



Dana-Farber
Cancer Institute

Susan F. Smith Center
for Women's Cancers

Dana-Farber Breast Oncology Center

Consensus Statement Regarding the First-Line Treatment of Patients with HER2-Positive Metastatic Breast Cancer

Consensus: Obtained at Breast Oncology Center meetings on 06/06/2025, 09/19/2025,
10/10/2025, 04/17/2026, 08/07/2026, and 09/18/2026.

Acknowledgments: Elia Segui Solis, MD; Otto Metzger, MD; and Adrienne G. Waks, MD
for their leadership in the consensus discussions and in writing of the statements.

Coordination and editorial support were performed by Mr. Scorzoni and
Timothy K. Erick, PhD.

Contents

Introduction	5
AFT-38/PATINA Clinical Trial	5
DESTINY-Breast09 Clinical Trial.....	8
HER2CLIMB-05 Clinical Trial	11
Development of the Consensus Statements	14
Clinical Questions.....	15
Q1. Which patients with HER2-positive (HER2+) metastatic breast cancer (MBC) should receive first-line trastuzumab deruxtecan (T-DXd) plus pertuzumab?....	15
Q2. Are there any patients for whom first-line T-DXd plus pertuzumab should be considered as an induction strategy, with switch to a maintenance strategy in the absence of progressive disease or toxicity?	15
Q3. Which patients with HER2+ MBC should receive induction taxane, trastuzumab, and pertuzumab (THP) followed by a maintenance strategy?	17
Q4. In patients being treated with an induction and maintenance strategy, in which HR+/HER2+ MBC patients should palbociclib be added to maintenance treatment with trastuzumab and pertuzumab (HP) plus endocrine therapy (ET)?	17
Q5. In patients being treated with an induction and maintenance strategy, in which HR+/HER2+ MBC patients should tucatinib be added to first-line maintenance treatment with HP plus ET?	18
Q6. In patients being treated with an induction and maintenance strategy, in which patients with HR-/HER2+ MBC should tucatinib be added to first-line maintenance treatment with HP?	19
Q7. Should palbociclib, trastuzumab, pertuzumab, and ET without induction chemotherapy be considered as a first-line treatment for patients with HR+/HER2+ metastatic breast cancer?	19
References	20

Synopsis

Consensus statements regarding the first-line treatment of patients with HER2+ metastatic breast cancer.

Clinical Question	Consensus Statement
Q1. Which patients with HER2-positive (HER2+) metastatic breast cancer (MBC) should receive first-line trastuzumab deruxtecan (T-DXd) plus pertuzumab?	The BOC group recommends first-line T-DXd plus pertuzumab for patients with HER2+ metastatic breast cancer at high-risk of early progression, including • Patients with recurrence ≤ 12-24 months after (neo)adjuvant HER2-directed therapy • Patients with <i>PIK3CA</i> mutations • Patients with central nervous system (CNS) involvement • Patients with high disease burden and/or symptomatic disease
Q2. Are there any patients for whom first-line T-DXd plus pertuzumab should be considered as an induction strategy, with switch to a maintenance strategy in the absence of progressive disease or toxicity?	The consensus was to consider a maintenance strategy after T-DXd induction on a case-by-case basis, taking into account patient- and disease-related factors, including, but not limited to, hormone receptor status, presence or absence of CNS metastases, and <i>PIK3CA</i> mutation status. Among patients for whom this approach is considered appropriate, the timing of the transition from induction T-DXd plus pertuzumab to maintenance therapy should also be individualized based on patient- and disease-related factors, including, but not limited to, tumor burden, depth and timing of response to induction T-DXd plus pertuzumab, tolerability of induction T-DXd plus pertuzumab, and patient preferences. There was no universal consensus regarding the duration of induction therapy. However, the group largely agreed that patients with a complete response to induction T-DXd plus pertuzumab (confirmed by at least two scans) should receive this regimen for at least six months before switching to maintenance therapy. All other patients are recommended to receive 9-12 months of induction T-DXd plus pertuzumab before switching to maintenance therapy.
Q3. Which patients with HER2+ MBC should receive induction taxane, trastuzumab, and pertuzumab (THP) followed by a maintenance strategy?	The BOC group recommends first-line THP induction followed by a maintenance strategy for patients with HER2+ metastatic breast cancer at low risk of early progression, including: • Patients with <i>de novo</i> metastatic disease or metastatic recurrence > 12-24 months after completion of neoadjuvant or adjuvant HER2-directed therapy for early-stage HER2+ breast cancer • Patients with <i>PIK3CA</i> wild-type disease • Patients with no CNS involvement • Patients with low disease burden and/or asymptomatic disease
Q4. In patients being treated with an induction and maintenance strategy, in which HR+/HER2+ MBC patients should palbociclib be added to maintenance treatment	The BOC group expressed a strong recommendation for the addition of ET to maintenance HP in all patients with HR+/HER2+ metastatic breast cancer who received an induction strategy. Adding palbociclib to maintenance HP is recommended for all patients with HR+/HER2+ metastatic breast cancer initiating maintenance HP with ET.

Consensus Statement Regarding Use of First-Line Trastuzumab Deruxtecan with Pertuzumab in HER2+ Metastatic Breast Cancer

© Dana-Farber Cancer Institute, September 2026

with trastuzumab and pertuzumab (HP) plus endocrine therapy (ET)?	Palbociclib may be added to maintenance HP plus ET in patients with high- or low-burden disease, including patients with visceral metastases as well as those with bone-only disease (including oligometastatic bone-only disease), regardless of age. Standard monitoring should include CBC + CMP every 3 weeks for the first 3 cycles with palbociclib dose adjustments per FDA label.
Q5. In patients being treated with an induction and maintenance strategy, in which HR+/HER2+ MBC patients should tucatinib be added to first-line maintenance treatment with HP plus ET?	The general consensus was that, in patients with HR+/HER2+ metastatic breast cancer treated with an induction and maintenance strategy, maintenance palbociclib, HP, and ET would be favored. There was no universal consensus on whether palbociclib or tucatinib should be favored in patients with brain metastases. The BOC group noted that data evaluating patients with brain metastases from both the PATINA and HER2CLIMB-05 trials were relatively limited.
Q6. In patients being treated with an induction and maintenance strategy, in which patients with HR-/HER2+ MBC should tucatinib be added to first-line maintenance treatment with HP?	The consensus was mixed. Half of the BOC group (50%) considered that most patients with HR-/HER2+ metastatic breast cancer treated with an induction and maintenance strategy should be recommended to receive tucatinib with maintenance HP. Other commonly held views included restricting this approach to patients with CNS involvement (21%) or individualizing its use on a case-by-case basis (21%).
Q7. Should palbociclib, trastuzumab, pertuzumab, and ET without induction chemotherapy be considered as a first-line treatment for patients with HR+/HER2+ metastatic breast cancer?	Currently, there is insufficient evidence to routinely recommend palbociclib with HP plus ET as first-line treatment for patients with HR+/HER2+ metastatic breast cancer without prior induction chemotherapy. First line palbociclib, HP, and ET (without induction chemotherapy) may be considered in patients for whom chemotherapy is contraindicated (64%) or in select patients for whom chemotherapy might not be necessary, such as those with low-burden disease (36%).

Additional considerations:

- Potential toxicities and benefits of T-DXd plus pertuzumab should be discussed with the patient ahead of initiating treatment. Particular attention should be dedicated to the potential for interstitial lung disease/pneumonitis.
- Potential toxicities and benefits of palbociclib in combination with trastuzumab, pertuzumab, and ET should be discussed with the patient ahead of initiating treatment.
- Potential toxicities and benefits of tucatinib in combination with trastuzumab and pertuzumab (+/- ET) should be discussed with the patient ahead of initiating treatment.
- Guidelines are subject to change with evolution of data from existing and future trials.

