Submitted by: Lori K. Pender, PharmD, MPH, BCOP, Associate Director, Medical Affairs
Name: Thomas Manley, MD, Vice President, Clinical Development and Medical Affairs
Company/Organization: Adaptive Biotechnologies
Address: 1551 Eastlake Ave East, #200 Seattle, WA 98102
Phone: (855) 466-8667
Email: tmanley@adaptivebiotech.com
Date of request: Thursday, March 25, 2021
NCCN Guidelines Panel: Multiple Myeloma

On behalf of Adaptive Biotechnologies, we respectfully request that the NCCN Multiple Myeloma (MM) Guideline Panel review and consider the following modifications around minimal residual (MRD) testing for the MM Guidelines.[1]

Specific Changes: Recommend MRD assessment at specific time points and expand Discussion as follows:

- MYEL-1: Incorporate "Consider baseline clone identification…" into "Initial Diagnostic Workup" by adding the following underlined text, "Unilateral bone marrow aspirate and biopsy, including IHC and/or multi-parameter flow cytometry (MFC) or baseline clone identification by NGS for future MRD testing."
- MYEL-4: Change, "Consider MRD as indicated for prognostication after shared decision with patient" to "Assess MRD for prognostication after each treatment stage as part of shared decision with patient," the timing of which is consistent with International Myeloma Working Group (IMWG) guidelines.[2]
- MYEL-5: Change, "Consider MRD…" to "Assess MRD for prognostication after shared decision with patients who achieve a very good partial response (VGPR), complete response (CR), or stringent CR (sCR) after primary therapy; repeat assessment every 12 months to assess for sustained MRD negativity."
- Expand Discussion section on the role of MRD assessment to include the importance of sustained negativity at the deepest level possible (i.e., 10^{-6}), the concept of dynamic risk assessment, and the ability of MRD to supersede conventional response criteria based on the data provided below,[3-10] and include data from contemporary clinical trials with NGS-based MRD assessments; ten such papers have been published since 2020.[3,10-18]

FDA Clearance: These changes are consistent with FDA clearance for clonoSEQ®, an NGS *in vitro* diagnostic test service provided by Adaptive Biotechnologies and cleared to detect MRD in bone marrow from patients with MM or B-cell ALL and blood or bone marrow from patients with CLL.[19]

Rationale: Since publication of the IMWG consensus criteria on response and MRD assessment in 2016, which underlie version 5.2021 of the NCCN guidelines, there has been an increasing body of evidence demonstrating the ability of MRD to supersede the prognostic value of VGPR, CR, and sCR and the importance of sustained MRD negativity, using the most sensitive methodology available (i.e., at 10^{-6}), to predict clinical outcomes in MM.

The following articles are submitted in support:

- **Dimopoulos MA, et al; on behalf of the EHA and ESMO Guidelines Committees. *Ann Oncol.* 2021.**[4] These updated clinical practice guidelines, co-authored by several of the IMWG panel members, state that MRD negativity in the bone marrow at the level of 1×10^{-6} "shows the best results for the prediction of both PFS and OS compared with higher cut-off values (i.e., 10^{-5})" in MM, and recommends NGS or next-generation flow (NGF) at diagnosis, at response, and every 12 months thereafter. In the US today, clonoSEQ is the only standardized, validated, and FDA-cleared test that can determine MRD negativity at the 10^{-6} threshold.[19]
- **Munshi NC, et al. *Blood Adv.* 2020.**[5] This meta-analysis, co-authored by several IMWG panel members, includes PFS and OS data from 8,098 and 4,297 patients, respectively, and "confirms the utility of MRD as a relevant surrogate for PFS and OS in MM." PFS and OS point estimates decreased with depth of response (hazard ratio [HR] for PFS: 0.38, 0.31, and 0.22 at sensitivity thresholds of 10^{-4}, 10^{-5}, and 10^{-6}, respectively; HR for OS: 0.50, 0.39, and 0.26, respectively), and the authors noted that, "every study that examined the depth of response supported the use of 10^{-6} as the optimal threshold for MRD negativity." This analysis also reveals the prognostic value of MRD negativity in patients who achieve at least a VGPR and proposed a biologic rationale for this finding. They concluded that MRD fulfills requirements to be a valid surrogate for PFS and OS and supersedes the prognostic value of CR.

