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Release date: June 10, 2023; Expiration date: June 10, 2024

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Breast Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Breast Cancer

Disclosure of Relevant Financial Relationships

None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Individuals Who Provided Content Development and/or Authorship Assistance:

The faculty listed below have no relevant financial relationship(s) with ineligible companies to disclose.

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The faculty listed below have the following relevant financial relationship(s) with ineligible companies to disclose. All of the relevant financial relationships listed for these individuals have been mitigated.

William J. Gradishar, MD, Panel Chair, has disclosed serving as a scientific advisor for AstraZeneca Pharmaceuticals LP, Biotheranostics, Daiichi-Sankyo Co., Eli Lilly and Company, ImmunoGen, Inc., MacroGenics, Puma Biotechnology, and Seattle Genetics, Inc.; and receiving honoraria from AstraZeneca Pharmaceuticals LP, Biotheranostics, Daiichi-Sankyo Co., and ImmunoGen, Inc.
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Rachel C. Jankowitz, MD, Panel Member, has disclosed serving as a scientific advisor to Biotheranostics.
Hope S. Rugo, MD, Panel Member, has disclosed receiving grant/research support from Astellas Pharma US, Inc., AstraZeneca Pharmaceuticals LP, Daiichi-Sankyo Co., Eli Lilly and Company, Gilead Sciences, Inc., GlaxoSmithKline, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, OBI Pharma, Inc., Pionyr Immunotherapeutics Inc., Pfizer, Inc., Roche Laboratories, Inc., Sermonix Pharmaceuticals, Taiho Pharmaceuticals Co., Ltd., and Veru Inc.; serving as a scientific advisor for Blueprint Medicines, Napo Pharmaceuticals, Inc., Puma Biotechnology, and Scorpion Therapeutics; and receiving consulting fees from Blueprint Medicines, Napo Pharmaceuticals, Inc., Puma Biotechnology, and Scorpion Therapeutics.
Hatem Soliman, MD, Panel Member, has disclosed receiving consulting fees from AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals Corporations, Puma Biotechnology, and SeaGen; receiving grant/research support from Amgen Inc.; and serving in a product/speakers bureau for Merck & Co., Inc.
Kari B. Wisinksi, MD, Panel Member, has disclosed receiving grant/research support from Context Therapeutics, Novartis Pharmaceuticals Corporation, Pfizer Inc., and Puma Biotechnology; and receiving consulting fees from Novartis Pharmaceuticals Corporation, Pfizer Inc., sanofi-aventis U.S., and Stemline Therapeutics Inc.
Kay Yeung, MD, Panel Member, has disclosed receiving grant/research support from BioFluidica, Dantari, Inc., Gilead Sciences, Inc., Immunomedics, Inc., Regeneron Pharmaceuticals, SeaGen, and Zymeworks.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

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Breast Cancer, Version 4.2023

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer address all aspects of management for breast cancer. The treatment landscape of metastatic breast cancer is evolving constantly. The therapeutic strategy takes into consideration tumor biology, biomarkers, and other clinical factors. Due to the growing number of treatment options, if one option fails, there is usually another line of therapy available, providing meaningful improvements in survival. This NCCN Guidelines Insights report focuses on recent updates specific to systemic therapy recommendations for patients with stage IV (M1) disease.

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*Provided content development and/or authorship assistance.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens

First-Line Therapy
- Aromatase inhibitor + CDK4/6 inhibitor[b]
  - Aromatase inhibitor + ribociclib (category 1)[c]
  - Aromatase inhibitor + abemaciclib
  - Aromatase inhibitor + palbociclib
- Fulvestrant[d] + CDK4/6 inhibitor[b]
  - Fulvestrant + ribociclib (category 1)[e]
  - Fulvestrant + abemaciclib (category 1)[e]
  - Fulvestrant + palbociclib

Second- and Subsequent-Line Therapy
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[f,g]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options, see BINV-Q (6)[h]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[i,j]

Other Recommended Regimens

First- and/or Subsequent-Line Therapy
- Selective ER down-regulator
  - Fulvestrant[k]
  - For *ESR1* mutated tumors, see BINV-Q (6)
- Selective ER down-regulator (fulvestrant, category 1) + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[k]
- Non-steroidal aromatase inhibitor
  - Anastrozole
  - Letrozole
- Selective ER modulator
  - Tamoxifen
- Steroidal aromatase inactivator
  - Exemestane

Useful in Certain Circumstances

Subsequent-Line Therapy
- Megestrol acetate
- Estradiol
- Abemaciclib[l]
- Addtional targeted therapy options, see BINV-Q (6)

HER2-Positive and Postmenopausal[m,n] or Premenopausal Receiving Ovarian Ablation or Suppression
- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

[a] Baseline assessment of bone density recommended for patients receiving an aromatase inhibitor who are at risk of osteoporosis (eg, age >65, family history, chronic steroids).
[b] There is controversy on the choice of CDK4/6 inhibitor as there are no head to head comparisons between the agents and there are some differences in the study populations in the phase 3 randomized studies.
[c] In phase 3 randomized controlled trials, ribociclib + endocrine therapy has shown OS benefit in the first-line setting.
[d] Consider for disease progression on adjuvant endocrine therapy or with early disease relapse within 12 months of adjuvant endocrine therapy completion.
[e] In phase 3 randomized controlled trials, fulvestrant + ribociclib or abemaciclib has shown OS benefit in the first-line setting.
[f] In phase 3 randomized controlled trials, fulvestrant in combination with a CDK4/6 inhibitor (abemaciclib, palbociclib, and ribociclib) has shown OS benefit in the second-line setting.
[g] If there is disease progression while on palbociclib, there are limited phase II data to support the use of ribociclib in the second line setting.
[h] If there is progression while on a PI3K inhibitor, there are limited data to support another line of therapy with a PI3K-pathway inhibitor-containing regimen.
[i] If there is disease progression while on an everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.
[j] A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal aromatase inhibitor).
[k] A single study (S0226) in patients with HR-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression and OS. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.
[l] Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.
[m] An FDA-approved biosimilar is an appropriate substitute for trastuzumab. Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.
[n] If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to trastuzumab + pertuzumab.

BINV-P

Overview

Female breast cancer is the most commonly diagnosed cancer worldwide.[1] The American Cancer Society estimates that 300,590 individuals will be diagnosed with female breast cancer, representing 15.4% of all cancers in the United States, in 2023.[2]

The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer include up-to-date guidelines for clinical management of patients with carcinoma in situ, invasive breast cancer, Paget's disease, Phyllodes tumor, inflammatory breast cancer, male breast cancer, and breast cancer during pregnancy. These guidelines have been developed and updated by a multidisciplinary panel of representatives from NCCN Member Institutions with breast cancer–focused expertise in the fields of medical oncology, surgical oncology, radiation oncology, pathology, reconstructive surgery, and patient advocacy.

