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NCCN Guidelines Panel: Breast Cancer

Dear Panel Members,

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

Requested Update #1 and Rationale: Include "HER2 testing by validated next-generation sequencing (NGS) assay" as an additional method to determine HER2 status in "Principles of Biomarker Testing: HER2 Testing" on page BINV-A, page 1 of 2.
With advances in genomic medicine, new clinically relevant biomarkers and targeted therapies are rapidly emerging, driving the need for comprehensive genomic profiling as an upfront assessment. *ERBB2* (HER2) amplification can be reliably determined by NGS, allowing efficient concurrent testing for other potentially actionable genomic alterations.

- FoundationOne® CDx, is an NGS-based assay that is FDA-approved as a companion diagnostic test to identify *ERBB2* (HER2) amplification for selecting patients with breast cancer for treatment with HER2 targeted therapy including trastuzumab, ado-trastuzumab emtansine or pertuzumab. Clinical validity was established by a retrospective concordance study demonstrating 89.4% positive percent agreement and 98.4% agreement, with greater concordance between the 324-gene assay and HER2 FISH testing than concordance between two replicate HER2 FISH tests[1].

Requested Update #2 and Rationale: Include next-generation sequencing (NGS) and comprehensive genomic profiling (CGP) as a method of detection for BRCA1/2 mutations, PIK3CA mutations, MSI-H status and dMMR mutations in the table "Biomarkers Associated with FDA-approved Therapies" on page BINV-R, page 1 of 3.
CGP utilizes next generation sequencing (NGS) technology to examine entire regions of cancer-relevant genes (in contrast to limited "hot spot" tests) for all tumor types, identifying the four main classes of genomic alterations - base substitutions, insertions or deletions, copy number alterations, gene rearrangements, and assesses patterns of mutations across related genes in established cancer pathways to report complex biomarkers such as tumor mutational burden (TMB) and microsatellite instability, to inform cancer treatment decisions or clinical trial options via a single assay[1].

- CGP may identify additional patients who can benefit from PARP inhibitor therapy. In phase II SWOG 1416, patients with metastatic and/or loco-regionally recurrent TNBC, BRCA-like (defined as HRD genomic instability score ≥ 42, somatic *BRCA1/2* mutation, *BRCA1* promoter methylation, other germline HR gene mutation) HER2- MBC, previously treated with 0-1 prior cytotoxic therapies and no prior platinum or PARP inhibitor, the addition of veliparib to cisplatin improved PFS by 47% (median PFS 5.7 vs 4.3 months; HR=0.58; p=0.023) with a trend toward improved OS[2]. In phase II TBCRC 048, patients with previously treated MBC and *sBRCA*1/2 demonstrated RR of 50%, and clinical activity was also noted with somatic *CDK12*, germline *PALB2* and somatic *BLM* mutations[3]. A genomic data base of 234,154 tumor specimens (including 21,164 breast cancer specimens) sequenced by hybrid capture-based CGP was analyzed to determine the landscape of *BRCA1/2* biallelic alterations with genome-wide loss-of-heterozygosity (gLOH) homologous recombination deficiency. Across every cancer type evaluated, biallelic *BRCA1/2* alteration was associated with increased gLOH and may represent a therapeutic vulnerability targetable by PARP inhibition[4].

- FoundationOne CDx, is an NGS-based assay that is FDA-approved as a companion diagnostic for alpelisib[1]. *PIK3CA* mutations are identified in 12-15% of breast cancers, most of which (95%) are double mutations. Double *PIK3CA* mutations are in cis on the same allele and result in increased PI3K activity, enhanced downstream signaling, increased cell proliferation, and tumor growth. Double *PIK3CA* mutations predict increased sensitivity to PI3Ka inhibitors compared with single hotspot mutations[5].

- JSCO-ESMO-ASCO-JSMO-TOS international expert consensus recommendations for determining MSI/MMR status in patients with advanced solid tumors for whom it is indicated include, "Validated NGS is recommended for testing either upfront or when IHC is equivocal or not available"[6]. Real world evidence for 129 patients across 33 tumor types (including breast cancer) receiving pembrolizumab demonstrated median OS exceeding 1 year which is consistent with pembrolizumab clinical trials[7]. Patients with MSI-H breast cancer are eligible for treatment with pembrolizumab[8].

