identified. The most common grade ≥ 3 TRAEs with Dato-DXd were stomatitis (8%) and ocular surface events (7%), including dry eye (1%) and keratitis (2%). Interstitial lung disease (ILD) of grade ≥ 3 was observed in <1% of patients treated with Dato-DXd. No treatment-related deaths were reported in the Dato-DXd arm.[14]

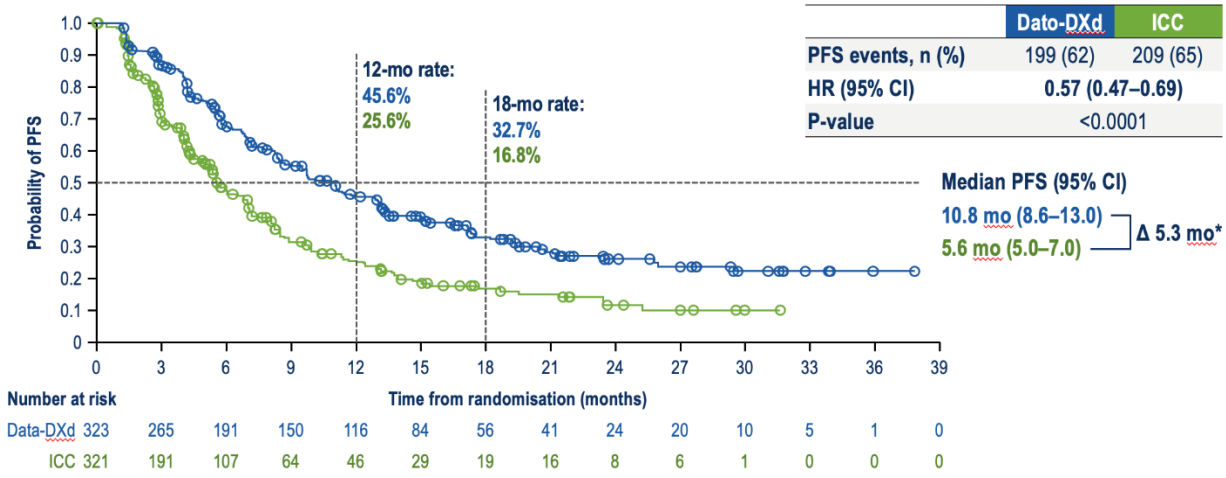

Figure 5: *PFS results from TROPION-Breast 02 trial*
Source: Dent et al. 2025. ESMO oral presentation[14]

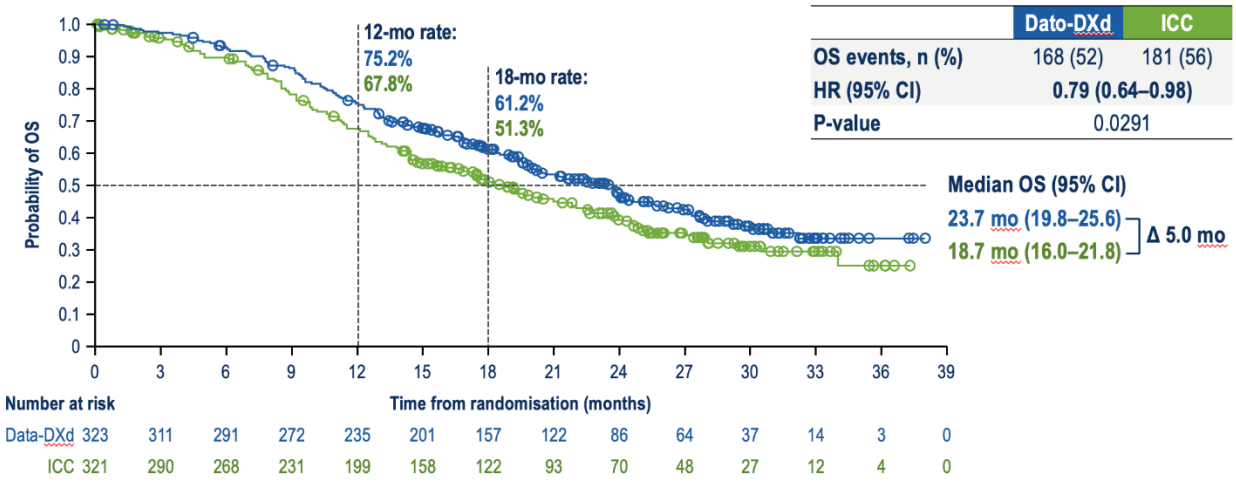

Figure 6: *OS results from TROPION-Breast 02 trial*
Source: Dent et al. 2025. ESMO oral presentation[14]