Introduction

For patients with HER2-positive (HER2+) metastatic breast cancer, including those with *de novo* metastatic disease or distant recurrence ≥ 12 months after completing (neo)adjuvant therapy, the historic standard-of-care first-line treatment has been 6-8 cycles of induction taxane chemotherapy (docetaxel or paclitaxel) combined with trastuzumab and pertuzumab (THP), followed by maintenance HP.¹

The THP regimen was established as the standard first-line therapy by the randomized phase 3 CLEOPATRA trial, in which participants with previously untreated HER2+ metastatic breast cancer were randomized 1:1 to receive pertuzumab or placebo in combination with trastuzumab and docetaxel. At the primary analysis, the median progression-free survival (PFS) was 18.5 months in the pertuzumab group and 12.4 months in the placebo group (HR: 0.62, 95% CI: 0.51 – 0.75; $p < 0.001$).¹ At the final analysis, the median overall survival (OS) was 57.1 months (95% CI: 50 – 72) in the pertuzumab group and 40.8 months (95% CI: 36 – 48) in the placebo group (HR: 0.69, 95% CI: 0.58 – 0.82).²

Approximately half of HER2+ breast cancer are hormone receptor-positive (HR+).^{1,3-7} In the CLEOPATRA trial, the addition of pertuzumab to trastuzumab and a taxane improved PFS (HR: 0.72, 95% CI: 0.55 – 0.95)¹ and OS (HR: 0.74, 95% CI: 0.58 – 0.96)² in patients with HR+ disease, despite the trial not permitting endocrine therapy (ET). Based on the PERTAIN study,⁸ in which all patients received ET with HER2-directed therapy, current guidelines recommend first-line THP with the addition of ET during the maintenance phase for patients with HR+/HER2+ metastatic breast cancer.⁹

Data from three recent randomized phase 3 clinical trials substantially change the treatment paradigm for first-line HER2+ metastatic breast cancer, introducing new therapeutic strategies for clinical practice. Here, we summarize the evidence from these three trials and discuss consensus-based clinical questions regarding their implementation in routine clinical practice.

AFT-38/PATINA Clinical Trial

CDK4/6 inhibition in HR+/HER2+ Metastatic Breast Cancer

The cyclin D1–CDK4 pathway plays a central role in HER2-driven tumor growth and is a known mechanism of resistance to HER2-targeted therapy.¹⁰ Preclinical studies have shown that combining CDK4/6 inhibitors with anti-HER2 therapy enhances anti-tumor activity,¹⁰ with even greater efficacy if combined with ET.¹¹ Several trials have evaluated combination regimens of CDK4/6 inhibitors with endocrine therapy, including monarchHER,^{12,13} DETECT V/CHEVENDO,¹⁴⁻¹⁶ KCSG BR 18-2 MINI,¹⁷ PATRICIA (SOLTI-1303),¹⁸ and ASPIRE.¹⁹

The PATINA Trial

AFT-38/PATINA was a randomized phase 3 trial that enrolled premenopausal or postmenopausal women and men with histologically confirmed HR+/HER2+ metastatic breast cancer in the first-line setting. Eligible patients had completed 6-8 cycles of induction

treatment, including trastuzumab (with or without pertuzumab) and taxane-based chemotherapy, without evidence of disease progression. No other systemic therapy for metastatic disease was permitted prior to enrollment. In addition, participants were required to have a disease-free interval of at least six months following completion of anti-HER2 therapy in the (neo)adjuvant setting. Patients with asymptomatic central nervous system (CNS) metastases were also eligible.²⁰

The trial enrolled 518 participants, who were randomized 1:1 to receive palbociclib plus trastuzumab (with or without pertuzumab) and endocrine therapy (n = 261) or trastuzumab (with or without pertuzumab) plus endocrine therapy (n = 257). Treatment continued until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed PFS, with OS as a key secondary endpoint. Stratification factors included: receipt of pertuzumab (yes vs. no; with the non-pertuzumab group capped at 20% of participants), prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs. no), response to induction therapy (complete response/partial response vs. stable disease per investigator assessment), and type of endocrine therapy (fulvestrant vs. aromatase inhibitor) (**Figure 1**).²⁰

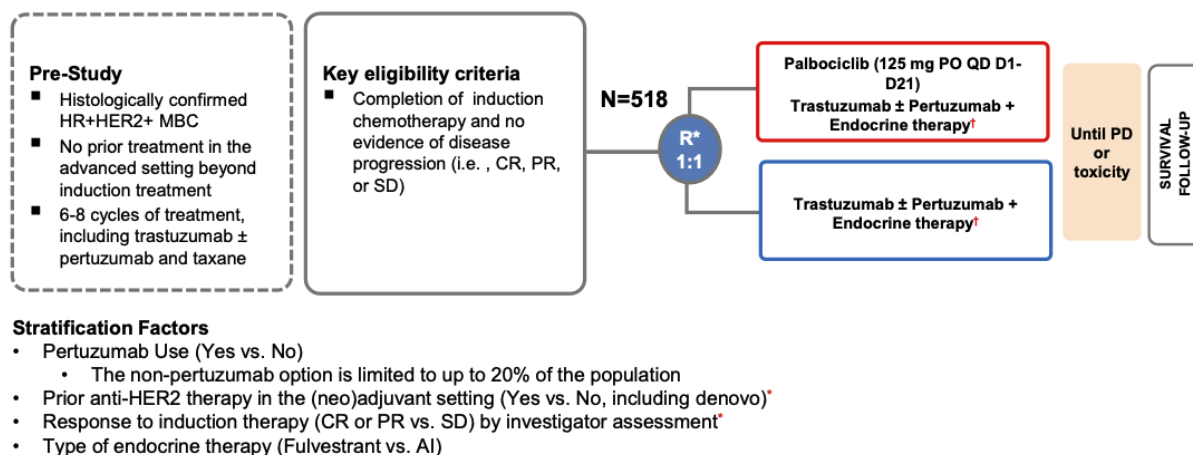


Figure 1. Design of the AFT-38 PATINA trial

Source: Metzger SABCS 2024 oral presentation²¹

The median age of trial participants was 53.4 years. Nearly all participants (99.4%) were female, and the majority (61.8%) were postmenopausal. More than half (54.4%) had *de novo* metastatic breast cancer. Participants received a median of 6 cycles of induction treatment (range: 4 – 8), with a best response of complete response (CR) or partial response (PR) in 70.1% of patients. Nearly all patients (94.0%) had received pertuzumab, 90.7% had received an aromatase inhibitor as ET, and 32.6% had received prior anti-HER2 therapy in the (neo)adjuvant setting.²⁰

After a median follow-up of 53.5 months, the median PFS was 44.3 months (95% CI: 32.4 – 56.8) in the palbociclib, HP, and ET arm versus 29.1 months (95% CI: 23.3 – 38.6) in the HP and ET arm (HR: 0.75, 95% CI: 0.59 – 0.96; two-sided unstratified p = 0.02; stratified p = 0.03).

Consensus Statement Regarding Use of First-Line Trastuzumab Deruxtecan with Pertuzumab in HER2+ Metastatic Breast Cancer

© Dana-Farber Cancer Institute, September 2026

The confirmed ORR was 32.9% (95% CI: 26.9% - 39.4%) in the palbociclib, HP, and ET arm versus 24.8% (95% CI: 19.3% - 30.0%) in the HP and ET arm. The CBR was 88.9% (95% CI: 84.4% - 92.4%) versus 80.9% (95% CI: 75.6% - 85.6%), respectively (**Figure 2**).²⁰

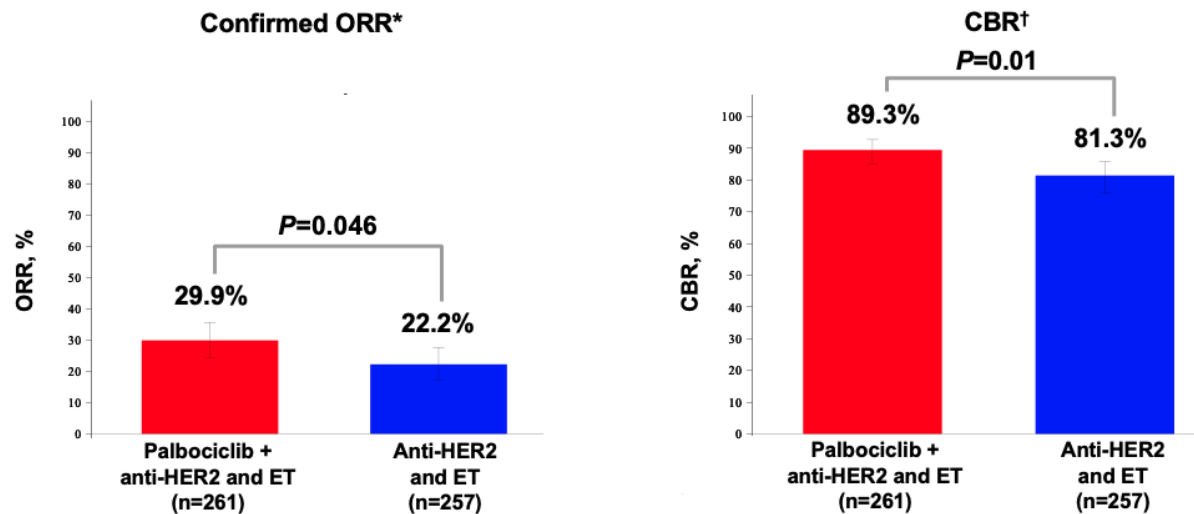


Figure 2. ORR and CBR in the PATINA trial

Source: Metzger SABCS 2024 oral presentation²¹

OS data were immature, with 123 of 247 planned events reported for the final OS analysis. At the time of the primary analysis, the OS hazard ratio was 0.86 (95% CI: 0.61 – 1.23) in favor of palbociclib, HP, and ET.²⁰