In the 2023 version of the NCCN Guidelines for Breast Cancer, the panel included updated recommendations/revisions for adjuvant radiation therapy, adjuvant systemic therapy for patients with hormone receptor (HR)–positive and HER2-negative breast cancer, and systemic therapy for metastatic disease. This report summarizes the rationale behind the recommendations specific to systemic therapy for metastatic disease.

NCCN Guidelines strive to use exclusively nongendered, inclusive, and sensitive language. The studies included in this report have not reported collection of sex and gender data. Therefore, in this report the use of terms including *women*, *men*, *female*, and *male* are as per cited statistics, recommendations, or data from organizations or sources that do not use inclusive terms.

Management of Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease

The median overall survival (OS) of all patients diagnosed with metastatic disease has improved due to treatment advances across all subtypes.[3] The goal of treatment for metastatic disease is to extend survival, alleviate symptoms, and enhance quality of life. Therefore, the preferred treatments are those associated with minimal toxicity, balanced against demonstrated improvements in OS.

HR-Positive/HER2-Negative Disease With No Visceral Crisis and Not Endocrine-Refractory

Patients with stage IV or recurrent disease characterized by tumors that are HR-positive and HER2-negative are evaluated for treatment based on whether they have

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan- nxki	Sacituzumab govitecan[f] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy see BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)

[†] According to the 5th ESO-ESMO international consensus guidelines (Cardoso F, et al. Ann Oncol 2020;31:1625) for advanced breast cancer visceral crisis is defined as: "severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy."

[a] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.
[b] Assess for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.
[c] PARPi can be considered for a later line for those with BRCA1/2 mutation, however available evidence suggests it is more effective if used earlier.
[d] See Principles of HER2 Testing (BINV-A).
[e] Fam-trastuzumab deruxtecan maybe considered in a later line for HER2 IHC 1+ or 2+/ISH negative, if not used in second–line. Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.
[f] Sacituzumab govitecan-hziy may be used for adult patients with HR-positive, HER2-negative metastatic/locally advanced unresectable breast cancer after prior treatment including endocrine therapy, a CDK4/6 inhibitor, and at least two lines of chemotherapy, one of which was a taxane, and at least one of which was in the metastatic setting. It may be considered for later line if not used as second line therapy.

visceral crisis. The updated guidelines now define visceral crisis according to the 5th ESO-ESMO international consensus guidelines for advanced breast cancer as "severe organ dysfunction, as assessed by signs and symptoms, laboratory studies, and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy"[4] (see BINV-Q, 1 of 14, above). In addition, it is also important to understand whether the disease progressed within 1 year of completion of adjuvant endocrine therapy or longer and to assess the ovarian function of the patient to determine the need for ovarian suppression/ablation if an aromatase inhibitor (AI) or fulvestrant would be used.

Endocrine-based therapy is less toxic than chemotherapy. Therefore, the current first-line treatment for most patients with HR-positive/HER2-negative disease and no visceral crisis is endocrine therapy in either combination with targeted therapy (preferred) or alone (in certain circumstances, such as when targeted therapy is unavailable/accessible or not appropriate for the patient). Chemotherapy is reserved for patients whose cancers are refractory (ie, no longer respond to) to endocrine therapy or who need rapid treatment response for visceral crisis. If initiating treatment with chemotherapy, in the updated version of the guidelines, the panel has noted that it is acceptable to switch from urgent treatment with chemotherapy to endocrine-based therapy after clinical improvement or disease response.

CDK4/6 Inhibitor in Combination With Endocrine Therapy in First-Line Setting

In the first-line setting (ie, for patients with disease that has progressed after at least 12 months after completion of adjuvant endocrine therapy) or for patients who present with de novo metastatic breast cancer, the panel has listed the CDK4/6 inhibitors with an endocrine therapy partner (either nonsteroidal AI or fulvestrant) as "preferred regimens" due to observed survival advantage and quality of life. Dual endocrine therapy–containing regimens with a selective estrogen receptor (ER) downregulator (fulvestrant) in combination with an AI (anastrozole, letrozole) are now listed under "other recommended regimens" in the guidelines given inconsistent results from a few phase III clinical trials (see BINV-P, opposite page).

Data for CDK4/6 Inhibitor in Combination With AI

Phase III studies in the first-line setting with the 3 currently available CDK4/6 inhibitors in combination

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10[g] regardless of germline *BRCA* mutation status[b]	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[h] (Category 1, preferred)
	PD-L1 CPS <10[g] and no germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	PD-L1 CPS <10[g] and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan[i] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)
	Any	Systemic chemotherapy see BINV-Q (5)

[a] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.
[b] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy
[d] See Principles of HER2 Testing (BINV-A).
[e] Fam-trastuzumab deruxtecan maybe considered in a later line for HER2 IHC 1+ or 2+/ISH negative, if not used in second–line. Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.
[g] PD-L1 expression is assessed using 22C3 antibody. Threshold for positivity combined positive score ≥10.
[h] While available data are in the first-line setting, this regimen can be used for second and subsequent lines of therapy if PD-1/PD-L1 inhibitor therapy has not been previously used. If there is disease progression while on a PD-1/PD-L1 inhibitor, there are no data to support an additional line of therapy with another PD-1/PD-L1 inhibitor.
[i] Sacituzumab govitecan-hziy may be used for adult patients with metastatic TNBC who have received at least 2 prior therapies, at least one of which was for metastatic disease. It may be considered for later line if not used as second line therapy.

with an AI have shown significant improvements in progression-free survival (PFS).

In the phase III PALOMA-2 trial, median PFS for patients treated with first-line palbociclib + letrozole was longer compared with letrozole alone (24.8 vs 14.5 months; hazard ratio, 0.58; $P<.001$).[5] In the phase III MONARCH 3 trial, PFS was significantly improved with first-line abemaciclib in combination with letrozole or anastrozole compared with letrozole or anastrozole alone (median, not reached vs 14.7 months, respectively; hazard ratio, 0.54; 95% CI, 0.41–0.72).[6] In the phase III MONALEESA-2 trial, the addition of ribociclib to letrozole in the first-line setting improved PFS from 16 to 25.3 months (hazard ratio, 0.57; $P<.001$).[7] The phase III MONALEESA-7 trial specifically studied efficacy of the CDK4/6 inhibitors in pre- or perimenopausal patients with HR-positive/HER2-negative disease. Patients were randomized to receive ribociclib or placebo, both in combination with goserelin and an AI or tamoxifen. The addition of ribociclib was associated with a significant improvement in PFS, with a median of 23.8 versus 13.0 months with placebo (hazard ratio, 0.55; 95% CI, 0.44–0.69; $P<.001$).