Based on the results of the TROPION-Breast02 trial, the U.S. Food and Drug Administration (FDA) approved the use of Dato-DXd as a first-line treatment for patients with unresectable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy.[15]

Moreover, Dato-DXd is included in the National Comprehensive Cancer Network (NCCN) Invasive Breast Cancer Guideline (version 2.2026)[7] as a preferred first-line treatment option for patients with PD-L1-negative (CPS < 10), *BRCA1/2*-wild type metastatic TNBC.

3. Key Differences Between ASCENT-03 and TROPION-Breast02

ASCENT-03 and TROPION-Breast02 were both phase 3 trials evaluating the efficacy of TROP2-directed, topoisomerase I inhibitor–based antibody–drug conjugates (ADCs) in patients with treatment-naive mTNBC who were not candidates for PD-1/PD-L1 inhibitors. In both trials, a significant improvement in median PFS was demonstrated compared with chemotherapy. However, there were important differences in patient populations and trial design between the two studies. In ASCENT-03, patients with recurrent disease were required to have a DFI of at least six months following curative-intent therapy. In contrast, TROPION-Breast02 allowed enrollment of patients with recurrent TNBC regardless of DFI, including a proportion of patients with early relapse within six months from treatment in the curative setting. Differences were also noted in the chemotherapy regimens used in the control arms. In ASCENT-03, patients received either taxane monotherapy or combination therapy with gemcitabine and carboplatin, whereas in TROPION-Breast02, the control arm consisted exclusively of single-agent chemotherapy, including taxane, eribulin, capecitabine, or carboplatin. With respect to primary endpoints, ASCENT-03 was designed with PFS as the sole primary endpoint, while TROPION-Breast02 included both PFS and OS as dual primary endpoints. In addition, crossover from the chemotherapy arm to SG was offered in ASCENT-03, whereas crossover to Dato-DXd was not

incorporated into TROPION-Breast02. While SG was shown to significantly improve OS in patients with pretreated mTNBC in the randomized phase 3 ASCENT trial[16], Dato-DXd had not been previously compared to chemotherapy in pretreated mTNBC in a randomized phase 3 study.

Differences in safety profiles were also observed between the two agents. SG was associated with a higher incidence of neutropenia and diarrhea, whereas Dato-DXd was associated with stomatitis, ocular surface events, and ILD. Moreover, SG 10 mg/kg IV is administered on days 1 and 8 of every 21-day cycle, whereas Dato-DXd 6 mg/kg IV is administered every 21 days.

Overall, data from the ASCENT-03 and TROPION-Breast02 trials support the use of topoisomerase I inhibitor–based, TROP2-directed ADCs as a new standard first-line treatment for patients with mTNBC who are not candidates for PD-1/PD-L1 inhibitors, including those with PD-L1–negative tumors. Differences in patient characteristics, trial design, dosing schedules, and safety profiles between ASCENT-03 and TROPION-Breast02 should be considered when evaluating TROP2 ADCs as first-line treatment options.

Development of the Consensus Statements

The Dana-Farber Cancer Institute Breast Oncology Center (BOC) held multidisciplinary meetings on 8/15/2025, 11/21/2025, 12/8/2025, 1/16/2026, 1/23/2026, and 5/1/2026 to discuss recommendations regarding first-line treatment for patients with mTNBC. Data were reviewed from several randomized phase 3 clinical trials, including ASCENT-04, ASCENT-03, and TROPION-Breast02. Additional relevant data were reviewed to address the questions in this document as noted below. The gathered evidence was presented for discussion to a multidisciplinary group, which included Dana-Farber physicians, advanced practice providers (nurse practitioners, physician assistants), nurses, clinical investigators, lab investigators, translational researchers, administrators, and patient advocates. The discussion and suggestions for improvements continued via email exchanges following the meeting. The final consensus statements were consolidated in May of 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:

First-line treatment for patients with **PD-L1-positive** metastatic triple-negative breast cancer

1. Which patient populations should be considered appropriate candidates for sacituzumab govitecan (SG) plus pembrolizumab?

