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NCCN Guidelines Panel: B-cell Lymphomas

On behalf of Adaptive Biotechnologies, we request that the NCCN B-cell Lymphoma Guideline Panel review and consider the following modifications to the B-cell Lymphomas Guideline.

Requested Modifications (based off version 4.2020)

Specific Changes:

1. On page 13 (DIAG-1, Essential Diagnosis):
    a. Current language: '(immunohistochemistry, flow cytometry, or PCR for IGHV and TCR gene rearrangements…)'.
        i. We believe there may be a small error here in that PCR cannot be used for the assessment of IGHV mutations, but sequencing (NGS) can be used.
    b. Suggested language: '(immunohistochemistry, flow cytometry, ~~or~~ PCR or NGS for ~~IGHV~~ BCR and TCR gene rearrangements, or NGS for IGHV mutational assessment…)'.
        i. We attempted to clarify that NGS or PCR can be used to assess BCR/TCR gene rearrangements while only NGS can be used for IGHV assessment.

Rationale:

While footnote A under Essential Diagnosis (DIAG-1) states, 'If a high suspicion of a clonal process remains and other techniques have not resulted in a clear identification of a clonal process, then next-generation sequencing (NGS) can be used', we believe that NGS should be considered a primary method for assessing Clonality. Several studies (Table 1) have demonstrated that in most patients who are assessed by next-generation sequencing, a clonal rearrangement can be identified.

Table 1

Publication	Disease State	Number of patients assessed by NGS at diagnosis	Number of patients in which a dominant DNA sequence(s) was identified	Percentage
Roschewski et al.	DLBCL	109	94	86%
Kurtz et al.	DLBCL	69	57	82%
Armand et al.	DLBCL	16	16	100%
Merryman et al.	MCL	23	20	87%
Ruan et al.	MCL	11	10	91%

This request is consistent with statements in other NCCN Guidelines, which have recommended Clonality assessment during the initial diagnostic workup:

- Multiple Myeloma: Consider baseline clone identification and storage of aspirate sample for future minimal residual disease (MRD) testing by NGS.

- Pediatric Acute Lymphoblastic Leukemia: Baseline characterization of leukemic clone to facilitate subsequent minimal residual disease (MRD) analysis.
- Adult Acute Lymphoblastic Leukemia: Baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent minimal/measurable residual disease (MRD) analysis.
- Primary Cutaneous Lymphomas: If adequate biopsy material available, flow cytometry or IgH gene rearrangement studies can be useful in diagnosing clonality.

We thank the committee for their review and look forward to future submissions in which we aim to show the correlation of NGS MRD assessment to PET/CT analysis.

References

1. Roschewski M, et al. *Lancet Oncology.* 2015;16:541-49.
2. Kurtz D, et al. I. 2015;125(24):3679-87. PMID: 25887775
3. Armand P, et al. *Br J of Haematol.* 2016;173(1):89-95.
4. Merryman R, et al. *Blood Adv.* 2020; 4(5):858-867.
5. Ruan J, et al. *Blood.* 2018;132(19):2016-2025.