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Date of request: June 17, 2020
NCCN Guidelines Panel: Soft Tissue Sarcoma

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Soft Tissue Sarcoma Panel consider the requested updates pertaining to the evaluation and management of patients with soft tissue sarcoma.

Requested Update: Update Principles of Ancillary Techniques Useful in the Diagnosis of Sarcoma (page SARC-C 1 of 3) as follows: *"Molecular genetic testing, including large validated NGS-based panels >50 genes and comprehensive genomic profiling, has emerged as a particularly powerful ancillary testing approach since many sarcoma types harbor characteristic genetic aberrations, including single base pair substitutions, deletions and amplifications, and translocations." Due to the significant presence of novel fusions in this patient population, comprehensive genomic profiling utilizing both DNA and RNA is recommended.*

Rationale:

Comprehensive genomic profiling (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 and microsatellite instability, to inform cancer treatment decisions via a single assay[1]. CGP testing may also include RNA sequencing to detect structural variations, such as translocations or large deletions, and to detect functional splicing mutations[2].

- In a large analysis (n=7564) of patients with soft-tissue or bone sarcoma tested with CGP over a 5 year period, 36.6% of all patients had actionable alterations known to respond to an FDA-approved or investigational drug[7]. Novel alterations (AKT, ESR1, BRCA, NTRK, PTCH1, SMARCB1, and others) and novel actionable kinase fusions (ALK, FGFR, NTRK1/2/3, and BRAF) were identified. There was a subset of 107 patients with clinical data available and analysis revealed that 57% (60 of 107) had at least one treatment-linked alteration, of which 31 (30%) patients enrolled in a matched trial.

- A total of 392 patients with sarcoma, including soft tissue sarcoma (STS), were evaluated with CGP at a single institution, including a subset of sarcoma patients who were prospectively followed to evaluate the decision impact of CGP testing in this population[3]. Overall, 75.3% (n=295 of 392) of CGP tests were successful and soft tissue sarcomas had higher passing rates than bone sarcomas (76.7% vs 65.3%; P=.0008). There were 34 patients who had CGP testing prior to progression on the current line of therapy and treating oncologists were blinded to the CGP results until progression (based on imaging). The treating oncologist first documented a treatment plan without CGP results and then reviewed the CGP results and documented any treatment changes as a result of the CGP test. Of the evaluable patients, 25% (n=7 of 28) had their treatment selection altered based on the CGP result. Analysis of this subgroup revealed that 6 of the 7 patients received the altered treatment (one patient died before initiating therapy) and the exploratory endpoint of median PFS in the CGP-selected group was 124 days versus 54 days in the non CGP–selection group (P = .03).

- In a cohort of 114 patients with sarcoma (non-GIST), CGP detected a median of three driver variants per tumor and at least one mutation was detected in 96.7% of tumors[4]. Across all sarcoma types, the most common alterations were found in *TP53* (36.8%), *CDKN2A/B* (20.2%), *CDK4/MDM2* (19.3%), *ATRX* (13.2%), and *RB1* (13.2%). In a subset of 106 patients for whom data were available, TMB was classified as low (< 6 mutations/Mb) in the majority of patients (84.9%), with smaller numbers having intermediate (six to 20 mutations/Mb) or high TMB (> 20 mutations/Mb) in 13.2% and 1.9% patients, respectively. Fifty-six patients (49.1%) had a clinically actionable alteration, defined as predicting response to approved drugs available for the patient's diagnosis (on-label), for another diagnosis (off-label), or investigational drugs being studied in humans for whom the genetic alteration has been shown to serve as a

suggested biomarker for response. Therapeutic selection was influenced in 15 patients (13.2%) by CGP in the opinion of the treating physician. Four of these 15 (26.7%) CGP-influenced therapies resulted in clinical benefit (partial response or stable disease > 6 months). Five patients (4.4%) had a diagnosis change as a result CGP findings