With respect to OS benefit of first-line CDK4/6 inhibitor with an AI, in a recent updated OS analysis of the PALOMA-2 trial after a median follow-up of 90 months, palbociclib + letrozole showed a numerical increase in OS but no statistically significant benefit compared with letrozole alone (52 vs 45 months; hazard ratio, 0.87; 95% CI, 0.71–1.1).[8] Ribociclib demonstrated OS benefit in the first-line setting in combination with AI or AI + ovarian function suppression in the MONALEESA-2 trial after 6.6 years of follow-up (64 vs 51 months; hazard ratio, 0.76; 95% CI, 0.63–0.93)[9] as well as in the MONALEESA-7 trial (58 vs 48 months; hazard ratio, 0.76; 95% CI, 0.61–0.96).[10] The interim analysis data from the MONARCH 3 trial, presented at the 2022 ESMO Congress, showed a clinically meaningful trend in OS benefit with the addition of abemaciclib to letrozole (67 vs 55 months; hazard ratio, 0.75; 95% CI, 0.58–0.97). However, these OS data have not yet reached statistical significance.[11] The final OS analysis of this trial is awaited.

NCCN Recommendations

Based on the significant improvement in PFS seen in the pivotal phase III trials described earlier, the panel has continued to list CDK4/6 inhibitor in combination with AI as preferred first-line options for postmenopausal patients (either naturally or induced) with HR-positive/HER2-negative metastatic breast cancer. Because ribociclib has shown OS benefit in this setting, it is currently listed as a category 1 option.

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[k]

HR-Positive or -Negative and HER2-Positive[j,k]	
Setting	**Regimen**
First Line[l]	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line[n]	Fam-trastuzumab deruxtecan-nxki[m] (Category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine[n] (Category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1)[o]
Fourth Line and Beyond (optimal sequence is not known)[p]	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents[q,r]
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Additional Targeted Therapy Options see BINV-Q (6)

[j] See additional considerations for those receiving systemic HER2-targeted therapy (BINV-Q 4).
[k] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA-indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline mutation. There is lower-level evidence for HER2-positive tumors, therefore category 2A for this setting.
[l] Maintenance trastuzumab/pertuzumab after response (with concurrent endocrine therapy if ER+ and HER2+ metastatic breast cancer).
[m] Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]). Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.
[n] Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression in the third-line setting and beyond; and it may be given in the second-line setting.
[o] May be used as an option for third-line and beyond; the optimal sequence for third-line therapy and beyond is not known. If not a candidate fam-trastuzumab T-DM1 could be considered in the second-line.
[p] Multiple lines of concurrent chemotherapy with anti-HER2 therapy (trastuzumab or a TKI) offer clinical benefit for recurrent unresectable HER2+ metastatic breast cancer and have been studied in phase 2 or 3 trials. Clinical experience suggests frequent clinical benefit for such treatment. However, there are no meaningful data for use of any of these regimens among patients previously treated with pertuzumab-based chemotherapy, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, or trastuzumab/capecitabine/tucatinib regimens. Thus, the optimal sequence or true benefit of therapy is not known.
[q] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[r] Trastuzumab may be safely combined with all non-anthracycline–containing preferred and other single agents listed on (BINV-Q 5) for recurrent or metastatic breast cancer.

Palbociclib and abemaciclib in combination with AI have now been listed as category 2A. The panel notes that there is controversy regarding the choice of CDK4/6 inhibitor, because there are no direct head-to-head comparison studies between the 3 CDK4/6 inhibitors in HR-positive/HER2-negative metastatic breast cancer (see BINV-P; page 596).

Data for CDK4/6 Inhibitor in Combination With Fulvestrant

All 3 CDK4/6 inhibitors have also been studied in randomized phase III trials in combination with fulvestrant and have demonstrated significant improvement in PFS. In addition, longer follow-up of all the phase III trials showed an OS benefit with the addition of CDK inhibitors to fulvestrant.[12–14] However, the panel discussed that comparisons between trials cannot be made due to the differences in study populations and settings that included patients receiving fulvestrant in the setting of first-line, second-line, and beyond.

In the MONALEESA-3 trial, postmenopausal women with HR-positive/HER2-negative metastatic breast cancer and with either no prior endocrine therapy (first-line) or with one prior line of endocrine therapy for advanced disease (second-line) were randomized to ribociclib + fulvestrant or fulvestrant alone. The addition of ribociclib to fulvestrant improved PFS from 12.8 to 20.5 months (hazard ratio, 0.60; $P<.001$).[15] According to the data presented at the 2022 ESMO meeting, after a median of 70.8 months, an OS benefit of 15.8 months was seen with first-line treatment with ribociclib + fulvestrant compared with fulvestrant alone with a hazard ratio for death of 0.67.[16]

The PALOMA-3 trial included women of any menopausal status (premenopausal women were treated with goserelin) with HR-positive/HER2-negative metastatic breast cancer with disease that relapsed or progressed during prior endocrine treatment, and no limit on the number of prior endocrine therapies received (second- and subsequent-line therapy). Patients who had received ≥1 lines of chemotherapy in the metastatic setting were also included.[17] The addition of palbociclib to fulvestrant improved PFS from 4.6 to 9.5 months (hazard ratio, 0.46; $P<.001$).[17] Among the overall study population, the median OS was *not* statistically significant. In the group that received palbociclib + fulvestrant, the median OS was 6.9 months longer than in the group that received fulvestrant alone; the hazard ratio for death was 0.81 (95% CI, 0.64–1.03; $P=.09$).[12]

The MONARCH 2 trial included both pre- and postmenopausal women (gonadotropin-releasing hormone agonist added for premenopausal women) with HR-positive/HER2-negative metastatic breast cancer who experienced

Systemic Chemotherapy for HR-Positive or -Negative and HER2-Negative[a,s,t,u]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/ methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Carboplatin + paclitaxel or albumin-bound paclitaxel

• For specific lines of systemic therapy options for HR-positive and HER2-negative with visceral crisis or endocrine refractory, see BINV-Q (1).
• For specific lines of systemic therapy options for HR-negative and HER2-negative (TNBC), see BINV-Q (2).
• For specific lines of systemic therapy options for HR-negative or -positive and HER2-positive, see BINV-Q (3).