At 36 months of follow-up, the cumulative incidence of CNS progression or death among all randomized patients was 13.8% in the palbociclib, HP, and ET arm versus 20.4% in the HP and ET arm (Gray's test $p = 0.0404$). Among patients without CNS metastases at baseline, CNS progression or death was observed in 12.8% (95% CI: 8.9% - 17.6%) of patients in the palbociclib, HP, and ET arm versus 19.0% (95% CI: 14.3% - 24.4%) of patients in the HP and ET arm. The cumulative incidence of CNS progression or death was 13.0% in the palbociclib, HP, and ET arm versus 19.2% in the HP and ET arm (Gray's test $p = 0.0378$).²²

The most common AEs of grade ≥ 2 in the palbociclib versus the control arms were neutropenia (77.8% vs. 7.7%), diarrhea (70.5% vs. 37.5%), fatigue (53.6% vs. 39.9%), and leukopenia (37.9% vs. 4.8%). In the palbociclib arm, 60.5% of patients experienced grade ≥ 3 neutropenia (vs. 2.0% in the control arm) and 4.6% of patients experienced grade 4 neutropenia (vs. 0% in the control arm). Febrile neutropenia was reported in two patients in the palbociclib group. Serious AEs were reported in 28.7% of patients in the palbociclib group and 21.8% of patients in the control group. Grade 5 AEs occurred in 3.8% of patients in the palbociclib group and 4.4% in the control group; none of the deaths were determined by the investigator to be related to trial therapy.²⁰

Based on the data from the PATINA trial, the U.S. Food and Drug Administration (FDA) approved the combination of palbociclib, trastuzumab (+/- pertuzumab), and ET for patients with newly diagnosed HR+/HER2+ metastatic breast cancer after completion of induction chemotherapy with trastuzumab (+/- pertuzumab).

DESTINY-Breast09 Clinical Trial

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate (ADC) in which trastuzumab is conjugated to the topoisomerase I inhibitor deruxtecan via a cleavable tetrapeptide-based linker with a drug-to-antibody ratio of 8:1.²³ Based on positive results from the randomized phase 3 DESTINY-Breast03 trial,²⁴⁻²⁷ T-DXd is considered the standard second-line therapy for patients with HER2+ metastatic breast cancer, regardless of hormone receptor status, and including patients with brain metastases.

The randomized phase 3 DESTINY-Breast09 trial (**Figure 3**) enrolled patients with treatment-naïve HER2+ metastatic breast cancer, who were randomized 1:1:1 to receive first-line T-DXd plus pertuzumab, T-DXd plus placebo, or THP. Randomization was blinded in terms of pertuzumab versus placebo but was open-label in terms of T-DXd versus THP. Participants were stratified according to *de novo* or recurrent disease, hormone receptor status, and *PIK3CA* mutation status (centrally tested prior to enrollment). Patients who were initially treated for early-stage HER2+ breast cancer must have had a disease-free interval of at least 6 months after the completion of adjuvant systemic therapy. Patients with HR-positive disease were allowed to have received one prior line of endocrine therapy in the metastatic setting. The primary endpoint was PFS by blinded independent central review (BICR). OS was a key secondary endpoint.²⁸

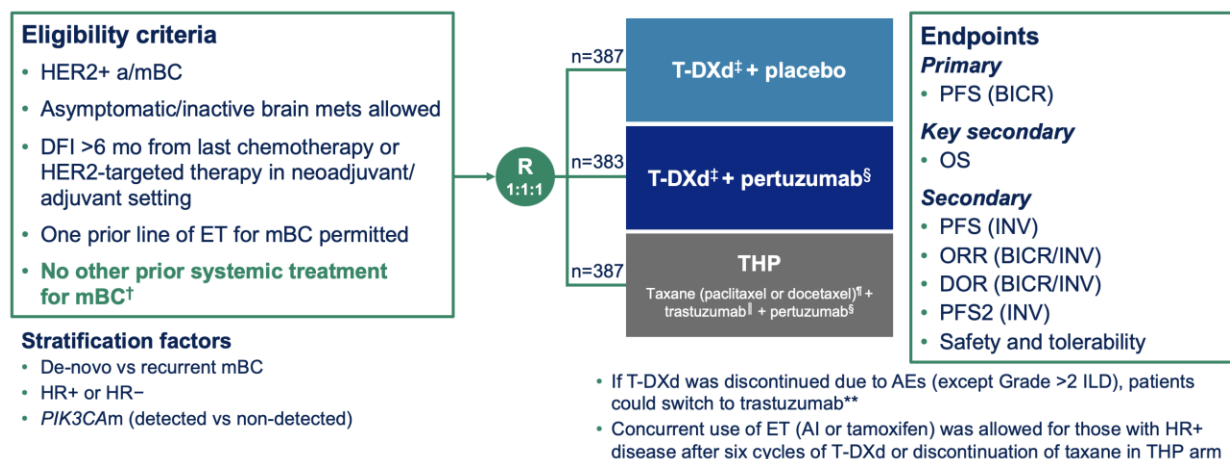


Figure 3. DESTINY-Breast09 trial schema

Source: Tolaney ASCO 2025 oral presentation²⁹

In the intent-to-treat (ITT) population (n = 1,157), 51.9% of patients had *de novo* metastatic breast cancer, 54.0% had HR+ disease, and 30.8% had *PIK3CA* mutations. Prior neoadjuvant or adjuvant therapy included chemotherapy (40.4%), trastuzumab (28.3%), and pertuzumab

(7.1%). Ten patients (1.3%) had received one line of endocrine therapy in the metastatic setting. Among participants with HR+ disease, 13.5% in the T-DXd plus pertuzumab group and 38.3% in the THP group received concurrent endocrine therapy.²⁹

The first interim analysis was conducted at a median follow-up of 29.2 months, upon which the interim efficacy threshold for superiority ($p < 0.00043$) was crossed for T-DXd plus pertuzumab versus THP. This analysis represented 37.7% PFS data maturity for these two groups. The efficacy data for T-DXd plus placebo will remain blinded until the final PFS analysis.²⁸

The median PFS by BICR was 40.7 months (95% CI: 36.5 – not calculable) in the T-DXd plus pertuzumab group versus 26.9 months (95% CI: 21.8 – not calculable) in the THP group (HR: 0.56, 95% CI: 0.44 – 0.71; $p < 0.00001$) (**Figure 4**). The PFS benefit of T-DXd plus pertuzumab was maintained across most patient subgroups, including HR status (positive versus negative), *PIK3CA* mutation status (detected versus not detected), presence or absence of baseline brain metastases, previous exposure to HER2-directed therapies, and previous exposure to endocrine therapy.^{28,29}

The confirmed ORR was 85.1% (95% CI: 81.2% - 88.5%) in the T-DXd plus pertuzumab group versus 78.6% (95% CI: 74.1% - 82.5%) in the THP group. The median duration of response (DOR) by BICR was 39.2 months (95% CI: 35.1 – not calculable) in the T-DXd plus pertuzumab group versus 26.4 months (95% CI: 22.3 – not calculable) in the THP group (**Figure 5**).^{28,29}

DESTINY Breast-09: PFS (BICR)