- Tumors from 133 patients at a single institution with a variety of sarcomas, including STS, were analyzed with CGP and 88% had at least one detectable alteration[5]. Across all sarcoma types, the most common alterations were in the cell cycle, including *TP53* (n=35), *CDKN2A/B* (n=23), and *RB1* (n=19). There were 27 *PI3K* pathway alterations, including PTEN (n=14), *PIK3Ca* (n=4), *TSC1* (n=1), *TSC2* (n=3), *STK11* (n=1), *mTOR* (n=3), and *RICTOR* (n=2). Also observed were known and/or expected disease-defining gene alterations including *KIT* (GIST), *CDK4/MDM2* amplification (liposarcoma), *IDH* (chondrosarcoma), and various gene fusions such as *EWSR1-FLI1*, *TWSR1-NR4A3*, *EWSR1-ATF1*, *FUS-DDIT3*, and others. There were 75 mutations in genes that are targetable with existing drugs (excluding KIT in gastrointestinal stromal tumor) that would allow enrollment onto clinical trials (including NCI-MATCH (NCT02465060) basket study and ASCO-TAPUR (NCT02693535)). In nearly all samples, tumor mutational burden (TMB) was in the low or intermediate range, however, two soft tissue sarcomas were identified with levels in the high range (one undifferentiated pleomorphic sarcoma, one high-grade soft tissue sarcoma with leiomyosarcoma features). CGP testing changed the clinical diagnosis in 2 (1.5%) patients.

- In a study of 102 patients with advanced sarcomas, including STS, CGP identified at least one genomic alteration in 93% (95 of 102)[6]. Of the 95 biopsy samples with identifiable genomic alterations, the most commonly affected genes were TP53 (31.4%), CDK4 (23.5%), MDM2 (21.6%), RB1 (18.6%), and CDKN2A/B (13.7%). Notable co-segregating amplifications included MDM2-CDK4 and FRS2-FGF. Of the overall cohort, 14 (14%) patients had an alteration that could be targeted with an approved drug in sarcoma (on-label); 45 (45%) patients had an alteration that could be targeted with a drug approved in another disease (off label); and 61 (60%) patients had an alteration that could potentially be targeted by a drug currently available in clinical trials. Fifty nine patients (58%) chose to participate in a clinical trial, and of these, 16 (16%) received therapy directed by the CGP result. Of these sixteen patients, eight (50%) had at least stable disease. The authors concluded that that future studies in sarcomas should be guided by CGP and actionable alterations rather than histologic subtypes.

Clinical Trials

Numerous promising therapeutic approaches are based upon genomic characterization of tumors and therefore many clinical trials require specified genomic alterations for patient enrollment, including trials offered by the NCI (MATCH NCT02465060) and ASCO (TAPUR NCT02693535). Consistent with the NCCN® recommendation to provide patients with opportunities to participate in therapeutic clinical trials, comprehensive genomic profiling assays like FoundationOne® CDx and FoundationOne® Heme, can potentially match more patients to targeted therapies in clinical trials based on detected alterations. Foundation Medicine is an approved testing platform for both NCI-MATCH and ASCO TAPUR and is accelerating accrual to these transformative trials using the combination of CGP and clinical trial matching capabilities.

Thank you for your review of this submission.

Sincerely,

Brian Alexander, M.D.
Chief Medical Officer
Foundation Medicine

1. FoundationOne CDx Technical Information (pdf included) found at https://assets.ctfassets.net/vhribv12lmne/6Rt6csmCPuaguuqmgi2iY8/26c3601c30e0d64c4f7e908543b8d62a/P170019.S015.Label.Technical_Info.FINAL.pdf
2. FoundationOne Heme Technical Information (pdf included) found at https://assets.ctfassets.net/vhribv12lmne/zBxaQC12cScqgsEk8seMO/a70860fea48927c7ff8b70e90c292182/F1H_TechnicalInformation.pdf
3. Hay MA, et al. Identifying Opportunities and Challenges for Patients with Sarcoma as a Result of Comprehensive Genomic Profiling of Sarcoma Specimens. *JCO Precision Oncology* no. 4 (2020) 176-182.
4. Boddu S, et al. Clinical Utility of Genomic Profiling in the Treatment of Advanced Sarcomas: A Single-Center Experience. *JCO Precision Oncology*- published online October 19, 2018.
5. Cote GM, He J, Choy E. Next-Generation Sequencing for Patients with Sarcoma: A Single Center Experience. *Oncologist*. 2018;23(2):234-242.
6. Groisberg R, Hong DS, Holla V, et al. Clinical genomic profiling to identify actionable alterations for investigational therapies in patients with diverse sarcomas. *Oncotarget*. 2017;8(24):39254-39267.
7. Gounder MM, et al. Impact of next-generation sequencing (NGS) on diagnostic and therapeutic options in soft-tissue and bone sarcoma. Presented at the 2019 Annual Connective Tissue Oncology Society Meeting, Tokyo Japan. November 14, 2019. *Publication In Progress*