Patients enrolled in the ASCENT-04 trial included those with mTNBC or previously untreated, locally advanced unresectable disease who had completed prior curative-intent therapy ≥6 months earlier. Patients with recurrence within 6 months of prior therapy were excluded.[5]

Among the 221 patients who received SG plus pembrolizumab, 75 (35%) had *de novo* disease, 40 (18%) recurred within 6–12 months, and 106 (48%) recurred ≥ 12 months after prior therapy. In subgroup analyses, consistent PFS improvement with SG plus pembrolizumab over chemotherapy plus pembrolizumab was observed across all subgroups (*de novo* mTNBC - median PFS: 8.1 vs. 7.7 months, HR: 0.89, 95% CI: 0.59 – 1.34; 6 – 12 months - median PFS: 9.9 vs. 7.2 months, HR: 0.62, 95% CI: 0.36 – 1.08; ≥12 months – median PFS: 16.6 vs. 8.7 months, HR: 0.52, 95% CI: 0.35 – 0.76). However, patients with *de novo* disease appeared to derive less benefit than those with recurrent disease.[5]

In the KEYNOTE-355 trial, the combination of chemotherapy plus pembrolizumab resulted in a median PFS of 9.7 months among patients with *de novo* mTNBC,[3] suggesting that this regimen could remain a reasonable first-line option for those who are not candidates for SG plus pembrolizumab.

Based on these findings, the BOC group generally favored considering first-line SG plus pembrolizumab for patients who meet the ASCENT-04 eligibility criteria.

Consensus Statement

The BOC group reached consensus to recommend first-line SG plus pembrolizumab for patients who meet the ASCENT-04 eligibility criteria, namely those with PD-L1-positive previously untreated, locally advanced unresectable or metastatic TNBC who completed prior curative-intent therapy ≥ 6 months earlier or those with *de novo* metastatic disease.

2. Should SG plus pembrolizumab be considered for patients with prior exposure to immune checkpoint inhibitors?

In the ASCENT-04 trial, patients with prior exposure to immune checkpoint inhibitors (ICI) were eligible. However, only a small proportion of patients had received prior anti–PD-1/PD-

L1 therapy, including 9 patients (4%) in the SG plus pembrolizumab arm and 11 patients (5%) in the chemotherapy plus pembrolizumab arm, which limits any subgroup conclusions.[5]

Evidence for ICI re-challenge remains limited and is largely extrapolated from retrospective studies in other tumor types, suggesting that re-challenge may be more appropriate in patients who previously responded and did not experience immediate progression after ICI treatment.[17,18] Although definitive data are lacking, the disease-free interval from prior ICI appears to be an important consideration. It is unknown whether patients that experience very early recurrences (i.e. within six months after completing perioperative ICI) still benefit from pembrolizumab reintroduction. By contrast, in patients who developed recurrence with a longer interval from treatment in the curative setting, and in the absence of contraindications, pembrolizumab re-challenge may be considered.

Based on these considerations, the BOC group agreed that for patients who meet the ASCENT-04 eligibility criteria, i.e., least six months since completion of prior treatment in the curative setting, treatment with SG plus pembrolizumab should be considered. In addition, prior immune-related adverse events (irAEs) should inform the decision, and patients with significant prior irAEs are generally not suitable for ICI re-challenge.

Furthermore, the BOC group recommended that PD-L1 evaluation should be performed routinely in all cases of mTNBC, including both *de novo* and recurrent disease.

Consensus Statement

Acknowledging the limited data on re-challenge with immune checkpoint inhibitor, the BOC group reached consensus that SG plus pembrolizumab should be considered as first-line treatment for patients with PD-L1-positive recurrent TNBC with a minimum interval of six months since the completion of treatment in the curative setting, including prior immune checkpoint inhibitor.

3. If SG plus pembrolizumab is used as first-line therapy, what is the preferred option for second-line treatment?

The BOC group discussed different treatment options following first-line SG plus pembrolizumab, addressing two scenarios:
(A) *de novo* disease without prior systemic therapy or recurrent disease > 12 months of prior taxane treatment, and
(B) recurrent disease within 12 months of prior taxane treatment.

For Scenario A (*de novo* mTNBC or recurrent disease > 12 months of prior taxane), the BOC group favored taxane monotherapy as the preferred second-line regimen. Even in the setting of HER2-low disease, the majority considered that taxane monotherapy should be preferred over an immediate switch to T-DXd.