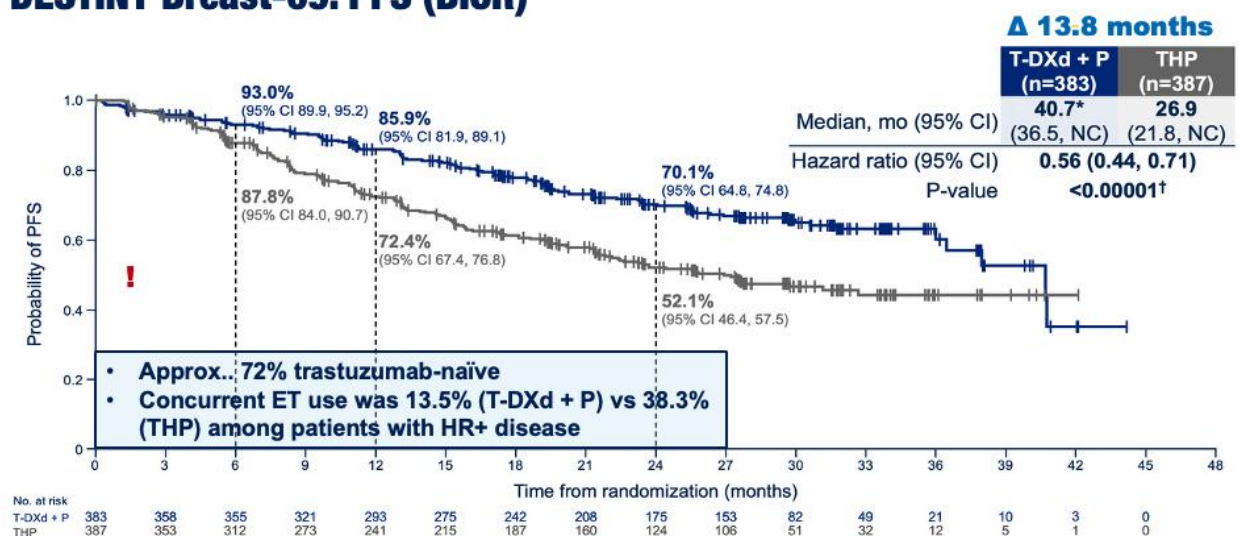


Figure 4. PFS by BICR in the DESTINY-Breast09 trial

Source: Tolaney ASCO 2025 oral presentation²⁹

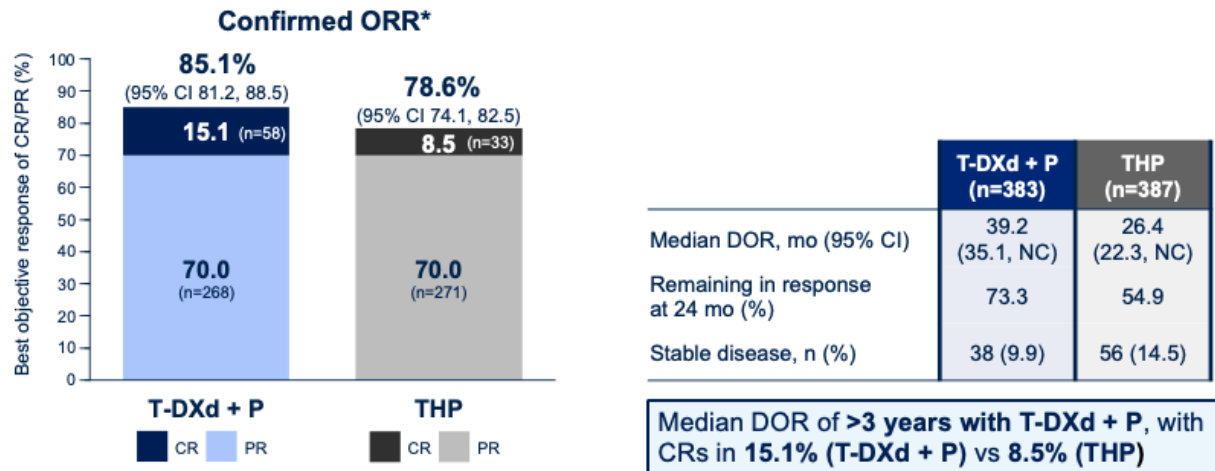


Figure 5. Confirmed ORR and median DOR in the DESTINY-Breast09 trial

Source: Tolaney ASCO 2025 oral presentation²⁹

The PFS benefit of T-DXd plus pertuzumab versus THP was maintained across all analyzed subgroups, including patients with *de novo* MBC (HR: 0.49, 95% CI: 0.35 – 0.70) versus recurrent disease (HR: 0.63, 95% CI: 0.46 – 0.87) and in patients with HR+ (HR: 0.61, 95% CI: 0.44 – 0.84) or HR- disease (HR: 0.52, 95% CI: 0.37 – 0.73). In patients with *PIK3CA*-mutant breast cancer, the median PFS was 36.0 months (95% CI: 29.7 – not calculable) with T-DXd plus pertuzumab versus 18.1 months (95% CI: 15.1 – 25.6) with THP (HR: 0.52, 95% CI: 0.35 – 0.77). In patients with *PIK3CA*-wild type breast cancer, the median PFS was 40.7 months (95% CI: 38.0 – not calculable) with T-DXd plus pertuzumab versus 32.7 months (95% CI: 24.4 – not calculable) with THP (HR: 0.57, 95% CI: 0.43 – 0.77) (**Figure 6**).³⁰

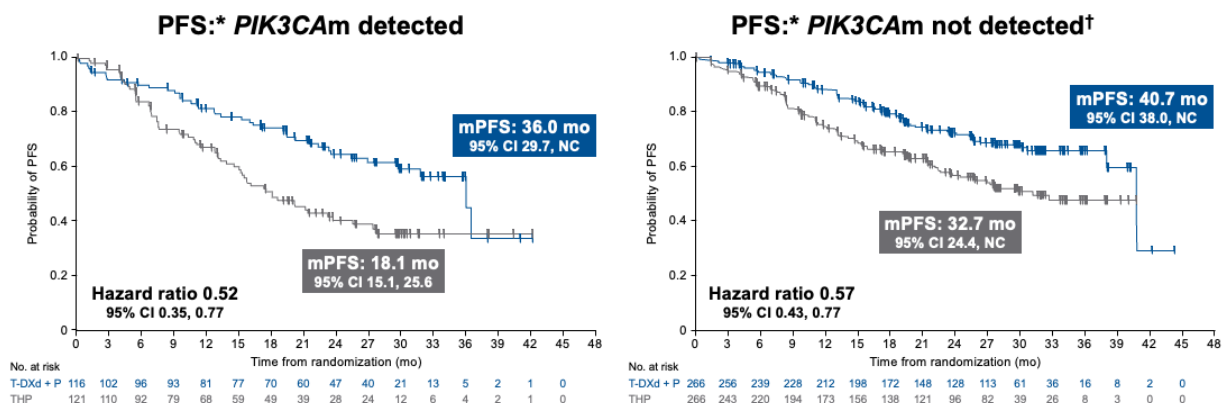


Figure 6. PFS by *PIK3CA* mutation status in the DESTINY-Breast09 trial

Source: Loibl ESMO 2025 oral presentation³⁰

Grade ≥ 3 treatment-related adverse events (TRAEs) occurred in 63.5% of patients in the T-DXd plus pertuzumab group and 62.3% of patients in the THP group. Serious adverse events occurred in 27.0% of patients in the T-DXd plus pertuzumab group and 25.1% of

patients in the THP group. Dose reductions due to adverse events occurred in 45.9% of patients in the T-DXd plus pertuzumab group and 19.9% of patients in the THP group. Dose interruptions due to adverse events occurred in 68.8% of patients in the T-DXd plus pertuzumab group and 49.0% of patients in the THP group. A total of 20.7% of patients in the T-DXd plus pertuzumab group and 28.3% of patients in the THP group discontinued any trial treatment due to adverse events.^{28,29}

