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NCCN Guidelines Panel: Multiple Myeloma

On behalf of Adaptive Biotechnologies, we request that the NCCN Multiple Myeloma (MM) Guideline Panel review and consider the following modifications for the MM Guidelines.

Rationale

On September, 28, 2018, the clonoSEQ® assay was granted De Novo designation by the FDA as the first and only test for minimal (measurable) residual disease (MRD) in the bone marrow of patients with MM and acute lymphoblastic leukemia.[1] The analytical and clinical validation studies included more than 40,000 unique MRD measurements demonstrating the precision and reproducibility of the clonoSEQ assay. Additionally, the FDA has publicly recognized the rigor of clonoSEQ validation[2] and has restated the need for a standardized MRD tool to aid in clinical management. Recently, FDA published draft guidance for the use of MRD in hematologic malignancies to support drug development,[3] and this guidance follows 3 new drug labels that incorporate MRD data.

To ensure that all patient populations have access to most standardized and specific technology, Adaptive Biotechnologies has secured a positive coverage determination by Medicare[4] and will continue to purse private payer coverage policies, thus removing a patient access barrier.

Because of clonoSEQ's FDA authorization and the publication of other clinical data since version 2.2019 of the MM Guidelines, we believe it is appropriate to update the Discussion section to include published clinical data that demonstrate use of clonoSEQ in patients with MM.[5-13] Specifically, pooled MRD data from the phase 3 CASTOR and POLLUX studies demonstrated that sustained MRD negativity is associated with prolonged progression-free survival (PFS) and overall survival and with a trend in better patient-reported outcomes, suggesting that sustained MRD negativity should be a treatment goal for patients with relapsed/refractory MM.[10,11] Moreover, analysis of the IFM2009 trial revealed that MRD negativity was a significant predictor of prolonged PFS regardless of treatment group, cytogenetic risk profile, or disease stage at diagnosis.[9]

We are also seeking parity of description of the validated clonoSEQ Assay with the description of flow cytometry present in version 2.2019 of the MM Guidelines.

Requested Modifications

- Page 6 (MYEL-1), Version 2.2019: Update the Initial Diagnostic Workup to include bone marrow for next-generation sequencing (NGS) (3rd bullet from bottom; suggested updates in *red*): Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry, bone marrow flow cytometry, and/or *bone marrow NGS-based analysis*.

- Page 7 (MYEL-2), Version 2.2019: Update the Follow-up/Surveillance section to include bone marrow for NGS or flow cytometry (3rd bullet from bottom; suggested updates in *red*): Bone marrow aspirate and biopsy, *including bone marrow flow cytometry and/or bone marrow NGS-based analysis,* as clinically indicated.

- Page 8 (MYEL-3), Version 2.2019: Update the Follow-up/Surveillance section to include bone marrow for NGS cytometry (2nd bullet from bottom; suggested updates in *red*): Bone marrow aspirate and biopsy with FISH, multiparameter flow cytometry*, and/or NGS,* as clinically indicated.

- Page 9 (MYEL-4), Version 2.2019: Update the Follow-up/Surveillance section to include measuring disease response by NGS and/or flow cytometry (3rd bullet from bottom; suggested updates in *red*): Bone marrow aspirate and biopsy at relapse with FISH, *flow cytometry, and/or NGS,* as clinically indicated.

- Page 14 (MYEL-B), Version 2.2019: Update text to include a footnote that specifies that the methods of clonal assessments. Suggested footnote text in *red*: *Clonal assessments can be performed by immunohistochemistry, flow cytometry, or NGS.*

- MYEL-D (Pages 16-18), Version 2.2019

  – Page 2 of 3, 3rd from last criteria for Progressive Disease (suggested updates in *red*): ~~*In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels,*~~ Bone marrow plasma-cell percentage*, measured by NGS or flow cytometry,* irrespective of baseline status (absolute increase must be ≥10%);

  – Page 3 of 3, Update footnote "d" to provide information on NGS consistent with that provided for flow cytometry, with proposed updated text (in *red*): DNA sequencing assay on bone marrow aspirate should use a validated assay. *The reference NGS method is the clonoSEQ® NGS-MRD Assay, which has been clinically validated and achieved FDA clearance for use in patients with MM, demonstrating that MRD measured by clonoSEQ significantly predicts progression-free survival based on analysis from the ALCYONE and DFCI Study 10-106.[1] The clonoSEQ Assay has been used globally and is currently being performed at a single-site. It has comparable sensitivity, standardization, and specificity to other methods of MRD assessment. To achieve sensitivity of a least 1 in 10^5 plasma cells, as called for in the IMWG Guidelines, at least 100,000 cells should be assessed. Perrot A, Lauwers-Cances V, Corre J, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. Blood. 2018;132(23):2456-2464. Dimopoulos MA, San-Miguel J, Belch A, et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica. 2018. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018;378(6):518-528. Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018.*

- Discussion section, Version 2.2019: Update the discussion of use of MRD in patients with MM to reflect recent clinical validation of clonoSEQ to measure MRD.[5-13]

References

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3. FDA. Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM623333.pdf. Published 2018. Accessed March 20, 2019.
4. CMS. Local Coverage Article: MolDX: Clonoseq® Assay for Assessment of Minimal Residual Disease (MRD) in Patients with Specific Lymphoid Malignancies (A56270). https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=56270&ver=5&Cntrctr=374&ContrVer=1&CntrctrSelected=374*1&DocType=Active&s=48&bc=AhAAAAIAgAAA&. Updated January 17, 2019. Accessed March 20, 2019.
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