For Scenario B (metastatic recurrence within 12 months after prior taxane therapy), the BOC group favored gemcitabine–carboplatin or other single-agent chemotherapies as second-line treatment. In HER2-low tumors, while many providers preferred sequential use of gemcitabine-carboplatin or other single-agent chemotherapies, a proportion of providers considered trastuzumab deruxtecan (T-DXd) a reasonable second-line option.

For patients with a germline mutation in *BRCA1* or *BRCA2*, a PARP inhibitor (olaparib or talazoparib) is the preferred second-line therapy, given the PFS and quality of life benefits compared to chemotherapy.[19-22]

Consensus Statement

The BOC group reached consensus to recommend taxane monotherapy as preferred second-line therapy for patients with *de novo* metastatic disease or recurrence > 12 months from prior taxane therapy. For those who recur within 12 months of prior taxane therapy, after first-line SG plus pembrolizumab, the group recommended gemcitabine–carboplatin or non-taxane single-agent chemotherapy. For patients with germline *BRCA1* or *BRCA2* mutations, treatment with a PARP inhibitor is preferred as second-line therapy, regardless of DFI history.

4. For patients with *BRCA1/2*-mutated, PD-L1–positive mTNBC, should SG plus pembrolizumab be favored over a PARP inhibitor as first-line therapy?

Current guidelines recommend pembrolizumab plus chemotherapy as the preferred first-line regimen for patients with PD-L1–positive mTNBC who have not received prior treatment in the advanced setting, regardless of germline *BRCA1/2* status, based on the results of the KEYNOTE-355 trial and significant improvement in survival with immune checkpoint inhibition in the first-line setting.[3] For patients with germline *BRCA1/2* mutations and PD-L1-positive mTNBC, olaparib or talazoparib is recommended as second-line therapy.[23] In ASCENT-04, patients with *BRCA1/2* mutations were eligible for enrollment and comprised 9% of participants in the SG arm and 6% of participants in the chemotherapy arm, respectively.[6] However, outcomes in this subgroup have not yet been reported. Evidence specific to *BRCA1/2*-mutated patients in the first-line metastatic setting therefore remains limited. While there is biological rationale to suggest that *BRCA1/2*-mutated tumors may be particularly sensitive to topoisomerase I payloads,[24,25] available biomarker analyses include small patient subgroups, and definitive comparative data in the first-line setting are lacking.[26,27]

Taken together, although OS data are not yet mature, the BOC group favored considering first-line SG plus pembrolizumab over a PARP inhibitor for PD-L1–positive disease and viewed subsequent use of a PARP inhibitor as a reasonable approach, while acknowledging the current absence of definitive evidence to mandate a single treatment sequence for all *BRCA1/2*-mutated patients. However, for some patients, the safety profile of each agent may favor the use of PARP inhibitors upfront.

Consensus Statement

Among patients with PD-L1–positive mTNBC harboring germline *BRCA1/2* mutations, SG plus pembrolizumab is generally favored over a PARP inhibitor as first-line treatment, while acknowledging the limited evidence in this patient population.

5. Should subcutaneous pembrolizumab be considered an alternative route of administration to intravenous pembrolizumab in routine clinical practice for eligible mTNBC patients, 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 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 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.[28]

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.[29]

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 mTNBC. 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[30], versus approximately 30 minutes for IV infusion for both 200 mg and 400 mg dosing).

For patients with mTNBC 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 mTNBC, 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 an alternative route of administration to intravenous pembrolizumab in routine clinical practice for eligible patients with mTNBC, including patients receiving concurrent intravenous chemotherapy, incorporating patient preference.

First-line treatment for patients with **PD-L1-negative** metastatic triple-negative breast cancer.

6. For patients without known *gBRCA1/2* or *PALB2* mutations, what is the preferred regimen for each of the scenarios described in Table 1, assuming no contraindications to any specific regimen?

Selection between SG and Dato-DXd as first-line treatment for PD-L1–negative mTNBC may be influenced by clinical factors. Both the ASCENT-03 and TROPION-Breast02 trials demonstrated significant improvements in PFS compared with standard chemotherapy in this population. However, differences in trial design, eligibility criteria, safety profiles, and treatment schedules suggest that individual patient characteristics may inform regimen selection. The BOC group identified common clinical scenarios in which preference for SG, preference for Dato-DXd, or consideration of patient preference may reasonably differ based on DFI, adverse event profiles, and treatment schedules. These scenarios are summarized in **Table 1**.