Grade 5 adverse events occurred in 3.4% of patients in the T-DXd plus pertuzumab group and 0.8% of patients in the THP group. Interstitial lung disease (ILD)/pneumonitis occurred in 12.1% of patients in the T-DXd plus pertuzumab group (grade ≤ 2 , 11.5%; grade 5, 0.5%) and 1.0% of patients in the THP group (all grade ≤ 2). Left ventricular dysfunction occurred in 11.0% of patients in the T-DXd plus pertuzumab group (grade 4, 0.3%) and 7.1% of patients in the THP group.^{28,29}

Based on these results, the U.S. FDA approved the combination of T-DXd and pertuzumab for the first-line treatment of patients with HR-/HER2+ unresectable or metastatic breast cancer.³¹

Induction T-DXd followed by maintenance HP

Given concerns regarding the toxicity of T-DXd given continuously until progression, new trials are evaluating induction strategies with T-DXd followed by maintenance approaches. These include the ongoing single-arm phase II DEMETHER trial, which is evaluating 6 cycles of T-DXd followed by maintenance HP as first-line therapy for HER2+ metastatic breast cancer.³²

HER2CLIMB-05 Clinical Trial

The randomized phase 3 HER2CLIMB-05 trial evaluated the efficacy and safety of adding the HER2 tyrosine kinase inhibitor (TKI) tucatinib to first-line HP maintenance therapy in patients with newly diagnosed HER2+ metastatic breast cancer who had completed THP induction therapy without disease progression. The trial enrolled 654 patients, who were randomized 1:1 to receive tucatinib (n = 326) or placebo (n = 328) with maintenance HP. The trial population was enriched for patients with *de novo* MBC (69.3%) and 12.4% had presence or history of brain metastases at baseline. HR-positive patients accounted for 52.6% of the trial population.³³

The median investigator-assessed PFS (the primary endpoint) was 24.9 months (95% CI: 21.3 – not determined) in the tucatinib arm versus 16.3 months (95% CI: 12.6 – 18.7) in the placebo arm (HR: 0.641, 95% CI: 0.517 – 0.828; two-sided p < 0.0001) (**Figure 7**). The PFS benefit of tucatinib over placebo was maintained in patients with HR+ disease (HR: 0.725, 95% CI: 0.535 – 0.983) and in patients with HR- disease (HR: 0.554, 95% CI: 0.403 – 0.761) (**Figure 8**). Among patients with HR+ disease, 44.0% in the tucatinib arm and 46.0% in the control arm received endocrine therapy with maintenance HP.³³

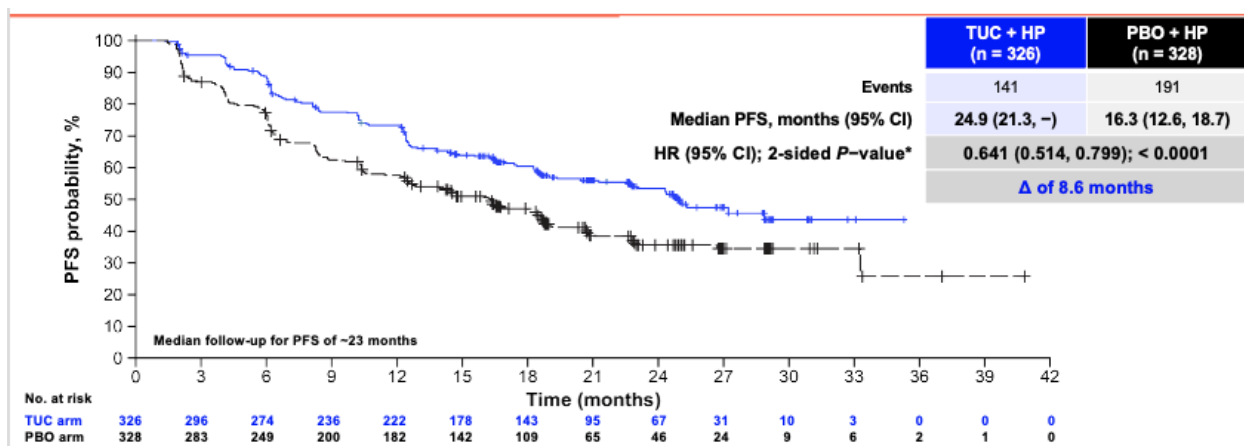


Figure 7. Investigator-assessed PFS among the overall study population in the HER2CLIMB-05 trial. *Source: Hamilton SABCS 2025 oral presentation.*³⁴

OS data were immature at the primary analysis (20.2% of events). The median OS was not reached in either treatment arm (OS hazard ratio for tucatinib versus placebo: 0.539, 95% CI: 0.303 – 0.957). Among patients with baseline brain metastases, the median CNS-PFS was 8.5 months (95% CI: 4.4 – 22.8) with tucatinib versus 4.3 months (95% CI: 2.3 – 10.6) with placebo (HR: 0.719, 95% CI: 0.406 – 1.273).³³

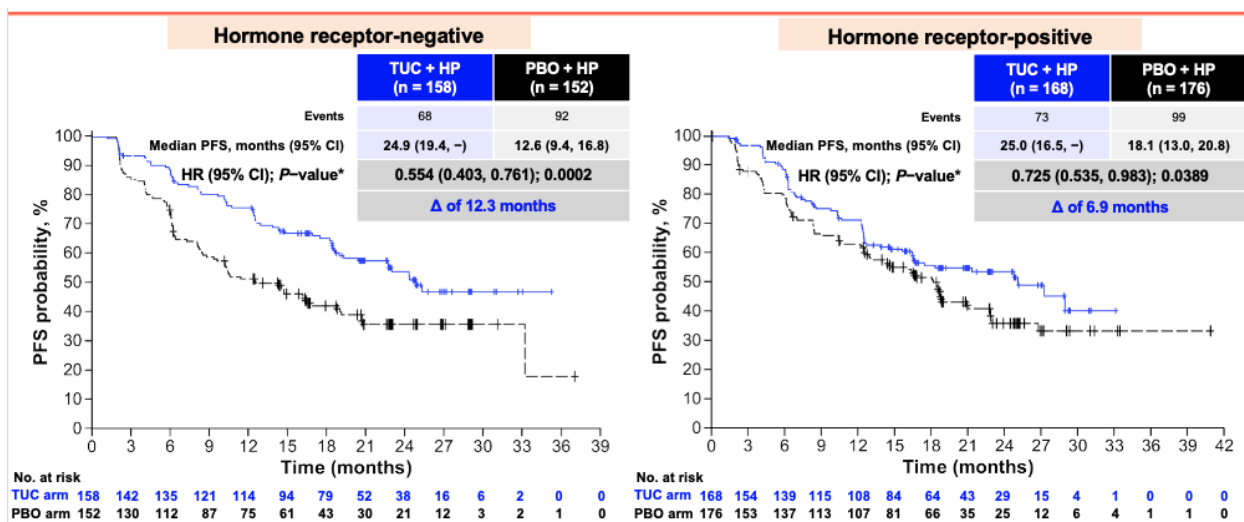


Figure 8. PFS by hormone receptor status in the HER2CLIMB-05 trial. *Source: Hamilton SABCS 2025 oral presentation.*³⁴

Among the ITT population, the median CNS-PFS was not reached in either treatment arm (HR for tucatinib vs. placebo: 0.846, 95% CI: 0.616 – 1.162). Among patients with baseline brain metastases, the median CNS-PFS was 8.5 months (95% CI: 4.4 – 22.8) in the tucatinib arm versus 4.3 months (95% CI: 2.3 – 10.6) in the placebo arm (HR: 0.719, 95% CI: 0.406 – 1.273).³⁴

The most common treatment-emergent adverse events (TEAEs) in the tucatinib arm were diarrhea (72.7%), nausea (33.1%), elevated ALT (28.2%), elevated AST (25.8%), arthralgia (20.6%), and fatigue (20.6%). The most common TEAEs in the placebo arm were diarrhea (51.2%), nausea (23.5%), and arthralgia (23.1%). Grade ≥ 3 TEAEs occurred in 42.3% of patients in the tucatinib arm and 24.4% of patients in the placebo arm. The most common grade ≥ 3 TEAEs in the tucatinib arm were elevated ALT (13.5%), elevated AST (7.1%), and diarrhea (6.1%). The relative frequencies were 0.6%, 0.6%, and 4.0% in the placebo arm, respectively.³³

Serious TEAEs were recorded in 16.9% of patients in the tucatinib arm and 8.0% of patients in the control arm. The most frequent serious TEAEs in the tucatinib arm were elevated ALT (1.5%) and drug-induced liver injury (1.2%). The frequency of both these serious TEAEs was 0% in the placebo arm. TEAEs leading to discontinuation of any study treatment occurred in 13.8% of patients in the tucatinib arm and 4.6% of patients in the placebo arm.³³

Comparison of the PATINA, DESTINY-Breast09, and HER2CLIMB-05 Trials

A summary of the outcome measures between the three trials is shown in **Table 1** below.

