Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Breast Cancer Guidelines Panel consider the requested updates below and enclosed references, pertaining to the evaluation and management of patients with advanced breast cancer.

Requested Update #1 and Rationale: Include validated next-generation sequencing assays such as FoundationOne® CDx in the “Principles of HER2 testing” (BINV-A) as an additional method to identify HER2 (ERBB2) amplification.

The FoundationOne CDx (F1CDx) assay is FDA-approved as a companion diagnostic test [2] to identify HER2 amplification for selecting patients with breast cancer for treatment with HER2 targeted therapy including Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab).

- Clinical validity was established by a retrospective concordance study comparing results from the F1CDx assay against the FDA-approved HER2 FISH PharmDx® Kit (Dako Denmark A/S) as a reference standard [2]: the Positive Percent Agreement was 89.4% (101/113 reference HER2 FISH-positive samples) and the Negative Percent Agreement was 98.4% (180/183 reference HER2 FISH-negative samples). Concordance between F1CDx and HER2 FISH testing was greater than concordance between two replicate HER2 FISH tests [2].

Requested Update 2 and Rationale: Include the option of comprehensive genomic profiling (CGP), via a single assay (as opposed to sequential testing of single biomarkers), in the initial evaluation of a patient with recurrent or Stage IV breast cancer (BINV-18).

Tissue biopsy at first recurrence/metastatic disease to evaluate ER/PR and HER2 status is standard of care [1] and is recommended by the NCCN® Guidelines (BINV-18), and provides an opportunity to obtain tissue for CGP.

- FoundationOne® CDx is FDA-approved as a companion diagnostic test [2] to identify HER2 amplification for selecting patients with breast cancer for treatment with HER2 targeted therapy including Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab).

