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NCCN Guidelines Panel: Multiple Myeloma

On behalf of Adaptive Biotechnologies, we respectfully request that the NCCN Multiple Myeloma Guideline Panel review the enclosed data for the addition of content within the following sections of the Guidelines.

Specific Changes:

1. Page 8, Version 3.2018: Add the phrase "baseline characterization of myeloma clone to define tumor burden, assess presence of somatic hypermutation, and facilitate subsequent minimal residual disease (MRD) analysis" under the '*Initial diagnostic workup'* section.

2. Page 19, Version 3.2018: Add additional context in footnote * under MYEL-C (page 3/3). Specifically, add the underlined text: "…information on MRD after each treatment stage is recommended to enable serial MRD assessments over time (e.g. after induction, high-dose therapy/ASCT, consolidation, maintenance, and as medically indicated)".

3. Page 19, Version 3.2018: Add additional context to footnote § (NGS) under MYEL-C (page 3/3), to parallel footnote ‡ related to NGF. Specifically, add, "Bone marrow NGS should be done using a validated and standardized method. Standardized NGS MRD methods are available for clinical use in the US through academic institutions and through a CLIA, CAP, and ISO certified commercial laboratory (clonoSEQ®, Adaptive Biotechnologies). It is recommended that at least one million total nucleated cells be assessed. The NGS method employed should have a sensitivity of detection of at least 10^{-5} nucleated cells. Both fresh and archived samples may be analyzed. Martinez-Lopez J, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. *Blood.* 2014;123(20):3073-9. Kumar S, at al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. L*ancet Oncology.* 2016;17(8):e328-46.

4. The end of this document lists recent evidence in multiple myeloma related to NGS MRD assessment. We ask that you please consider adding this data into the *'Discussion'* section of the Guidelines.

Rationale:

Request #1: We believe that the statement suggested is necessary to support the growing adoption of NGS-based MRD in patients with myeloma. The NCCN and IMWG Guidelines both recommend MRD assessment by NGF and NGS. NGS analysis begins with an assessment of tumor burden in a high-disease load sample and proceeds with the tracking of index sequences residing within the malignant clonal

population in follow up samples from the same patient. In NCCN ALL Guidelines, the need for "baseline characterization of (leukemic) clone to facilitate subsequent minimal residual disease (MRD) analysis" is described in the '*Diagnosis'* section (ALL NCCN Guidelines Version 1.2018). We believe that the statement provided is appropriate for inclusion in the Multiple Myeloma Guidelines.

Request #2: Several recent publications that highlight the importance of NGS MRD assessment over time to understand changes and trends of disease. Mateos, et al. assessed NGS-MRD at the time of CR or sCR, and at 12, 18, 24, and 30 months after the first dose of daratumumab in patients having a CR or sCR. Results showed that "negative status for minimal residual disease was associated with longer progression-free survival than positive status, irrespective of trial treatment. In patients with persistent minimal residual disease, progression-free survival was longer in the daratumumab group than in the control group. The value of persistent MRD is also supported by the study of Dimopoulos et al. referenced below.

Request #3: Under MYEL-C (page 3/3), there is a footnote that extensively reviews the NGF approach including its validation, reliability, consistency, sensitivity, specificity, availability, adoption, efficiency, time, cost, and sample requirements. The next footnote related to NGS simply states, "DNA sequencing on bone marrow aspirate should use a validated assay". Several recent publications and white papers have reviewed the above criteria in relation to NGS MRD. For example, a recent white paper by Ken Anderson noted that the limit of detection of NGS approaches 10^{-6}, is robustly quantitative, allows for the use of fresh or stored samples, provides more objective interpretation than MFC, and can be standardized. Additionally, a recent update to the daratumumab package insert includes information on a study that assessed MRD by NGS using a threshold of 10^{-5}. We recommend adding this descriptive information for the NGS-MRD analysis, comparable to the content already presented in the NGF footnote.

Request # 4: This request is being made to provide a fair and balanced addition to the information already present in this guideline for other methodological approaches to MRD determination.

The following articles are submitted in support of this proposed change.

1. Mateos V, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. *New England Journal of Medicine.* 2018;378:518-528.
2. Dimopoulos MA, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma *New England Journal of Medicine*. 2016;375:1319-31.
3. Martinez-Lopez J, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. *Blood.* 2014;123(20):3073-9.
4. Kumar S, at al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. L*ancet Oncology.* 2016;17(8):e328-46
5. Anderson K, et al. The Role of Minimal Residual Disease Testing in Myeloma Treatment Selection and Drug Development: Current Value and Future Applications. *Clinical Cancer Research.* 2017;23(15):3980-93.
6. DARZALEX® Prescribing Information. Horsham, PA: Janssen Biotech, Inc; 2018.