[a] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.
[t] Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.
[s] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.
[t] Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline containing regimens.
[u] Consider cryotherapy of hands and feet to decrease the risk of peripheral neuropathy when receiving taxane therapies.

disease progression ≤12 months after adjuvant endocrine therapy or while receiving endocrine therapy for metastatic disease and received no more than one line in the metastatic setting. In this study, the addition of abemaciclib to letrozole improved PFS from 9.3 to 16.4 months (hazard ratio, 0.55; $P<.001$).[18] The median OS was 46.7 months within the abemaciclib + fulvestrant arm versus 37.3 months with fulvestrant alone, showing a statistically significant OS improvement of 9.4 months with abemaciclib, with a hazard ratio of 0.757 (95% CI, 0.606–0.945; $P=.01$).[14]

Among the phase III studies of CDK4/6 inhibitors in combination with fulvestrant, only the MONALEESA-3 trial included a small subset (~30%) of patients who did not receive prior endocrine therapy (first-line setting), and the MONARCH 2 trial included patients who had rapid disease progression ≤12 months after adjuvant endocrine therapy. A randomized phase II trial compared palbociclib + fulvestrant to palbociclib + letrozole in patients with HR-positive/HER2-negative advanced breast cancer and no prior endocrine therapy (first-line setting). No statistically significant difference was seen in median PFS with palbociclib + fulvestrant compared with palbociclib + letrozole (27.9 vs 32.8 months).[19]

NCCN Recommendations

Based on these data, in the first-line setting, the panel continues to include CDK4/6 inhibitors in combination with fulvestrant, as a preferred option. However, in the updated guidelines, the panel has noted that a regimen comprising a CDK4/6 inhibitor in combination with fulvestrant may be considered for those with disease progression on adjuvant endocrine or those with early disease relapse (within 12 months of adjuvant endocrine therapy completion). Because the evidence for palbociclib + fulvestrant in the first-line setting is based on phase II data, this combination is a category 2A recommendation.

The panel discussed that while choosing between the CDK4/6 inhibitors, clinical judgement is needed in addition to considering the randomized trial data and inclusion criteria. There are distinct differences in the toxicity profiles among the 3 CDK4/6 inhibitors. Although phase III data with ribociclib have shown OS benefit in the first-line setting, ribociclib has a higher incidence of abnormalities in liver transaminases than the other CDK4/6 inhibitors and can cause QTc prolongation. Both palbociclib and ribociclib are associated with higher rates of neutropenia than abemaciclib, whereas diarrhea is more frequent with abemaciclib.

Elacestrant for *ESR1*-Mutated HR-Positive/ HER2-Negative Disease

In the EMERALD trial, elacestrant was compared against endocrine therapy of physician choice (fulvestrant or AI) in patients (n=477) who had received 1 or 2 prior lines of

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[v]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative[x]	*ESR1* mutation	NGS, PCR (blood)	Elacestrant	Category 2A	Other recommended regimen
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[y] Entrectinib[y]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR (tissue block)	Pembrolizumab[z,aa] Dostarlimab-gxly[bb]	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab[z,aa]	Category 2A	
Any	*RET*-fusion	NGS	Selpercatinib[cc]	Category 2A	

[v] For HR-positive/HER2-negative breast cancer, assess for PIK3CA mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant. PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.

[w] The safety of alpelisib in patients with Type 1 or uncontrolled Type 2 diabetes has not been established.

[x] For postmenopausal females or adult males with ER-positive, HER2-negative, *ESR1*-mutated disease after progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor.

[y] Larotrectinib and entrectinib are indicated for the treatment of solid tumors that have an NTRK gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment.

[z] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

[aa] Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, or TMB-H tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

[bb] Dostarlimab-gxly is indicated for adult patients with MSI-H/dMMR unresectable or metastatic tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

[cc] Selpercatinib is indicated for adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

endocrine therapy, including 1 line containing a CDK4/6 inhibitor and up to 1 line of chemotherapy in the metastatic setting.[20] The *ESR1* mutational status of patients in the trial was evaluated in cell-free circulating tumor DNA (ctDNA). At 1 year, all patients who received elacestrant had a better PFS compared with the control group (22.3% vs 9.5%). Significantly higher PFS improvements at 1 year were observed in the subgroup that received elacestrant and had *ESR1* mutations (26.8% vs 8.2%). When comparing the hazard ratios, there was a 30% relative reduction in progression or death with elacestrant compared with control group in the overall cohort and a 45% relative reduction in the *ESR1*-mutant cohort. In addition, updated results show that duration of prior treatment impacts response to elacestrant. Patients who previously received a CDK4/6 inhibitor for a longer period (≥12 months) had longer PFS when treated with elacestrant.[21] Nausea is the most reported symptom in those receiving elacestrant.

NCCN Recommendations

In the recently updated guidelines, the panel has included elacestrant as a new treatment option for postmenopausal females or adult males with ER-positive, HER2-negative, *ESR1*-mutated tumors after disease progression on 1 or 2 prior lines of endocrine therapy, including 1 line containing a CDK4/6 inhibitor (see BINV-P and BINV-Q, 6 of 14; page 596 and above, respectively). The panel recommends evaluating *ESR1* mutational status using next-generation sequencing or by assessing the ctDNA in the blood using PCR. Because *ESR1* mutations are acquired during treatment, primary archived breast cancer should not be used as a source of tumor tissue for *ESR1* mutation testing.

HR-Positive/HER2-Negative Disease With Visceral Crisis or Endocrine-Refractory Disease

Chemotherapy is reserved for patients whose cancers are refractory to endocrine therapy or who need rapid treatment response for visceral crisis. In this version of the guidelines, the panel has included additional guidance related to the order of using systemic chemotherapy and targeted therapy (see BINV-Q, 1 and 2 of 14; pages 597 and 598, respectively).

Approximately 5% of patients with metastatic breast cancer carry germline *BRCA1/2* mutations.[22] PARP inhibitors (olaparib and talazoparib) have shown PFS benefit compared with chemotherapy in these patients.

In the phase III OlympiAD trial, 302 patients with germline *BRCA1/2* mutations and HER2-negative metastatic breast cancer were randomized to receive olaparib or chemotherapy of physician's choice.[23] Patients with HR-positive disease received prior endocrine therapy and all

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH STAGE IV (M1) DISEASE

Breast Cancer Subtype	Emerging Biomarkers	Detection	Potential targeted therapy[dd]	NCCN Category of Evidence	NCCN Category of Preference
ER+/HER2- ER-/HER2-	HER2 activating mutations	NGS[ee]	Neratinib ± fulvestrant[ff] Neratinib ± trastuzumab/ fulvestrant[gg]	Category 2B	Useful in certain circumstances • If ER+/HER2-, in patients who have already received CDK4/6 inhibitor therapy.
Any	Somatic *BRCA1/2* mutations	NGS[ee]	Olaparib[hh]	Category 2B	Useful in certain circumstances
Any	Germline *PALB2*	Germline sequencing	Olaparib[hh]	Category 2B	Useful in certain circumstances