- In addition, FoundationOne CDx is FDA-approved to detect genomic alterations and signatures including PIK3CA mutations, NTRK1/2/3 fusions, BRCA1/2 alterations, and the microsatellite instability-High (MSI-H) that are biomarkers for FDA-approved therapies for patients diagnosed with advanced breast cancer.
  - On May 24th, 2019, the FDA approved PIQRAY® (alpelisib) in combination with fulvestrant for the treatment of postmenopausal women and men with hormone receptor-positive (HR+), HER2-negative, PIK3CA-mutated advanced breast cancer following progression on or after an endocrine-based regimen. The SOLAR-1 trial has demonstrated that patients treated with alpelisib plus fulvestrant saw significantly improved progression free survival (PFS) and overall response rate (ORR) versus those treated with fulvestrant alone among patients with mutated PIK3CA. [3]
  - Vitrakvi® (larotrectinib) is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment. [13-14]
  - MSI-H is significantly associated with overall survival in numerous tumor types treated with pembrolizumab or nivolumab [25, 26]; pembrolizumab is FDA-approved for solid tumors with MSI-H status. Although MSI-H status is relatively rare in breast cancer, responses to immunotherapy have been observed for patients with MSI-H breast cancer [27-28]. Routine broad-based testing of patients with breast cancer using CGP may be a rational approach to identify both common genomic alterations and rare alterations such as MSI-H. F1CDx can detect high MSI (MSI-H), and identify patients who are eligible to receive pembrolizumab based on its FDA approval for treatment of MSI-H solid tumors.
  - The FoundationOne CDx assay can detect alterations in BRCA1/2, which are mutated in approximately 10% of all breast tumors [17], and are predictive of responses to PARP inhibitors such as olaparib [18], which is FDA-approved for patients with BRCA-mutated HER2-negative metastatic breast cancer.
• Consistent with the NCCN® recommendation to provide patients with opportunities to participate in therapeutic clinical trials, CGP assays, such as F1CDx, can potentially match patients with breast cancer to targeted therapies in genomically-matched clinical trials including the following: ERBB2 mutations, PTEN/PIK3CA/AKT1 alterations; FGFR1 amplification, ESR1 mutations, and high tumor mutational burden (TMB). Foundation Medicine has joined both the NCI-MATCH and ASCO TAPUR studies as an approved testing platform, and is accelerating accrual to these transformative trials using the combination of CGP and clinical trial matching capabilities.
  o ERBB2 (HER2) amplification testing is a routine part of the breast cancer work-up; however, other types of targetable ERBB2 alterations that are not detected by standard-of-care FISH or IHC tests occur in up to 3% of breast cancers, including diverse activating ERBB2 short variant mutations that occur in 2% of cases that lack ERBB2 amplification [4]. ERBB2 short variant mutations are enriched in invasive lobular breast cancer where they are detected up to 18% of cases [5, 6]. The efficacy of HER2 inhibition in patients with ERBB2-mutated, but not amplified, breast cancer, was evaluated in a Phase 2 trial of neratinib alone or in combination with fulvestrant and best response rates of 33.3% (95% CI: 15.6%-55.3%) were reported for patients with estrogen receptor-negative [ER(−)] breast cancer and 58.3% (95% CI: 23.4%-83.3%) for patients with ER-positive [ER+] breast cancer [7]. Responses to HER2 monoclonal antibodies or tyrosine kinase inhibitors have also been described in case reports for patients with ERBB2 sequence mutations [8–11].
  o Genomic alterations in the PI3K/AKT/MTOR pathway are common in breast cancer. PIK3CA, PTEN and AKT1 alterations are observed in 35%, 5%, and 2.4% of cases, respectively, and are candidate predictive biomarkers in clinical trials for therapies targeting this pathway [12]. In a Phase 2 trial of the AKT inhibitor ipatasertib plus paclitaxel for metastatic TNBC, in comparison to unselected patients, the pre-defined subgroup with PIK3CA, AKT1, or PTEN genomic alterations derived the greatest benefit from ipatasertib plus paclitaxel compared to placebo plus paclitaxel (PFS, 9.0 vs 4.9 months) [15]. In a Phase 1 trial of the AKT inhibitor AZD5363 for patients with AKT1 E17K mutation, best ORRs were 30% and 33% for ER+ breast cancer and TNBC, respectively [16].
  o FGFR1 amplification is detected in 13% of breast cancer cases [12] and preliminary data from a Phase 1/2a study of the multikinase inhibitor lucitanib demonstrated partial responses in 4/8 (50%) patients with FGFR1-amplified breast cancer [22]. Patients with tumors harboring alterations in EGFR or ERBB3, each mutated at frequencies of 1-2% in breast cancer, have experienced antitumor responses to matched targeted therapies [23, 24].
  o ESR1 mutations result in estrogen-independent ER activation and are detected in 25%-39% of patients with metastatic ER+ breast cancer who have progressed on endocrine therapy [19]. Analyses of Phase 2 and 3 trials for patients with ER+ breast cancer suggest that patients whose tumors harbored ESR1 mutations may not derive clinical benefit from aromatase inhibitors such as exemestane in comparison to fulvestrant-containing treatment regimens [19–21].
  o TMB-H has been shown to be associated with response to immunotherapy across multiple cancer types [29]. In the TAPUR phase 2 basket study, pembrolizumab demonstrated clinical activity in patients with heavily pre-treated TMB-H metastatic breast cancer, with 21% response rate and 37% disease control rate [30].

**Requested Update 3 and Rationale:** Add a table outlining available FDA-approved companion diagnostics for identifying biomarkers leading to approved therapeutic options and/or clinical trials in patients with breast cancer, similar to that which currently exists for multigene assays for consideration of addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy on page BINV-N 1 of 2.

There are multiple assays currently available that identify one or more biomarkers with subsequent therapeutic treatment options. Outlining the available assays, their FDA-approval status, and treatment implications will clarify and streamline the decision-making process for ordering physicians.

Thank you for your review of this submission.

Sincerely

[Signature]

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