	Prefer SG	Prefer Dato-DXd	Patient preference
DFI		DFI < 6 months	
			DFI 6-12 months
			DFI > 12 months
			De novo disease
AEs	History of ILD		
		High risk of neutropenia	
	Ocular symptoms, patient preference to continue use of contact lenses		
		Clinically significant gastrointestinal disorder	
Schedule		Long distance from treatment center	

Table 1: *Clinical scenarios influencing first-line regimen selection*

The Consensus Statement

The BOC group did not identify a single preferred regimen across all scenarios, but instead outlined common clinical scenarios in which SG or Dato-DXd may be favored, or where patient preference should be considered, as summarized in Table 1.

7. What is the preferred first-line regimen for patients with g*BRCA1/2* or *PALB2* mutations?

Current guidelines recommend PARP inhibitor or platinum-based chemotherapy as the preferred first-line regimen for patients with PD-L1–negative, germline *BRCA1/2* (*gBRCA1/2*) pathogenic variant TNBC.[10] In the ASCENT-03 and TROPION-Breast 02 trials, patients with *gBRCA1/2* mutations were not excluded. However, outcomes in this subgroup have not yet been reported. As such, evidence specific to patients with germline *BRCA1/2* mutations in the first-line metastatic setting remains limited. While there is biological rationale to suggest that *BRCA1/2*-mutated tumors may be particularly sensitive to topoisomerase I payloads[24,25], available biomarker analyses include small patient subgroups, and definitive comparative data in the first-line setting are lacking.[26,27]

In the metastatic setting, the phase 3 OlympiAD trial demonstrated that olaparib monotherapy significantly improved the median PFS compared to treatment of physician's choice (7.0 vs. 4.2 months; HR: 0.58, 95% CI: 0.43 – 0.80; $p < 0.001$), with a higher ORR (59.9% vs. 28.8%) and a favorable safety profile in patients with up to 2 prior lines of chemotherapy.[31] In addition, among patients treated in the first-line metastatic setting, the median OS was longer for olaparib than TPC (22.6 vs. 14.7 months; HR: 0.55, 95% CI: 0.33 – 0.95)[32], highlighting the benefit in early line use. Health-related quality of life (HRQoL), as measured by the EORTC QLQ-C30 questionnaire, was significantly better among patients who received olaparib compared to treatment of physician's choice (mean change from baseline in QLQ-C30 Global HRQoL scale: 3.9 vs. -3.6; $p = 0.0035$).[21]

Similarly, in the EMBRACA trial, talazoparib prolonged the median PFS (8.6 vs. 5.6 months; HR: 0.54, 95% CI: 0.41 – 0.71; $p < 0.001$), improved ORR (62.6% vs. 27.2%), and had a favorable safety profile in patients treated with up to 3 prior chemotherapy regimens.[33] To evaluate HRQoL, patients completed the EORTC QLQ-30 and its breast cancer module, the QLQ-BR23. Patients randomized to receive talazoparib reported a significant improvement in HRQoL (3.0), whereas those randomized to receive chemotherapy reported a significant deterioration (-5.4; $p < 0.0001$).[22]

Taken together, the BOC group favored consideration of a PARP inhibitor as first-line therapy over a TROP2-directed ADC (SG or Dato-DXd) for patients with PD-L1–negative, germline *BRCA1/2*-associated metastatic TNBC. However, in selected patients with clinically aggressive disease, use of a TROP2 ADC as an alternative first-line option may be considered.

Consensus Statement

Among patients with PD-L1–negative mTNBC harboring germline *BRCA1/2* mutations, a PARP inhibitor is generally favored over TROP2-directed ADCs as first-line treatment, while acknowledging the limited supporting evidence in this patient population.

8. What regimen is recommended in the first-line setting for patients with HR-low/HER2-negative metastatic breast cancer?

In the ASCENT-03 and TROPION-Breast02 trials, TNBC status was defined as <1% of tumor cells positive for estrogen receptor (ER) or progesterone receptor (PgR), and HER2 IHC 0, 1+, or 2+ with negative *in situ* hybridization. Therefore, patients with HR-low disease (ER 1–9%) were not included in these trial populations. However, accumulating evidence suggests that HR-low tumors share biological features and a clinical course similar to TNBC.[34,35]

On this basis, a TNBC-aligned treatment approach is reasonable for patients with HR-low/HER2-negative metastatic breast cancer, including use of a TROP2 ADC (SG or Dato-DXd) in the first-line metastatic setting.