Table 1. Comparison of the PATINA²⁰, DESTINY-Breast09²⁸, and HER2CLIMB-05³³ trials.

	Overall mPFS (mos)	HR+ mPFS (mos)	HR- mPFS (mos)	ORR (%)	CNS data	OS benefit in experimental arm
THP → HP (DB09)^a	26.9	27.7	22.6	78.6% (8.5% CR)	Few patients with BMs at baseline enrolled (5.7-6.5%)	No (immature)
T-DXd + P (DB09)^a	40.7	38.0	40.7	85.1% (15% CR)		
THP → HP (HER2CLIMB-05)^b	16.3	18.1	12.6	-	CNS-PFS (BMs): 4.3	
THP → HP/tucatinib (HER2CLIMB-05)^b	24.9	25.0	24.9	-	CNS-PFS (BMs): 8.5	No (immature)
THP → HP/ET (PATINA)^b	-	29.1	-	22.2%	CNS PD at 36m: 19.2%	
THP → HP/ET/palbociclib (PATINA)^b	-	44.3	-	29.9%	CNS PD at 36m: 13.0%	No (immature)

^aPFS was measured from treatment initiation (true baseline) to progression or death.

^bPFS was measured from the end of induction therapy to progression or death.

Abbreviations: DB09, DESTINY-Breast09; mos, months; HR, hormone receptor; mPFS, median progression-free survival; ORR, objective response rate; OS, overall survival; CNS, central nervous system; BM, brain metastases; CR, complete response; PD, progressive disease; T-DXd, trastuzumab deruxtecan; P, pertuzumab; THP, tucatinib, trastuzumab, and pertuzumab; HP, trastuzumab and pertuzumab; ET, endocrine therapy.

Development of the Consensus Statements

Dana-Farber Cancer Institute's Breast Oncology Center (BOC) held multidisciplinary meetings on 06/06/2025, 09/19/2025, 10/10/2025, 04/17/2026, 08/07/2026, and 09/18/2026 to discuss recommendations for the use of T-DXd and pertuzumab, palbociclib, and tucatinib in patients with HER2+ metastatic breast cancer. Data were reviewed from the AFT-38 PATINA, HER2CLIMB-05, and DESTINY-Breast09 trials. 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, 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 September 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.

Q1. Which patients with HER2-positive (HER2+) metastatic breast cancer (MBC) should receive first-line trastuzumab deruxtecan (T-DXd) plus pertuzumab?

Given the efficacy data from the DESTINY-Breast09 trial,²⁸⁻³⁰ together with the broader available evidence, the BOC group recommended first-line T-DXd plus pertuzumab for selected patients with HER2+ metastatic breast cancer, as outlined in the consensus statement below.

Consensus Statement

The BOC group recommends first-line T-DXd plus pertuzumab for patients with HER2+ metastatic breast cancer at high-risk of early progression, including:

- Patients with recurrence ≤ 12 -24 months after (neo)adjuvant HER2-directed therapy
- Patients with *PIK3CA* mutations
- Patients with central nervous system (CNS) involvement
- Patients with high disease burden and/or symptomatic disease

Q2. Are there any patients for whom first-line T-DXd plus pertuzumab should be considered as an induction strategy, with switch to a maintenance strategy in the absence of progressive disease or toxicity?

The single-arm phase 2 DEMETHER trial is evaluating induction T-DXd followed by maintenance strategy as a first-line treatment strategy for patients with HER2+ metastatic breast cancer. Trial participants include patients with treatment-naïve HER2+ MBC, who receive six cycles of induction T-DXd followed by maintenance HP (plus ET for patients with HR+ disease).³² The trial is currently ongoing, and efficacy results are not yet available.

In this context, the BOC group considered a maintenance strategy after T-DXd induction to be a reasonable approach in selected patients, with treatment decisions individualized according to patient- and disease-related features, including hormone receptor status, CNS involvement, and *PIK3CA* mutation status.

Among patients for whom this approach is considered appropriate, the timing of the transition from induction T-DXd plus pertuzumab to maintenance therapy must also be considered. In the DESTINY-Breast 09 trial, among patients in the T-DXd plus pertuzumab group (n = 383), the median time to achieve maximum tumor reduction (nadir) was approximately 11 months (16 cycles). Among evaluable patients treated with T-DXd plus pertuzumab whose best response was complete response, the median time to complete response was 8.4 months (95% CI: 5.6 – 11.1). Among evaluable patients treated with T-DXd plus pertuzumab whose best response was deep partial response, the median time to deep partial response was 9.6 months (95% CI: 6.8 – 11.0). Deep partial response was defined as an $\geq 80\%$ to $< 100\%$ reduction in the target lesion sum and complete response or non-complete response/non-progressive disease in non-target lesions, or complete response in target lesion and non-complete response/non-progressive disease in non-target lesions.³⁵

Based on these findings, it is recommended that patients with a complete response to induction T-DXd plus pertuzumab (confirmed by at least two scans) should receive this regimen for at least six months before switching to maintenance therapy. All other patients are recommended to receive 9-12 months of induction T-DXd plus pertuzumab before switching to maintenance therapy.

Consensus Statement

The consensus was to consider a maintenance strategy after T-DXd induction on a case-by-case basis, taking into account patient- and disease-related factors, including, but not limited to, hormone receptor status, presence or absence of CNS metastases, and *PIK3CA* mutation status.

Among patients for whom this approach is considered appropriate, the timing of the transition from induction T-DXd plus pertuzumab to maintenance therapy should also be individualized based on patient- and disease-related factors, including, but not limited to, tumor burden, depth and timing of response to induction T-DXd plus pertuzumab, tolerability of induction T-DXd plus pertuzumab, and patient preferences.

There was no universal consensus regarding the duration of induction therapy. However, the group largely agreed that patients with a complete response to induction T-DXd plus pertuzumab (confirmed by at least two scans) should receive this regimen for at least six months before switching to maintenance therapy. All other patients are recommended to receive 9-12 months of induction T-DXd plus pertuzumab before switching to maintenance therapy.

Q3. Which patients with HER2+ MBC should receive induction taxane, trastuzumab, and pertuzumab (THP) followed by a maintenance strategy?

Approximately 16% of patients remain progression free at 8 years with first-line THP.² Long-term responders are more likely to have low-risk disease features, including *de novo* metastatic disease, a longer disease-free interval, non-visceral disease, *PIK3CA* wild-type tumors, HER2 IHC 3+ expression, and high *ERBB2* mRNA expression.² For these patients, THP likely remains the preferred first-line treatment option, particularly given the availability of T-DXd at the time of disease progression.³⁶

Consensus Statement

The BOC group recommends first-line THP induction followed by a maintenance strategy for patients with HER2+ metastatic breast cancer at low risk of early progression, including:

- Patients with *de novo* metastatic disease or metastatic recurrence > 12-24 months after completion of neoadjuvant or adjuvant HER2-directed therapy for early-stage HER2+ breast cancer
- Patients with *PIK3CA* wild-type disease
- Patients with no CNS involvement
- Patients with low disease burden and/or asymptomatic disease

Q4. In patients being treated with an induction and maintenance strategy, in which HR+/HER2+ MBC patients should palbociclib be added to maintenance treatment with trastuzumab and pertuzumab (HP) plus endocrine therapy (ET)?

The BOC group confirmed that ET should be added to maintenance HP in all patients with HR+/HER2+ MBC.

Based on the positive results of the PATINA trial,²⁰ the consensus was to consider adding palbociclib during the first year of maintenance therapy with HP and ET, acknowledging that the trial enrolled patients only during the 12 weeks following completion of induction chemotherapy. Patients who have maintained a response on maintenance HP and ET for more than one year likely do not require the addition of palbociclib.

The BOC group recommends adding palbociclib to maintenance HP and ET in patients with high-burden and low-burden disease, including patients with bone-only disease (including oligometastatic bone-only disease) and those with visceral metastases, regardless of age.