[dd] At the present time, the data for the emerging biomarkers for the potential targeted agents noted in the table are promising but limited.
[ee] Tumor tissue or ctDNA.
[ff] Ma CX, Luo J, Freedman RA, et al. The phase II MutHER study of neratinib alone and in combination with fulvestrant in HER2-mutated, non-amplified metastatic breast cancer. Clin Cancer Res 2022; 28:1258-1267.
[gg] Jhaveri KL, Goldman JW, Hurvitz SA, et al. Neratinib plus fulvestrant plus trastzuzumab (N+F+T) for hormone receptor-positive (HR+), HER2-negative, HER2-mutant metastatic breast cancer (MBC): Outcomes and biomarker analysis from the SUMMIT trial. Journal of Clinical Oncology 2022;40:1028-1028.
[hh] Tung NM, Robson ME, Ventz S, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. J Clin Oncol 2020;38:4274-4282.

patients received an anthracycline and a taxane in either the adjuvant or metastatic setting. At a median follow-up of approximately 14 months, PFS of the overall study population treated with olaparib was higher compared with those treated with chemotherapy (7.0 vs 4.2 months, respectively; hazard ratio, 0.58; 95% CI, 0.43–0.80).[23] During the prespecified final analysis, the median OS was found to be numerically longer with olaparib versus treatment of physician's choice (19.3 vs 17.1 months; hazard ratio, 0.90; 95% CI, 0.66–1.23; *P*=.513). However, this difference in OS is not statistically significant. The results also noted that among patients who received olaparib, those who had not received prior chemotherapy for metastatic breast cancer achieved longer median OS (7.9 months) compared with the control group.

In the EMBRACA trial, 431 patients were randomized to receive talazoparib or chemotherapy of physician's choice. This trial also showed an improvement in PFS compared with those treated with chemotherapy (median, 8.6 vs 5.6 months; hazard ratio, 0.54; 95% CI, 0.41–0.71).[24] No benefit was seen in terms of OS after 3 years of follow-up.[24]

In the workup of patients with metastatic breast cancer, in addition to testing for ER/progesterone receptor and HER2, the panel recommends comprehensive germline and somatic profiling to identify candidates for additional targeted therapies (see BINV-18, in the complete version of these guidelines at www.nccn.org). If the patient has visceral crisis or is endocrine-refractory and a germline *BRCA1* or *BRCA2* mutation is present, the panel recommends either olaparib or talazoparib (see BINV-Q, 2 of 14; page 598). If the patient does not have germline *BRCA1/2* mutations and their disease is refractory to endocrine therapy, systemic chemotherapy would be the treatment option. The systemic chemotherapy options for HER2-negative disease are now listed on a separate page (see BINV-Q, 5 of 14; page 600). Taxanes have been reported to cause peripheral neuropathy, which has a significant impact on the quality of life in many patients. The panel has added a new footnote on the chemotherapy page to consider use of frozen socks and gloves (cryotherapy) to decrease taxane-induced peripheral neuropathy.[25–27]

Second-Line Options

Systemic therapy is an option for second and subsequent lines of therapy as well based on patient's clinical characteristics and preference. Historically, tumors with immunohistochemistry (IHC) 0 or IHC 1+ were grouped as HER2-negative. In the updated guidelines, on the page that outlines principles of HER2 testing, the panel notes

that distinction between HER2 IHC 0 and 1+ is currently clinically relevant in the metastatic setting (see BINV-A, 1 of 2, in the complete version of these guidelines at www.nccn.org). Primary or metastatic tumors with HER2 1+ or 2+/in situ hybridization (ISH)–negative results may be eligible for treatment that targets nonamplified or low levels of HER2 expression.

Fam-Trastuzumab Deruxtecan-nxki

Currently, fam-trastuzumab deruxtecan-nxki (T-DXd) is approved by the FDA for patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-negative) breast cancer who have received at least one prior chemotherapy in the metastatic setting or who have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. The randomized phase III DESTINY-Breast04 trial included patients (n=557) with metastatic breast cancer who had received 1 to 2 previous lines of chemotherapy and had tumors that were centrally determined to be 1+ on IHC, or 2+ on IHC with negative fluorescence ISH results for HER2 expression.[28] Patients were randomized to receive T-DXd or chemotherapy of physician's choice. The primary endpoint was PFS in patients with HR-positive/HER2-low disease. Of the trial participants, 88.7% (n=494) had HR-positive disease and 11% (n=63) had HR-negative disease. In the HR-positive group, the median PFS was 10.1 months with T-DXd and 5.4 months in the group with physician's choice of chemotherapy (hazard ratio, 0.51; $P<.001$), and OS was 23.9 versus 17.5 months (hazard ratio, 0.64; $P=.003$).[28]

NCCN Recommendations

The panel has included T-DXd as a preferred *second-line* option for patients with HER2-low IHC 1+ or IHC 2+/ISH-negative, HR-positive disease (category 1). The panel notes that is associated with a risk of developing drug-induced interstitial lung disease (ILD)/pneumonitis, which can be fatal. Regular monitoring for this serious side effect is recommended, along with carefully following specific guidelines for holding, discontinuing, and managing the drug.[29] For patients with a history of ILD/pneumonitis, there are no data on the safety or toxicity of T-DXd, and these patients were not eligible for T-DXd clinical trial participation.

Sacituzumab Govitecan

TROPiCS-02, a multicenter, open label trial, included patients (n=543) with unresectable locally advanced or HR-positive/HER2-negative metastatic breast cancer who had received 2 to 4 prior chemotherapy regimens for metastatic disease. The patients were also required to have received at least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting.[30] Patients were randomized to sacituzumab govitecan or single-agent chemotherapy of physician's choice. Median PFS in the sacituzumab govitecan arm was 5.5 months versus 4.0 months in the single-agent chemotherapy arm (hazard ratio, 0.661; 95% CI, 0.529–0.826; $P=.0003$).[31] Median OS for those receiving sacituzumab govitecan was 14.4 months versus 11.2 months for those receiving single-agent chemotherapy (hazard ratio, 0.789; 95% CI, 0.646–0.964; $P=.0200$).[32]

NCCN Recommendations

Considering the data from TROPiCS-02 trial, the panel has included sacituzumab govitecan as a category 1, preferred second-line option, after prior treatment including endocrine therapy, a CDK4/6 inhibitor, and at least 2 lines of chemotherapy, one of which included taxane and at least one line in the metastatic setting. The panel notes that treatment with sacituzumab govitecan may be considered for later lines of therapy if not used as second-line therapy.

Options for Third Line and Beyond

In addition to the option of treatment with a systemic chemotherapy regimen, the panel has also included additional targeted therapies as options for third line and beyond, especially for patients with the specific biomarkers (ie, MSI-H, *NTRK* fusion, *RET* fusion, TMB-H) for approved targeted agents and when other highly effective treatment options are not available (BINV-Q, page 597).