Consensus Statement

The BOC group agreed that a TNBC-aligned approach, including consideration of a TROP2 ADC in the first-line metastatic setting, is appropriate for patients with HR-low/HER2-negative metastatic breast cancer.

9. If a TROP2-directed ADC (SG, Dato-DXd) becomes the preferred first-line regimen in PD-L1-negative metastatic TNBC, would you consider using a HER2-directed ADC (trastuzumab deruxtecan) in a subsequent line of therapy?

There are currently no randomized clinical trial data evaluating the optimal sequencing of ADCs in patients with mTNBC. Retrospective real-world studies suggest that sequential use of topoisomerase I–based ADCs may be associated with reduced clinical efficacy compared to the initial ADC.[36,37]

The BOC group reached consensus that use of a subsequent ADC, including T-DXd, in patients with HER2-low disease may be considered following progression on a first-line TROP2-directed ADC. The timing of ADC sequencing, whether immediate or after an intervening therapy, should be individualized based on factors such as the response to the initial TROP2-directed ADC.

Consensus Statement

The BOC group agreed that use of a subsequent ADC may be considered following progression on a first-line TROP2-directed ADC, while acknowledging that there are limited data on the role of sequencing of ADCs. The timing of ADC sequencing should be individualized based on factors such as the response to the initial TROP2-directed ADC.

10. If a baseline ophthalmologic exam cannot be scheduled immediately, how would you recommend starting datopotamab deruxtecan in a patient without ocular symptoms?

In the TROPION-Breast02 trial, ocular surface events were observed in 47% of patients receiving Dato-DXd, including 7% grade ≥ 3 (**Figure 7**). Ocular surface events include dry eye (any grade: 24%; grade ≥ 3: 1%), keratitis (any grade: 13%; grade ≥ 3: 2%), and conjunctivitis (any grade: 7%; grade ≥ 3: < 1%).[14] The FDA label recommends a complete ophthalmologic examination, including visual acuity testing, slit lamp examination (with fluorescein staining), measurement of intraocular pressure, and fundoscopy at treatment initiation, at end of treatment, and as clinically indicated. In addition, visual acuity testing and slit lamp examination are recommended every 3 cycles (9 weeks) during treatment. Finally, patients are advised to use preservative-free lubricating eye drops at least four times daily as needed and avoid wearing contact lenses during treatment.[38]

However, if a baseline ophthalmologic exam cannot be scheduled immediately in an asymptomatic patient, mitigation strategies were discussed within the BOC group. Most participants favored initiating Dato-DXd and performing the ophthalmologic exam afterward, whereas some preferred waiting for the baseline exam unless there was clinical urgency to treat. Finally, others recommended waiting for completion of the baseline exam prior to treatment initiation.

AESI category, n (%) Preferred term*	Dato-DXd (n=319)			ICC (n=309)		
	Grade 1	Grade 2	Grade ≥3	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis†	78 (24)	87 (27)	27 (8)	22 (7)	8 (3)	0
Stomatitis	72 (23)	83 (26)	27 (8)	19 (6)	8 (3)	0
Ocular surface events‡§	76 (24)	50 (16)	23 (7)	9 (3)	5 (2)	1 (<1)
Dry eye	51 (16)	21 (7)	4 (1)	6 (2)	3 (1)	0
Keratitis	21 (7)	14 (4)	7 (2)	1 (<1)	0	0
Conjunctivitis	7 (2)	13 (4)	1 (<1)	0	0	0
Adjudicated drug-related ILD/pneumonitis¶	1 (<1)	7 (2)	1 (<1)#	1 (<1)	1 (<1)	0

Figure 7: *TRAEs from the TROPION-Breast 02 trial*
Source: Dent et al. 2025. ESMO oral presentation[14]

Consensus Statement

The BOC group agreed that initiation of Dato-DXd may be considered in asymptomatic patients if a baseline ophthalmologic exam cannot be completed prior to treatment. A full ophthalmologic exam should be completed when possible, including at initiation of therapy, annually while on treatment, at end of treatment, and as clinically indicated. In addition, visual acuity testing and slit lamp examination should be performed every 3 cycles while on treatment.

11. For interstitial lung disease (ILD) monitoring during Dato-DXd therapy, how often would you recommend chest computed tomography (CT) scans?