- **Avet-Loiseau H, et al. *J Clin Oncol.* 2021.**[3] Extended follow-up from the POLLUX and CASTOR trials reveals that sustained MRD negativity is associated with prolonged PFS in relapsed/refractory myeloma, including among patients who achieve at least a CR. The authors concluded that there is "limited value in using CR without MRD negativity as a prognostic marker for survival outcomes in MM" and that "measuring deeper responses is necessary to predict and improve long-term outcomes."
- **Goicoechea I, et al; for the PETHEMA/GEM Cooperative Group. *Blood.* 2021.**[6] This study found that achieving MRD negativity overcomes the adverse prognosis associated with high-risk cytogenetics in transplant-eligible MM and has led to calls to recognize risk dynamics.[7-9] That is, the prognosis established at diagnosis can change during treatment, and MRD is the only tool capable of facilitating dynamic risk assessment.
- **Cedena M-T, et al. *PLOS One*. 2020.**[10] This analysis found that MRD status refines the prognosis of patients with sCR, and that those MRD-negative by NGS have superior outcomes to those who are MRD-positive, calling into question the value of sCR when sensitive MRD testing is available.

References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Multiple Myeloma. Version 5.2021 – March 15, 2021. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.
2. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016; Aug;17(8):e328-e346. doi: 10.1016/S1470-2045(16)30206-6.
3. Avet-Loiseau H, San-Miguel J, Casneuf T, et al. Evaluation of sustained minimal residual disease negativity with daratumumab-combination regimens in relapsed and/or refractory multiple myeloma: analysis of POLLUX and CASTOR. *J Clin Oncol*. 2021 Jan 29;JCO2001814. doi: 10.1200/JCO.20.01814.
4. Dimopoulos MA, Moreau P, Terpos E, et al; on behalf of the EHA Guidelines Committee and ESMO Guidelines Committee. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(3):309-322.
5. Munshi NC, Avet-Loiseau H, Anderson KC, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. *Blood Adv*. 2020;4(23):5988-5999.
6. Goicoechea I, Puig N, Cedena M-T, et al; for the PETHEMA/GEM Cooperative Group. Deep MRD profiling defines outcome and unveils different modes of treatment resistance in standard- and high-risk myeloma. *Blood*. 2021;137(1):49-60.
7. Corre J, Munshi NK, Avet-Loiseau H. Risk factors in MM: is it time for a revision? *Blood*. 2021;137(1):16-19.
8. Corre J. Undetectable MRD can change the deal. *Blood*. 2021;137(1):5-6.
9. Costa LJ, Usmani SZ. Usmani. Defining and managing high-risk MM: current concepts. *JNCCN*. 2020;18(12):1730-1737.
10. Cedena M-T, Martin-Clavero E, Wong S, et al. The clinical significance of stringent complete response in multiple myeloma is surpassed by minimal residual disease measurements. *PLOS One*. 2020;15(8):e0237155.
11. Voorhees PM, Rodriguez C, Reeves B, et al. Daratumumab plus RVd for newly diagnosed multiple myeloma: final analysis of the safety run-in cohort of GRIFFIN. *Blood Adv*. 2021;5:4.
12. Weisel K, Spencer A, Lentzsch S, et al. Daratumumab, bortezomib, and dexamethasone in R/R MM: subgroup analysis of CASTOR based on cytogenetic risk. *J Hematol Oncol*. 2020;13:115.
13. Chari A, Rodriguez-Otero P, McCarthy H, et al. Subcutaneous daratumumab plus standard treatment regimens in patients with MM across lines of therapy (PLEIADES): an open-label Phase II study. *Br J Haematol*. 2020 Jul 30. doi: 10.1111/bjh.16980.
14. Kumar S, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with R/R MM (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2020;21(12):1630-1642.
15. Jasielec JK, Kubicki T, Raje N, et al. Carfilzomib, lenalidomide, and dexamethasone plus transplant in newly diagnosed multiple myeloma. *Blood.* 2020;136(22):2513-2523.
16. Kaufman JL, Dimopoulos MA, White D, et al Daratumumab, lenalidomide, and dexamethasone in relapsed/refractory myeloma: a cytogenetic subgroup analysis of POLLUX. *Blood Cancer J.* 2020;10:111.
17. Alonso R, Cedena M-T, Wong S, et al. Prolonged lenalidomide maintenance therapy improves the depth of response in multiple myeloma. *Blood Adv.* 2020;4(10):2163-2171.
18. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene vicleucel in R/R MM. *N Engl J Med*. 2021;384:705-716.
19. clonoSEQ®. Seattle, WA: Adaptive Biotechnologies Corporation; 2020. https://www.clonoseq.com/technical-summary.