The BOC group largely agreed to adopt similar monitoring guidelines to those used in the PATINA trial,²⁰ while adapting the schedule to align with HP infusions and improve patient

convenience. Recommended monitoring includes CBC and CMP every 3 weeks during the first 3 cycles, with dose adjustments per FDA label for palbociclib. After that, laboratory assessments may be extended to every 6–12 weeks based on physician discretion and patient preference.

Consensus Statement

The BOC group expressed a strong recommendation for the addition of ET to maintenance HP in all patients with HR+/HER2+ metastatic breast cancer who received an induction strategy.

Adding palbociclib to maintenance HP is recommended for all patients with HR+/HER2+ metastatic breast cancer initiating maintenance HP with ET.

Palbociclib may be added to maintenance HP plus ET in patients with high- or low-burden disease, including patients with visceral metastases as well as those with bone-only disease (including oligometastatic bone-only disease), regardless of age.

Standard monitoring will include CBC + CMP every 3 weeks for the first 3 cycles with palbociclib dose adjustments per FDA label.

Q5. In patients being treated with an induction and maintenance strategy, in which HR+/HER2+ MBC patients should tucatinib be added to first-line maintenance treatment with HP plus ET?

Among patients with HR+/HER2+ metastatic breast cancer enrolled on the PATINA trial, the median PFS was 44.3 months on maintenance palbociclib, HP, and ET following THP induction.²⁰ Among patients with HR+/HER2+ metastatic breast cancer enrolled on the HER2CLIMB-05 trial, the median PFS was 25.0 months on maintenance tucatinib with HP following THP induction.³⁴ However, direct cross-trial comparisons should be interpreted with caution given differences in study design, patient populations, eligibility criteria, and prior treatment exposure across studies. Notably, only 44.0% of patients with HR+ disease enrolled in the tucatinib arm received ET as part of their maintenance therapy.³³

Both regimens have demonstrated CNS efficacy, albeit by different metrics. In the HER2CLIMB-05 trial, among patients with baseline brain metastases, the median CNS-PFS was 8.5 months (95% CI: 4.4 – 22.8) in the tucatinib arm versus 4.3 months (95% CI: 2.3 – 10.6) in the control arm (HR: 0.719, 95% CI: 0.406 – 1.273).³⁴ In the PATINA trial, the 3-year cumulative incidence of CNS progression in the overall study population was 13.8% in the palbociclib, HP, and ET arm versus 20.4% in the HP and ET arm (Gray's test $p = 0.0404$). Among patients without baseline CNS metastases, the 3-year cumulative incidence of CNS progression was 13.0% versus 19.2%, respectively (Gray's test $p = 0.0378$).²²

The BOC group consensus was divided, with 50% stating they would never employ this treatment strategy in patients with HR+ disease and the remaining 50% stating they would consider it only in patients with CNS involvement.

Consensus Statement

The general consensus was that, in patients with HR+/HER2+ metastatic breast cancer treated with an induction and maintenance strategy, maintenance palbociclib, HP, and ET would be favored. There was no universal consensus on whether palbociclib or tucatinib should be favored in patients with brain metastases. The BOC group noted that data evaluating patients with brain metastases from both the PATINA and HER2CLIMB-05 trials were relatively limited.

Q6. In patients being treated with an induction and maintenance strategy, in which patients with HR-/HER2+ MBC should tucatinib be added to first-line maintenance treatment with HP?

In the HER2CLIMB-05 trial, the addition of tucatinib to maintenance HP after THP induction in patients with HR-/HER2+ metastatic breast cancer yielded a significant PFS benefit over HP (24.9 months versus 16.3 months; HR: 0.641, 95% CI: 0.517 – 0.828; two-sided $p < 0.0001$).³³ Given these findings, the BOC group generally considered the addition of tucatinib to maintenance HP to be a reasonable option for patients with HR-/HER2+ metastatic breast cancer without disease progression after THP induction. Potential reservations included concerns about introducing tucatinib too early in the treatment course, given the established efficacy of tucatinib, trastuzumab, and capecitabine in patients with HER2+ metastatic breast cancer progressing after first-line THP.^{37,38}

Consensus Statement

The consensus was mixed. Half of the BOC group (50%) considered that most patients with HR-/HER2+ metastatic breast cancer treated with an induction and maintenance strategy should be recommended to receive tucatinib with maintenance HP. Other commonly held views included restricting this approach to patients with CNS involvement (21%) or individualizing its use on a case-by-case basis (21%).

Q7. Should palbociclib, trastuzumab, pertuzumab, and ET without induction chemotherapy be considered as a first-line treatment for patients with HR+/HER2+ metastatic breast cancer?

Currently, there is insufficient evidence to recommend the combination of palbociclib, trastuzumab, pertuzumab, and ET as first-line treatment in the absence of induction chemotherapy. In the PATINA trial, only patients with HR+/HER2+ metastatic breast cancer

who had completed induction therapy with a taxane and trastuzumab (with or without pertuzumab), and had no evidence of disease progression, were enrolled.

Emerging data from several small phase 2 studies, including ASPIRE,¹⁹ DETECT V/CHEVENDO,¹⁴⁻¹⁶ and KCSG BR 18-2 MINI,¹⁷ suggest potential activity of combining CDK4/6 inhibitors, anti-HER2 therapy, and endocrine therapy as an upfront regimen. However, robust phase 3 evidence remains limited to the PATINA trial,²⁰ in which all patients received prior induction chemotherapy.

However, in patients for whom chemotherapy is contraindicated, the combination of palbociclib, trastuzumab, pertuzumab, and ET could be considered based on available safety and efficacy data. Notably, current guidelines already recommend ET with trastuzumab and pertuzumab in this setting, supported by results from the PERTAIN study.^{8,9}

Consensus Statement

Currently, there is insufficient evidence to routinely recommend palbociclib with HP plus ET as first-line treatment for patients with HR+/HER2+ metastatic breast cancer without prior induction chemotherapy.

First-line palbociclib, HP, and ET (without induction chemotherapy) may be considered in patients for whom chemotherapy is contraindicated (64%) or in select patients for whom chemotherapy might not be necessary, such as those with low-burden disease (36%).

References

1. Baselga, J., *et al.* Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* **366**, 109-119 (2012).
2. Swain, S.M., *et al.* Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* **21**, 519-530 (2020).
3. Howlader, N., *et al.* US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst* **106**(2014).
4. Cancer Genome Atlas, N. Comprehensive molecular portraits of human breast tumours. *Nature* **490**, 61-70 (2012).
5. Prat, A., *et al.* Molecular features and survival outcomes of the intrinsic subtypes within HER2-positive breast cancer. *J Natl Cancer Inst* **106**(2014).
6. Cejalvo, J.M., *et al.* Clinical implications of the non-luminal intrinsic subtypes in hormone receptor-positive breast cancer. *Cancer Treat Rev* **67**, 63-70 (2018).