Requested Update #3 and Rationale: Include tumor mutational burden (TMB) as determined by validated and/or FDA approved next-generation sequencing panel to inform the use of pembrolizumab in the table "Biomarkers Associated with FDA-approved Therapies" on page BINV-R, page 1 of 3.
Please refer to previous submission on 6/22/2020 by Foundation Medicine outlining requested updates pertaining to recommended validation standards for TMB measurement and reporting by targeted NGS panels and inclusion of the FDA-approved all solid tumor indication for pembrolizumab for TMB≥10 mutations per megabase (mut/MB).

- High tumor mutational burden (TMB-H) of ≥10 mutations per mut/MB, as identified by whole exome sequencing or targeted NGS panel, may occur in 8.4% of metastatic breast cancers[9]. In the TAPUR phase II basket trial, pembrolizumab demonstrated clinical activity in patients with heavily pretreated TMB-H (≥9 mut/MB) metastatic breast cancer with 21% response rate and 37% disease control rate[10].

Requested Update #4 and Rationale: Add footnote on page BINV-R, page 1 of 3, to indicate that "tumor/somatic profiling via large validated NGS panels (>50 genes) or comprehensive genomic profiling is recommended to determine rare and actionable mutations and fusions for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials."
Genomically-matched clinical trials and registries are increasingly adopted, and the NCCN should encourage breast cancer patient and health care provider participation by listing CGP as a biomarker for those considering such an option.

- Activating *ERBB2* (HER2) mutations, which are not detected by immunohistochemistry or fluorescence in situ hybridization, but are detected by DNA sequencing, occur in up to 3% of breast cancer, including diverse activating *ERBB2* short variant mutations that occur in 2% of cases[11]. *ERBB2* short variant mutations are enriched in invasive lobular breast cancer where they are detected in up to 18% of cases[12,13]. In updated results from the phase 2 SUMMIT basket trial, the combination of neratinib + fulvestrant + trastuzumab resulted in a response rate of 39% in patients with HR+ breast cancer and known oncogenic driver *ERBB2* mutations from genomic profiling of tumor tissue or ctDNA[14]. Additionally, single agent neratinib demonstrated a CBR of 31% (90% CI, 13-55%), in a heavily pretreated population with *ERBB2* mutated non-amplified MBC by either tumor tissue or ctDNA genomic profiling[15].

- 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[16]. The addition of the AKT inhibitor capivasertib to first-line paclitaxel therapy for TNBC to first-line paclitaxel resulted in significantly longer median PFS and OS . Benefits were more pronounced in patients with *PIK3CA/AKT1/PTEN*-altered tumors, defined as ≥1 of the following mutations per central NGS assay: *AKT1*(E17K) or *PIK3CA*(R88Q, N345K, C420R, E542X, E545X, Q546X, M10431, H1047X, G1049R mutations) and/or deleterious mutation in *PTEN* or loss of *PTEN* gene. In this subgroup, the ORR, CBR, mDOR, mPFS and mOS were 35.3%, 52.9%, 13.3 months, 9.3 months and not reached, respectively, versus 18.2%, 27.3%, 3.5 months, 3.7 months and 10.4 months with placebo[17].

- *RET* genomic alterations were reported from a large cohort of 9693 breast cancers that were genomically profiled in the course of routine clinical care. *RET* alterations were found in 121 patients (1.2%) and were detected across all breast cancer subtypes, although a majority were ER negative (65%) or *ERBB2* non-amplified (82%). *RET* alterations demonstrated sensitivity to in vitro and in vivo models, as well as in a patient with *NCOA4-RET* fusion who had progressed on HER2-targeted therapy and was treated with cabozantinib[18].

- Pathway analysis of candidate resistance genes demonstrated that the *FGFR, ERBB2,* insulin receptor and MAPK pathways represented key modalities of resistance to ER-directed therapies in ER+ breast cancer. In vitro experiments in ER+ breast cancer cells confirmed that *FGFR/FGF* alterations led to fulvestrant resistance as well as cross-resistance through ER reprogramming and activation of the MAPK pathway. The resistant phenotypes were reversed by FGFR inhibitors, a MEK inhibitor, and/or a SHP2 inhibitor[19].

Thank you for your review of this submission.

Sincerely,

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