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NCCN Guidelines Panel: Myelodysplastic Syndromes

Dear Panel Members:

On behalf of Foundation Medicine, I respectfully request the NCCN® Myelodysplastic Syndromes Panel consider the following updates pertaining to the evaluation and management of individuals with myelodysplastic syndromes:

Requested Updates and Rationale: Update the initial algorithm on page MDS-1 and corresponding footnote (d) on page MDS-1A to state: "multiplex gene panels and comprehensive next generation sequencing analysis are recommended for the initial diagnostic evaluation and ongoing management of patients with myelodysplastic syndromes."

Comprehensive NGS analysis, also referred to as comprehensive genomic profiling (CGP), examines 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. [1,2]

CGP assays have been validated against traditional orthogonal methods for hematologic malignancies and show a high level of concordance for detecting somatic alterations, which provide tumor classification, risk assessment, prognosis, disease monitoring, and treatment optimization.[3,4] A CGP approach has proven effective in identifying all types of genomic alterations, including fusion transcripts, which increases the ability to identify clinically relevant genomic alterations with therapeutic relevance.[3,4] In addition, comprehensive NGS analysis is recommended in the work-up of acute myeloid leukemia as it "may assist with selection of therapy and appropriate clinical trials." (See NCCN Guidelines Acute Myeloid Leukemia V3.2021, EVAL-1A and AML-10).

CGP has been shown to increase clinical trial enrollment across a spectrum of refractory solid tumor and hematologic malignancies by identifying biologically relevant alterations recommended in current NCCN guidelines, as well as those with emerging relevance.

- CGP analysis of 235 patients with hematologic malignancies, including MDS, identified that most patients had complex and unique molecular profiles. The majority of patients (75%) had ≥1 potentially actionable alteration and while most of the patients with evaluable tumor mutational burden (TMB) had a low TMB, 12% of patients had intermediate or high TMB. The authors conclude that CGP testing provides opportunity for clinical trials in hematologic malignancies to rationally test the application of genomically-targeted therapeutics or immunotherapy, particularly in relapsed/refractory patients who have either exhausted or are unable to tolerate standard chemotherapy.[5]
- In a database review of clinical CGP results for 4,800 patients with hematologic malignancies, the majority of alterations identified were in genes included in current NCCN guidelines, however, 17-26% of samples had biologically relevant alterations identified beyond those included in the guidelines, suggesting clinical utility of a CGP test approach to inform treatment planning, including clinical trial options.[6]
- In a prospective trial of patients with a wide variety of refractory tumors at an academic institution, a CGP test strategy with a large (409) gene NGS panel increased clinical trial enrollment from 11% to 19 % compared to a smaller (46 or 50) gene NGS hotspot panel[6].
- A retrospective analysis of medical records at a community oncology practice over a three-year period for patients with advanced solid and hematologic malignancies concluded that clinical trial enrollment was facilitated by CGP use in the community setting[7].
- In a review of emerging treatment options for patients with high-risk myelodysplastic syndrome, an NGS approach is promising in identifying targetable mutations in addition to those with FDA- approved medications - *IDH1/2* and *FLT3.* For example, *SP3B1* may be a predictive marker for high-response rate to luspatercept in patients with low-risk MDS and ringed sideroblasts, and the small molecule APR-246, a molecularly targeted therapy, may stabilize and restore

wild-type activity of mutant p53 and induce apoptosis selectively in *TP-53* mutant cells and has demonstrated activity in phase I/II clinical trials in combination with azacitidine.[7]

- A search of ClinicalTrials.gov lists 32 actively recruiting/not yet recruiting clinical trials for targeted therapy/MDS and 22 actively recruiting/not yet recruiting for immunotherapy/MDS. (ClinicalTrials.gov, accessed March 5, 2021)

Thank you for your review of this submission,

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