HR-Negative/HER2-Negative Disease

HR-negative (ER-negative/PR-negative)/HER2-negative breast cancer, also referred to as triple-negative breast cancer (TNBC), is an aggressive subtype.

Pembrolizumab + Chemotherapy for PD-L1–Expressing Metastatic TNBC

In KEYNOTE-355, patients (n=847) with locally recurrent, inoperable, or metastatic TNBC and who were disease-free for ≥6 months were randomized to chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin) ± pembrolizumab. In terms of PFS among patients with a PD-L1 combined positive score (CPS) ≥10, an improvement was seen with the addition of pembrolizumab to chemotherapy versus chemotherapy alone (9.7 vs 5.6 months; HR, 0.65; 95% CI, 0.49–0.86).[33] In the final OS analysis of the KEYNOTE-355 trial, the addition of pembrolizumab to chemotherapy improved OS among patients with a CPS ≥10 (23.0 vs 16.1 months; hazard ratio, 0.73; 95% CI, 0.55–0.95).[34]

PARP Inhibitors

The PFS improvements with olaparib and talazoparib in patients with germline *BRCA1/2* mutations were described in an earlier section. In the OlympiAD trial, the

PFS benefit in the TNBC subgroup (hazard ratio, 0.43; 95% CI, 0.29–0.63) was higher than the PFS seen with HR-positive disease (hazard ratio, 0.82; 95% CI, 0.55–1.26).[23] In the EMBRACA trial, the PFS outcomes were improved with talazoparib compared with physician's choice of chemotherapy, and were similar for TNBC and HR-positive/HER2-negative disease.[24]

Platinum Therapy for Metastatic TNBC With Germline *BRCA1/2* Mutations

A small phase II study first showed that that germline *BRCA1* mutation carriers are sensitive to cisplatin chemotherapy.[35] The phase III TNT trial compared docetaxel with carboplatin in the first-line setting in patients (n=376) with TNBC. In the unselected population, carboplatin was not more active than docetaxel (objective response rate [ORR], 31.4% vs 34.0%; *P*=.66).[36] Patients with a germline *BRCA1/2* mutation, however, had a significantly better response to carboplatin versus docetaxel (ORR, 68.0% vs 33.3%; absolute difference, 34.7%; *P*=.03).[36] PFS was also improved with carboplatin treatment in patients with a germline *BRCA1/2* mutation (median PFS, 6.8 vs 4.4 months). No difference was found in OS, although the sample size was quite small.[36]

NCCN Recommendations

Taking these data into consideration, in the updated guidelines, the NCCN panel has included pembrolizumab in combination with chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin) as a category 1, preferred first-line treatment option for tumors with PD-L1 CPS ≥10, regardless of the germline *BRCA1/2* mutation status. PD-L1 expression is assessed using the 22C3 antibody and the threshold for positivity is a tumor CPS ≥10.

For tumors with PD-L1 CPS <10, the treatment of choice is based on germline *BRCA1/2* mutation status. In those with PD-L1 CPS <10 and germline *BRCA1/2* mutations, the panel recommends treatment with a PARP inhibitor (olaparib or talazoparib) or a platinum agent (carboplatin or cisplatin). PARP inhibitors have not been compared with a platinum agent in this setting. The PARP inhibitors and platinum agents are category 1, preferred options in the first-line setting for the indication listed (see BINV-Q, 2 of 14; page 598). For tumors with PD-L1 CPS <10 and no germline *BRCA1/2* mutations, the panel recommends treatment with a systemic therapy regimen listed on BINV-Q, 5 of 14 (page 600).

Second-Line Options for Metastatic TNBC

The ASCENT trial data showed PFS and OS benefits for sacituzumab govitecan over the physician's choice of chemotherapy in patients who had at least 2 prior lines, including progression that occurred within a 12-month period after completion of preoperative or adjuvant therapy.[37] The median PFS with sacituzumab govitecan was 5.6 months compared with 1.7 months with chemotherapy (hazard ratio for disease progression or death, 0.41; 95% CI, 0.32–0.52; *P*<.001).[37] The median OS was 12.1 months with sacituzumab govitecan versus 6.7 months with chemotherapy (hazard ratio for death, 0.48; 95% CI, 0.38–0.59; *P*<.001).[37] In the DESTINY-Breast04 trial (described in earlier sections), 11% (n=63) of patients had TNBC.

The benefit of T-DXd was observed in both HR-positive/HER2-negative disease as well as in an exploratory analysis in the TNBC subgroup for tumors that were HER2 IHC 1+ or IHC 2+ and ISH-negative.[28]

NCCN Recommendations

According to the updated NCCN Guidelines, if a patient has germline *BRCA1/2* mutation and did not receive PARP inhibitor therapy in the first line for metastatic disease, it may be given in the second line. The panel has listed this as a category 1, preferred option in this setting. The other category 1, preferred options in the second-line setting for TNBC are sacituzumab govitecan and T-DXd. Although sacituzumab govitecan is indicated for anyone with TNBC in the second-line setting based on the phase III ASCENT trial, T-DXd is for those with no known germline *BRCA1/2* mutation and tumors that are HER2 IHC 1+ or 2+/ISH-negative based on the subset analysis of the DESTINY-Breast04 trial. There are no data comparing sacituzumab govitecan with T-DXd in patients with metastatic breast cancer (see BINV-Q, 2 of 14; page 598).

Options for Third Line and Beyond

In addition to the option of treatment with a systemic chemotherapy regimen listed on BINV-Q, 5 of 14 (page 600), the panel has also included additional targeted therapies as options for the third line and beyond, especially if the patients have the specific biomarkers (ie, MSI-H, *NTRK* fusion, *RET* fusion, TMB-H) for approved targeted agents and when no other highly effective treatment options are available (see BINV-Q, page 6 of 14; page 601).

HR-Positive or HR-Negative and HER2-Positive

The preferred first-line treatment options for HR-positive or HR-negative and HER2-positive metastatic disease include pertuzumab, trastuzumab, and taxane (docetaxel or paclitaxel).[38–40] In the 2023 version of these guidelines, the panel has provided updated guidance on sequencing of HER2-targeted therapy in the second, third, and fourth line and beyond.

