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NCCN Guidelines Panel: Melanoma

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Melanoma Guidelines Panel review the enclosed data supporting updates to the Guidelines and include FoundationOne®, our currently available assay, and FoundationOne *CDx*™, currently under parallel and expedited review by FDA and CMS with anticipated approval later this year, as examples of "broad molecular profiles" in the work-up of patients with metastatic melanoma. This anticipated FDA approved product would include variant calling across all 324 genes, genomic signatures for MSI (microsatellite instability) and TMB (tumor mutational burden) as well as clinical claims in diseases in which current companion diagnostics exist, including melanoma, and NSCLC, breast, colorectal and ovarian cancers in the intended use. As such, we plan to submit analogous requests to respective NCCN disease panels contemporaneously in those cancers. It is anticipated that this FDA approval across solid tumors will be accompanied by a CMS NCD (National Coverage Determination) at the time of approval. In order to achieve this broad approval, this process, unlike conventional bridging studies for a single biomarker in one tumor type, involved a submission with genomic analysis of more than 6,000 samples across all four classes of genomic alterations (base substitutions, indels, copy number variations and rearrangements). Validation and concordance was demonstrated using more than 36 distinct tumor types across a spectrum of specimen types (e.g., core biopsies, fine needle aspirates, etc.). The FoundationOne *CDx* assay will thus serve as a single test to identify patients whose tumors contain alterations tied to currently FDA approved therapies and also as a molecular screen to facilitate and expedite access to clinical trials, overall permitting more rapid testing of novel therapies and shortening the time and cost of drug development.

Specific Changes: This request is to include comprehensive genomic profiling (CGP), via a single (as opposed to sequential testing) assay, in the initial evaluation of a patient with metastatic melanoma in order to identify *BRAF* and *KIT* alterations, other alterations recurrently identified in melanoma such as *NRAS, NF1, GNAQ* and *GNA11*, as well as additional rare driver alterations that may inform the patient's treatment , including the option to enroll in a genomically matched clinical trial (pages ME-7 and ME-13). TMB, as measured via CGP, has been shown to identify patients with metastatic melanoma more likely to respond to single agent immunotherapy and as such may inform clinical decision-making (page ME-G).

FDA Clearance: FoundationOne is a laboratory developed test (LDT) currently available for clinical use. FoundationOne *CDx* is currently under parallel and expedited review by FDA and CMS with anticipated FDA approval the second half of 2017.

Rationale: The BRAF inhibitors (dabrafenib, vemurafenib) and MEK inhibitors (trametinib, cobimetinib) are approved for *BRAF* V600E/K-mutated melanoma. However, mutations other than V600E or V600K constitute approximately 5% of *BRAF* mutations in melanoma [1, 2]. Numerous responses to BRAF inhibitors alone or in combination with trametinib have been reported for patients with rare *BRAF* mutations at the V600 position (such as V600R and V600M) [3, 4], including one study that reported response to vemurafenib or dabrafenib in 5 of 6 patients with *BRAF* V600R mutation [3]. Responses to trametinib have been reported for patients with melanoma with *BRAF* non-V600 mutations including K601E, L597R, L597Q, L597S and *BRAF* fusions [1, 2, 5, 6]. Kinase fusions are most frequently observed in Spitzoid melanomas (33%) [7], but have also been observed in other types of melanoma [8–10]. *BRAF* fusions have been reported in up to 8% of melanomas lacking mutations in *BRAF*, *NRAS* or *KIT* [8]. Case reports have described responses to targeted therapy, including responses to trametinib in melanoma patients with *BRAF*-fusion [1, 2]. CGP can identify the full spectrum of *BRAF* mutations including non-V600 alterations that are

associated with clinical benefit and are not evaluated by approved companion diagnostics. Responses to targeted therapy have also been reported for *NTRK* and *ROS1* kinase fusions. In a Phase 1/2 basket trial, treatment of patients with *NTRK1-3* fusions with the NTRK inhibitor larotrectinib resulted in an overall response rate of 76%; responses were observed in diverse tumor types, including patients with *NTRK1* and *NTRK3* fusion-positive melanoma [10]. A response to entrectinib was reported in a patient with acral melanoma with *GOPC-ROS1* fusion [9].

KIT mutations are detected in 12% of acral or mucosal melanomas but have also been observed in 4% of cutaneous melanomas [11]. The activity of KIT inhibition in those melanomas driven by *KIT* alterations has been reported in prospective trials of imatinib [12, 13], sunitinib [14], dasatinib [15], and nilotinib [16]. Response rates observed in prospective clinical trials of imatinib and nilotinib in patients with melanoma harboring *KIT* alterations have ranged from 16-29% [12, 13] and up to 26% [16], respectively. The NCCN recommends imatinib for treatment of tumors with *KIT* activating mutations, which are diverse and are distributed across the gene (exons 9, 11, 13, 17, and 18). Therefore, reliable detection of *KIT* activating mutations requires broad-based sequencing of the *KIT* gene using assays such as CGP [13].

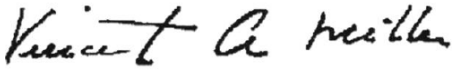
NRAS mutations are observed in 28% of melanomas [11] and have been targeted in clinical trials of MEK inhibitors alone or in combination with CDK4/6 inhibitors. The phase 3 study of binimetinib versus dacarbazine in patients with advanced *NRAS*-mutant melanoma demonstrated an improvement in PFS with binimetinib [17].

TMB is a promising biomarker for response to immune checkpoint inhibitors (ICPI) and can only be accurately estimated using a CGP (or WES) approach. In patients with melanoma, high TMB is associated with higher response rates and improved overall survival to single agent treatment with the anti-CTLA-4 therapy ipilimumab [18, 19] and anti-PD-1 or anti-PD-L1 therapies [20]. Although the combination of ipilimumab/nivolumab is more effective than either agent alone [21], the combination is also associated with increased toxicity. Currently there is no consensus as to the appropriate selection of patients for treatment with single agent anti-PD-1 versus combination therapy with ipilimumab/nivolumab (ME-G). High TMB defines a subset of patients more likely to benefit from ICPI monotherapy [18, 20], whereas low TMB is associated with inferior outcomes with ICPI monotherapy [18, 20] and may define a subset of patients who may be candidates for initial treatment with the combination of ipilimumab/nivolumab, despite higher costs and increased toxicities, or clinical trial approaches.

Consistent with the NCCN® recommendation to steer patients to therapeutic clinical trials, hybrid capture CGP, like FoundationOne® and FoundationOne *CDx*™, finds alterations (including *BRAF* V600 and non-V600 mutations, *NRAS, GNAQ* and *GNA11* mutations, *BRAF, RAF1, FGFR, NTRK1/3, RET, ROS1* kinase fusions, *AKT1/3, ARAF, EGFR, FGFR, HER2, KIT, MEK1/2, MET, MTOR, PIK3CA, RAF1* kinase activating mutations, *HER2* and *MET* amplification, *ATM, BRCA1, BRCA2, NF1, NF2, PALB2, PTEN, TSC1/2* inactivating alterations, *IDH1/2* mutation, *SMO/PTCH1* mutations, and *CCND1/2/3* and *CDK4/6* amplification) that indeed provide a potential match to targeted therapies in clinical trials in >90% of patients with melanoma. Foundation Medicine has recently joined NCI-MATCH and has formally joined the ASCO TAPUR study, using the combination of CGP and clinical trial matching to accelerate accrual to these transformative efforts. Taken together, these data suggest CGP is an essential addition to clinical care of patients with this often deadly malignancy.

Thank you for your review of this submission.

Sincerely,



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