7. Cejalvo, J.M., *et al.* Intrinsic Subtypes and Gene Expression Profiles in Primary and Metastatic Breast Cancer. *Cancer Res* **77**, 2213-2221 (2017).
8. Arpino, G., *et al.* Pertuzumab, Trastuzumab, and an Aromatase Inhibitor for HER2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer: PERTAIN Final Analysis. *Clin Cancer Res* **29**, 1468-1476 (2023).
9. Nader-Marta, G., Martins-Branco, D. & de Azambuja, E. How we treat patients with metastatic HER2-positive breast cancer. *ESMO Open* **7**, 100343 (2022).
10. Goel, S., *et al.* Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers with CDK4/6 Inhibitors. *Cancer cell* **29**, 255-269 (2016).
11. O'Brien, N., *et al.* Preclinical Activity of Abemaciclib Alone or in Combination with Antimitotic and Targeted Therapies in Breast Cancer. *Mol Cancer Ther* **17**, 897-907 (2018).
12. Tolaney, S.M., *et al.* Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarchHER): a randomised, open-label, phase 2 trial. *Lancet Oncol* **21**, 763-775 (2020).
13. Tolaney, S.M., *et al.* Overall Survival and Exploratory Biomarker Analyses of Abemaciclib plus Trastuzumab with or without Fulvestrant versus Trastuzumab plus Chemotherapy in HR+, HER2+ Metastatic Breast Cancer Patients. *Clin Cancer Res* **30**, 39-49 (2024).
14. Janni, W., *et al.* 350MO Omission of chemotherapy and addition of the CDK4/6 inhibitor ribociclib in HER2-positive and hormone-receptor positive metastatic breast cancer – Second interim efficacy analysis of the randomized phase III DETECT V trial. *Annals of Oncology* **35**, S362 (2024).
15. Krause, S., *et al.* Abstract OT2-07-01: DETECT V/CHEVENDO – Comparison of dual HER2-targeted therapy with trastuzumab plus pertuzumab in combination with chemo- or endocrine therapy in addition with CDK4/6 inhibition in patients with HER2-positive and hormone-receptor positive metastatic breast cancer. *Cancer Research* **79**, OT2-07-01-OT02-07-01 (2019).
16. Friedl, T.W.P., *et al.* Abstract OT2-01-03: DETECT V - Comparison of dual HER2-targeted therapy with trastuzumab and pertuzumab plus CDK4/6 inhibition in combination with either chemo- or endocrine therapy in patients with HER2-positive and hormone-receptor positive metastatic breast cancer. *Cancer Research* **80**, OT2-01-03-OT02-01-03 (2020).
17. Sohn, J., *et al.* Phase IB and II study of ribociclib with trastuzumab plus endocrine therapy in HR+/HER2+ advanced breast cancer patients: Korean Cancer Study Group BR 18-2 MINI trial. *Journal of Clinical Oncology* **43**, 1016-1016 (2025).
18. Ciruelos, E., *et al.* Primary results from PATRICIA cohort C (SOLTI-1303), a randomized phase II study evaluating palbociclib with trastuzumab and endocrine therapy in pretreated HER2-positive and PAM50 luminal advanced breast cancer. *Journal of Clinical Oncology* **42**, 1008-1008 (2024).
19. Patel, R., *et al.* Abstract RF02-01: A Multicenter, Phase I/II Trial of Anastrozole, Palbociclib, Trastuzumab, and Pertuzumab in Hormone Receptor (HR)-Positive, HER2-

- Positive Metastatic Breast Cancer (ASPIRE). *Cancer Research* **84**, RF02-01-RF02-01 (2024).
20. Metzger, O., *et al.* Palbociclib for Hormone-Receptor-Positive, HER2-Positive Advanced Breast Cancer. *N Engl J Med* **394**, 451-462 (2026).
 21. Otto Metzger, S.M., Angela DeMichele, Luca Gianni, Joseph Gligorov, Elgene Lim, Eva Ciruelos, Sibylle Loibl, Travis Dockter, Xavier González Farré, Prudence Francis, Filipa Lynce, Jane Lanzillotti, Carter DuFrane, Ian Krop, Ines Vaz-Luis, Pinuccia Valagussa, Debu Tripathy, Sherene Loi, Aleix Prat, Mathew Goetz, Santiago Escrivá-de-Romaní, David Porter, Jennifer Spoenlein, Sagar Sardesai, Pierre Heudel, Maria Koehler, Cynthia Huang Bartlett, Ariadna Holynskij, Prashanth Gopalakrishna, Eric Gauthier, Yuan Liu, Suzette Delaloge, Kathy Miller, Eric Winer, Ann Partridge, Shom Goel, Lisa Carey. AFT-38 PATINA: A Randomized, Open Label, Phase III Trial to Evaluate the Efficacy and Safety of Palbociclib + Anti-HER2 Therapy + Endocrine Therapy vs. Anti-HER2 Therapy + Endocrine Therapy after Induction Treatment for Hormone Receptor-Positive (HR+)/HER2-Positive Metastatic Breast Cancer in *San Antonio Breast Cancer Symposium* (San Antonio, TX, USA, 2024).
 22. Metzger, O., *et al.* Abstract RF4-01: Central Nervous System Outcomes from the Phase III PATINA Trial (AFT-38). *Clinical Cancer Research* **32**, RF4-01-RF04-01 (2026).
 23. Doi, T., *et al.* Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. *Lancet Oncol* **18**, 1512-1522 (2017).
 24. Hurvitz, S.A., *et al.* Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet* **401**, 105-117 (2023).
 25. Sara Hurvitz, S.-B.K., Wei-Pang Chung, Seock-Ah Im, Yeon Hee Park, Roberto Hegg, Min-Hwan Kim, Ling-Ming Tseng, Vanessa Petry, Chi-Feng Chung, Hiroji Iwata, Erika Hamilton, Giuseppe Curigliano, Binghe Xu, Caleb Lee, Yali Liu, Jillian Cathcart, Emarjola Bako, Sunil Verma, Javier Cortés. GS3-01. Trastuzumab deruxtecan (T-DXd; DS-8201a) vs. trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): subgroup analyses from the randomized phase 3 study DESTINY-Breast03. in *San Antonio Breast Cancer Symposium* (2021).
 26. Hurvitz SA, H.R., Chung W-P, Im S-A, Jacot W, Ganju V, Chiu JWY, Xu B, Hamilton E, Madhusudan S, Iwata H, Altintas S, Henning J-W, Curigliano G, Pérez-García JM, Egorov A, Liu Y, Cathcart J, Ashfaq S, Cortés J. GS2-02: Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: Updated survival results of the randomized, phase 3 study DESTINY-Breast03. in *San Antonio Breast Cancer Symposium* (San Antonio, TX, USA, 2022).
 27. Hurvitz, S.A., *et al.* Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer patients with brain metastases from the randomized DESTINY-Breast03 trial. *ESMO Open* **9**, 102924 (2024).

28. Tolaney, S.M., *et al.* Trastuzumab Deruxtecan plus Pertuzumab for HER2-Positive Metastatic Breast Cancer. *N Engl J Med* (2025).
29. Tolaney, S.M., *et al.* Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for first-line (1L) treatment of patients (pts) with human epidermal growth factor receptor 2–positive (HER2+) advanced/metastatic breast cancer (a/mBC): Interim results from DESTINY-Breast09. *Journal of Clinical Oncology* **43**, LBA1008-LBA1008 (2025).
30. Loibl, S., *et al.* LBA18 Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for patients (pts) with HER2+ advanced/metastatic breast cancer (a/mBC): Additional analyses of DESTINY-Breast09 in key subgroups of interest. *Annals of Oncology* **36**, S1563-S1564 (2025).
31. U.S. Food and Drug Administration. FDA approves fam-trastuzumab deruxtecan-nxki with pertuzumab for unresectable or metastatic HER2-positive breast cancer. December 15, 2025. Accessed May 19, 2026. <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-fam-trastuzumab-deruxtecan-nxki-pertuzumab-unresectable-or-metastatic-her2-positive>.
32. Cortés, J., *et al.* Abstract P5-03-11: DEMETHER: A single-arm phase II trial to evaluate the efficacy & safety of subcutaneous pertuzumab & trastuzumab maintenance after induction treatment w/ trastuzumab deruxtecan (T-DXd) for previously untreated HER2-positive advanced breast cancer. *Clinical Cancer Research* **31**, P5-03-11-P05-03-11 (2025).
33. Dieras, V., *et al.* HER2CLIMB-05: A Phase III Study of Tucatinib Versus Placebo in Combination With Trastuzumab and Pertuzumab as First-Line Maintenance Therapy for HER2+ Metastatic Breast Cancer. *J Clin Oncol*, JCO2502600 (2025).
34. Hamilton, E., *et al.* Abstract GS1-01: Her2climb-05: a randomized, double-blind, phase 3 study of tucatinib versus placebo in combination with trastuzumab and pertuzumab as maintenance therapy for her2+ metastatic breast cancer. *Clinical Cancer Research* **32**, GS1-01-GS01-01 (2026).
35. Park, Y.H., *et al.* A DESTINY-Breast09 analysis of treatment duration and clinical outcomes by best response to trastuzumab deruxtecan (T-DXd) + pertuzumab (P). *Journal of Clinical Oncology* **44**, 1021-1021 (2026).
36. Cortes, J., *et al.* Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *N Engl J Med* **386**, 1143-1154 (2022).
37. Curigliano, G., *et al.* Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. *Ann Oncol* **33**, 321-329 (2022).
38. Lin, N.U., *et al.* Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. *JAMA Oncol* **9**, 197-205 (2023).