Fam-Trastuzumab Deruxtecan-nxki

The phase III DESTINY-Breast03 trial included patients (n=524) with HER2-positive metastatic breast cancer

who experienced disease progression while on a first-line trastuzumab- and taxane-containing regimen (second-line setting). The trial randomized patients to receive T-DXd or ado-trastuzumab emtansine (T-DM1).[41] The median PFS of patients treated with T-DXd was approximately 4 times longer compared with T-DM1 (28.8 vs 6.8 months; hazard ratio, 0.33; $P<.0001$).[42] Although the median OS was not reached in ether of the arms in this trial, treatment with T-DXd resulted in a statistically significant improvement in OS compared with T-DM1, reducing the risk of death in patients by approximately 36% (hazard ratio, 0.64). Adverse events of grade ≥3 were similar in patients who received T-DXd or T-DM1 (56% [n=145] vs 52% [n=135]). ILD or pneumonitis occurred with higher frequency in patients treated with T-DXd (15% [n=39]) versus T-DM1 (3% [n=15]).[42]

Ado-Trastuzumab Emtansine

T-DM1 has shown activity in the second-line setting in the phase III EMILIA trial that evaluated the efficacy of T-DM1 compared with lapatinib + capecitabine for patients with HER2-positive breast cancer (n=991).[43] Results of the EMILIA trial showed improvement in both PFS (9.6 vs 6.4 months; hazard ratio, 0.65; $P<.001$) and OS (30.9 vs 25.1 months; hazard ratio, 0.68; $P<.001$).[44] Data from the phase III TH3RESA study have confirmed the efficacy of T-DM1 in heavily pretreated patients.[45] In this trial, patients (n=602) with metastatic HER2-positive breast cancer were randomized to receive either T-DM1 or a treatment of the physician's choice. All patients had at least 2 previous HER2-targeted regimens. Patients treated with T-DM1 had improved PFS (6.2 vs 3.3 months; hazard ratio, 0.52; $P<.001$) and OS (22.7 vs 15.8 months; hazard ratio, 0.68; $P<.001$).[45]

There were no patients enrolled in the EMILIA or TH3RESA trials who had received trastuzumab, pertuzumab, and a taxane—the current first-line standard of care. Results of the DESTINY-Breast03 trial clearly showed that T-DXd was better than T-DM1 in terms of improved PFS and OS, when compared in the second-line setting. In DESTINY-Breast03, all patients had received taxane and trastuzumab, and approximately 60% had received pertuzumab.

NCCN Recommendations

Based on these data, the panel voted to move T-DM1 to the third-line setting (category 2A, preferred) and clarified in a footnote that it may be used in later lines as well, and that the optimal sequence is unknown. It is also noted that T-DM1 may be considered in the second line if the patient is not a candidate for T-DXd (see BINV-Q, 3 of 14; page 599).

The panel voted to continue to list T-DXd as a category 1, preferred regimen in the second-line setting, with a footnote that it may be considered as an option in the first-line setting for select patients, such as those experiencing rapid disease progression within 6 months of neoadjuvant or adjuvant therapy (or disease progression within 12 months following pertuzumab-containing regimens). The panel also included a cautionary statement related to T-DXd–associated ILD/pneumonitis (see BINV-Q, 3 of 14; page 599).

Tucatinib in Combination With Capecitabine and Trastuzumab

In the randomized HER2CLIMB trial, patients with HER2-positive metastatic breast cancer heavily treated with multiple lines of prior therapy (median 4 prior lines) were randomized (2:1) to tucatinib in combination with capecitabine and trastuzumab or placebo with capecitabine and trastuzumab. The addition of tucatinib improved both duration of PFS and OS. At the end of 1 year, PFS with the tucatinib regimen was 7.8 months versus 5.6 months in the placebo group (hazard ratio for progression or death, 0.54; 95% CI, 0.42–0.71; $P<.001$) and at 2 years, the OS with the tucatinib containing regimen was 21.9 months compared with 17.6 months in the placebo group (hazard ratio for progression or death, 0.54; 95% CI, 0.42–0.71; $P<.001$).[46] This trial specifically included patients with active, untreated, or stable brain metastases. In total, 47% had brain metastases (48.3% in the tucatinib group and 46% in the placebo group). The initial analysis showed that the addition of tucatinib to trastuzumab and capecitabine led to an OS benefit irrespective of brain metastases.

A subgroup analysis of this trial, specifically in patients with central nervous system (CNS) metastases, highlights the efficacy of this regimen for those with brain metastases. In patients with brain metastases, at 1 year, PFS was 24.9% in the tucatinib combination group compared with 0% in the placebo group (hazard ratio, 0.48; 95% CI, 0.34–0.69; $P<.001$). Longer follow-up of the subgroup of patients with brain metastases showed that the OS benefit was also improved. After median 29.6 months of follow-up, median OS was 9.1 months longer in the tucatinib combination group compared with the group receiving capecitabine and trastuzumab (21.6 vs 12.5 months; hazard ratio, 0.52; 95% CI, 0.36–0.77).[47] In the subset of patients who had stable brain metastases at baseline, the median OS was longer with the tucatinib regimen compared with the placebo group (21.6 vs 16.4 months; 95% CI, 15.3–42.4 vs 10.6–21.6).[47] In this subset of patients with stable brain metastases, the risk of death was reduced by 30.5% with the tucatinib regimen, although the difference was not statistically significant (hazard ratio, 0.70; 95% CI, 0.42–1.16; $P=.16$). In the subset of patients with active brain metastases at baseline, the median OS was longer in the group that received the tucatinib regimen compared with the placebo group (21.4 vs 11.8 months; 95% CI, 18.1–28.9 vs 10.3–15.2 months).[47] In this subset of patients with active brain metastases, the risk of death was significantly reduced by 47.6%

with the tucatinib regimen (hazard ratio, 0.52; 95% CI, 0.36–0.77; $P<.001$).

The CNS-PFS, defined as time to disease progression in the brain or death, was assessed in both the tucatinib and placebo groups in all patients with brain metastases. Overall, the risk of CNS progression was reduced by 61.4% with the tucatinib regimen (hazard ratio, 0.39; 95% CI, 0.27–0.56; $P<.001$). This benefit was seen in the subgroups with active as well as stable brain metastases. In those with stable brain metastases, the risk of progression was reduced by 59.4% in the tucatinib combination group versus the placebo combination group (hazard ratio, 0.41; 95% CI, 0.20–0.85; $P=.014$). Similarly, in those with active brain metastases, the risk of progression was reduced by 66.1% with the tucatinib regimen (hazard ratio, 0.34; 95% CI, 0.22–0.54; $P<.001$).

NCCN Recommendations

Based on the result of the HER2CLIMB trial, tucatinib in combination with capecitabine and trastuzumab is recommended as third-line therapy and *preferred* for those with CNS metastases. Based on the results of the subset analysis of patients with brain metastasis in the HER2CLIMB trial, the panel has noted that tucatinib may be considered in the second-line setting if the patient has CNS metastases.

Additional Targeted Therapies and Associated Biomarkers

The panel has included biomarkers with associated targeted therapies approved by the FDA for the specific settings in a table titled "Additional Targeted Therapies and Associated Biomarker Testing for Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease" (see BINV-Q, 6 of 14; page 601). The table provides recommendations for individual biomarkers that should be evaluated for targeted therapy and techniques to detect the biomarkers, but does not endorse any specific commercially available biomarker assays or commercial laboratories.