In the TROPION-Breast02 trial, ILD was observed in 3% of patients receiving Dato-DXd, including <1% of grade ≥ 3 (**Figure 7**).[14] Mitigation strategies were discussed within the group, reaching the following consensus: patients should be monitored for ILD with computed tomography (CT) scans of the chest, to be conducted ideally every 6 or 9 weeks, and no longer than every 12 weeks, depending on the clinical scenario.

Consensus Statement

The BOC group agreed that patients receiving Dato-DXd should be monitored for ILD with CT imaging every 6–12 weeks, and as clinically indicated.

Additional considerations for all patients receiving first-line treatment for metastatic triple-negative breast cancer (PD-L1-positive or PD-L1-negative).

12. If a TNBC patient received a TROP2-directed, topoisomerase I-based ADC in the (neo)adjuvant setting, should a TROP2-directed ADC be offered as first-line treatment for metastatic disease?

The ASCENT-03, ASCENT-04, and TROPION-Breast02 trials did not include patients with prior exposure to TROP2-directed, topoisomerase I-based ADCs. However, the growing evaluation of topoisomerase I–based ADCs in the (neo)adjuvant setting[27,39-44] raises new considerations for treatment sequencing in mTNBC. At present, no prospective data address the efficacy of sequential re-exposure to topoisomerase I–based ADCs. Retrospective real-world studies suggest that the use of sequential topoisomerase I–based ADCs is associated with reduced efficacy.[36,37] When considering re-treatment, the response to prior SG and the duration since last exposure should be taken into account.

The BOC group favored offering a TROP2-directed, topoisomerase I-based ADC as first-line therapy for patients who previously received a topoisomerase I–based ADC if the disease-free interval was more than 12 months.

Consensus Statement

The BOC group favored recommending a TROP2-directed, topoisomerase I-based ADC as first-line therapy for patients who previously received a topoisomerase I–based ADC in the (neo)adjuvant setting if the disease-free interval from prior ADC therapy exceeds 12 months.

13. Should routine primary prophylaxis with granulocyte colony-stimulating factor (G-SCF) be recommended for mTNBC patients receiving SG (+/- pembrolizumab) in the first-line setting?

In the ASCENT-03 trial, neutropenia was the most common grade ≥3 adverse event in both treatment arms, occurring in 43% of patients receiving SG and 41% of those receiving chemotherapy. Among patients who received SG, 6 patients (2%) had TRAEs leading to death; all were due to infections, five of which were secondary to neutropenia in the absence of primary G-CSF prophylaxis.[12] Moreover, in the ASCENT-04 trial, neutropenia was the most common grade ≥ 3 adverse event in both treatment arms, occurring in 43% of patients receiving SG plus pembrolizumab and 45% of those receiving chemotherapy plus pembrolizumab.[5]

Given that a substantial proportion of patients eligible for first-line SG plus pembrolizumab will have previously received multi-agent chemotherapy in the (neo)adjuvant setting, they may be at increased risk of neutropenia. Clinical experience also indicates that SG can cause severe or prolonged neutropenia, particularly in patients with limited bone marrow reserve. Based on these considerations, the BOC group recommended primary prophylaxis for most patients. Current SG prescribing information[45] recommends primary prophylaxis starting in the first cycle of treatment in all patients at increased risk of febrile neutropenia, including older patients, patients with previous neutropenia, poor performance status, organ dysfunction, or multiple comorbidities. In patients with *de novo* metastatic disease who have not received prior cytotoxic therapy, primary prophylaxis may be considered on an individualized basis.

The BOC group also discussed practical aspects of growth factor support. Most members endorsed the use of long-acting granulocyte colony-stimulating factor (G-CSF) on day 8 (+/- short-acting G-CSF on days 2-4) to minimize the risk of severe neutropenia and treatment delays.

The group also discussed the role of UGT1A1 testing, given the known association between UGT1A1*28 homozygosity and increased risk of neutropenia and diarrhea when SG is administered.[46] Routine testing is not currently performed at Dana-Farber, as it is not required by the FDA label and is limited by logistical delays in obtaining results. However,

if UGT1A1*28 homozygosity is known prior to treatment, consideration of dose modification may be warranted, particularly with respect to gastrointestinal toxicity.

Consensus Statement

The BOC group recommended primary G-CSF prophylaxis for most patients receiving SG (+/- pembrolizumab) in the first-line setting, including all patients at increased risk of febrile neutropenia, such as older patients, patients with previous neutropenia, poor performance status, organ dysfunction, or multiple comorbidities.

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