Elacestrant

ESR1 encodes ERα, and the activating mutations in *ESR1* result in constitutive activation of the ER pathway in the absence of estrogen.[48,49] The increase in detectable *ESR1* mutations is caused by the selective outgrowth of *ESR1*-mutated cancer cells in response to the low estrogen state during AI therapy.[50] Elacestrant is approved for *ESR1*-mutated disease in the setting discussed in the earlier section titled "HR-Positive/HER2-Negative Disease With No Visceral Crisis and Not Endocrine-Refractory" (see page 596).

Selpercatinib

The LIBRETTO-001 phase I/II trial studied selpercatinib in patients with advanced solid tumors, including *RET* fusion–positive non–small cell lung cancer and thyroid cancer, and other tumors with *RET* activation. Two patients on the trial had *RET* fusion–positive breast cancer. Of these, one patient treated with selpercatinib achieved a complete response, and the other patient achieved a partial response.[51] Based on the FDA tumor-agnostic approval of selpercatinib for patients with solid tumors with a *RET* gene fusion that has progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

NCCN Recommendations

The option of treatment with elacestrant for *ESR1*-mutated tumors and selpercatinib for tumors with *RET* gene fusion are new additions to the table on BINV-Q, page 6 of 14 (page 601).

Emerging Biomarkers to Identify Novel Therapies for Patients With Stage IV (M1) Disease

There are additional somatic and germline mutations for which targeted therapy options are available.

Somatic *BRCA1/2* and Germline *PALB2* Mutations

The single-arm phase II TBCRC 048 trial studied mutations in the homologous recombination pathway beyond germline *BRCA1/2* that are sensitive to PARP inhibition in patients with metastatic disease. The trial included patients (n=54) with somatic *BRCA1/2* mutations and germline mutations other than *BRCA1/2*, including germline *PALB2*, *ATM*, and *CHEK2* mutations. Treatment with olaparib led to an improved overall response rate and median PFS *specifically* in patients with somatic mutations in *BRCA1/2* and in those with germline mutations in *PALB2*, but not in those with germline mutations in *ATM* or *CHEK2*.[52] The overall response rate was 82% for those with germline *PALB2* and 50% for those with somatic *BRCA1/2* mutations. The median PFS with olaparib treatment was 13.3 months in those with germline *PALB2* and 6.2 months in those with somatic *BRCA1/2*.[52] There is an expanded clinical trial underway to further define this response with olaparib, and a clinical trial is ongoing to evaluate the efficacy of talazoparib in a similar setting (in patients with somatic or germline mutations in homologous recombination genes other than *BRCA1/2)* (ClinicalTrials.gov identifier: NCT02401347).

HER2 Mutations

HER2 mutations have been identified with tumor genome sequencing and are rare—seen in 2% of patients with HER2-negative metastatic breast cancer.[53] The frequency of the *HER2* mutation is slightly higher in those with ER-positive (3.2%) and lobular tumors (7.8%).[54] *HER2* mutations are mainly found in the tyrosine kinase and extracellular dimerization domains of HER2, and these mutations increase kinase activity and promote tumor growth.

The clinical significance of these mutations is that they make the tumor cells sensitive to HER2-targeted therapy.

In a small phase II study in which 16 heavily pretreated patients with *HER2*-mutated metastatic breast cancer received single-agent neratinib, a clinical benefit seen in 5 patients and duration of the clinical benefit was 24 weeks. There was one patient who received prior therapy with ribociclib for metastatic disease. A prolonged disease stabilization on neratinib (PFS of 37 weeks) was seen in this patient.[54]

In the phase II MutHER multicohort trial, the efficacy of neratinib in combination with fulvestrant was evaluated in patients with ER-positive, HER2-mutated, nonamplified fulvestrant-treated or fulvestrant-naïve metastatic breast cancer.[55] The study also evaluated single-agent neratinib in patients with ER-negative, HER2-mutated metastatic breast cancer. The clinical benefit rate with neratinib + fulvestrant was 38% and 30% in the fulvestrant-treated and fulvestrant-naïve cohorts, respectively. In the ER-negative cohort, the clinical benefit rate with single-agent neratinib was 25%.[55]

The phase II SUMMIT trial studied the efficacy of neratinib, fulvestrant (for HR-positive), and trastuzumab in patients (n=51) with HR-positive/HER2-negative metastatic breast cancer with activating *HER2* mutations who had received prior CDK4/6 inhibitor therapy, and in patients (n=18) with TNBC, all of whom had somatic mutations in the *HER2* gene. The unpublished data (presented at the 2022 ASCO Annual Meeting) showed an ORR of 35.3% in patients with HR-positive disease treated with neratinib in combination with fulvestrant and trastuzumab and a clinical benefit rate of 47.1%. The median PFS with the triplet therapy was 8.2 months and the median duration of response was 14.3 months.[56] The ORR in patients with TNBC treated with neratinib and trastuzumab was 33%, with a median PFS of 6.2 months and a median duration of response of 4.4 months.

NCCN Recommendations

The data supporting olaparib for patients with somatic *BRCA1/2* mutations and germline *PALB2* mutations and the neratinib-containing regimens for those with *HER2* mutations are promising; however, they are derived from small phase II trials. Also, the targeted agents (neratinib and olaparib) are currently not FDA approved as treatment for these mutations. Therefore, the panel has listed the new biomarkers described (*HER2* mutations, somatic *BRCA1/2* mutations, and germline *PALB2* mutation) and their associated therapeutic regimens on a new page titled "Emerging Biomarkers to Identify Novel Therapies for Patients With Stage IV (M1) Disease" (see BINV-Q, 7 of 14; page 602). Due to the lack of large, randomized trial data, panel consensus was not uniform regarding whether intervention for the associated biomarkers is appropriate, and therefore these treatments are included as category 2B recommendations and useful in certain circumstances. Olaparib may be a treatment option for patients with metastatic breast cancer with somatic *BRCA1/2* or germline *PALB2* mutations. The neratinib combinations are specifically for patients with ER-positive or ER-negative and HER2-negative metastatic disease with HER2-activating mutations (see BINV-Q, 7 of 14; page 602).

Summary

These NCCN Guidelines Insights focus on the updates related to new therapeutic options, guidelines revisions, and the guidance from the panel on specific lines of systemic therapy (including endocrine therapy, chemotherapy, and targeted therapy) for patients with stage IV (M1) breast cancer of all 4 subtypes. For a complete list of the 2023 updates to the NCCN Guidelines for Breast Cancer, visit www.nccn.org.

To participate in this journal CE activity, go to https://education.nccn.org/node/92917

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