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NCCN Guidelines Panel: B-cell Lymphoma

On behalf of Adaptive Biotechnologies, we respectfully request that the NCCN B-cell Lymphoma Guideline Panel review the enclosed data for the addition of content within the following sections of the Guidelines:

Specific Changes (to Version 4.2018):

1. On page 12 (DIAG-1): Add NGS as an additional option to PCR for assessing IGH and TCR gene rearrangements under *Essential Diagnosis*: '(immunohistochemistry, flow cytometry, NGS or PCR for *IGHV* and *TCR* gene rearrangements…)".

Rationale:
Request #1: Several studies have demonstrated the ability of next-generation sequencing (clonoSEQ®) to detect IGHV and TCR gene rearrangements at diagnosis.

Roschewski et al. demonstrated the ability of NGS to identify gene rearrangements in patients with DLBCL using FFPE tumor biopsies Of the 109 patients analyzed with pretreatment biopsy samples, NGS identified a dominant DNA sequence in 94 patients (86%).

Kurtz et al. demonstrated the ability of NGS to identify gene rearrangements in patients with DLBCL using FFPE tumor biopsies or archived DNA. Of the 69 patients analyzed, NGS identified a dominant DNA sequence in 57 patients (82%).

Armand et al. demonstrated the ability of NGS to identify gene rearrangements in patients with DLBCL using FFPE tumor biopsies. Of the 16 patients analyzed, NGS identified a dominant DNA sequence in 16 patients (100%).

Summary:

Publication	Number of patients assessed by NGS at diagnosis	Number of patients in which a dominant DNA sequence(s) was identified	Percentage
Roschewski et al.	109	94	86%
Kurtz et al.	69	57	82%
Armand et al.	16	16	100%

This request is consistent with that mentioned in other NCCN Guidelines which have recommended the assessment of IGH and TCR gene rearrangements, IGHV status, or Clonality during the initial diagnostic workup:

- T-Cell Lymphoma Guidelines
    - Peripheral T-cell Lymphoma: “Molecular analysis to detect clonal T-cell antigen receptor (TCR) gene rearrangements or other assessments of clonality”
    - Mycosis Fungoides/Sezary Syndrome:
        - “Molecular analysis to detect clonal T-cell antigen receptor (TCR) gene rearrangements or other assessments of clonality”
        - “TCR gene rearrangements in peripheral blood lymphocytes if blood involvement suspected”
- Acute Lymphoblastic Leukemia: Baseline characterization of leukemic clone to facilitate subsequent minimal residual disease (MRD) analysis
- CLL Guidelines
    - “Molecular analysis to detect IGHV mutational status”

In addition, several studies have demonstrated the ability for NGS to assess treatment response in comparison to PET-CT, shown the ability of NGS to predict outcomes, and demonstrate the potential use of NGS in monitoring patients with NHLs, including DLBCL.

Roschewski et al. assessed ctDNA in plasma to determine if NGS could identify relapse earlier than evidence of disease by PET-CT. ctDNA NGS MRD identified recurrence a median of 3.5 months (range 0-200) before evidence of disease by PET-CT. It should be noted that MRD assessment in the blood was done more frequently than PET-CT scans. Additionally, MRD status assessed by ctDNA post cycle 2 was associated with 5-year PFS (ctDNA- = 80.2%; ctDNA+ = 41.7%; $P<0.0001$). Of the 107 patients who achieved a CR, presence of ctDNA MRD was also correlated with a higher likelihood of progression ($P<0.0001$).

Kurtz et al. assessed the correlation between specificity and sensitivity of NGS and PET-CT. The authors concluded that ctDNA NGS MRD assessment during surveillance had increased specificity (100% vs 56%, $P<0.0001$) and similar sensitivity (31% vs 55%, $P=0.4$) compared to PET-CT.

Armand et al. assessed 16 DLBCL patients for evidence of disease by PET/CT and NGS using cfDNA. In patients with evidence of disease by PET/CT, all had evidence of circulating tumor DNA by NGS.

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

1. Roschewski M, et al. Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study. Lancet Oncology. 2015;16:541-49. PMID: 25842160
2. Kurtz D, et al. Noninvasive monitoring of diffuse large B-cell lymphoma by immunoglobulin high-throughput sequencing. Blood. 2015;125(24):3679-87. PMID: 25887775
3. Armand P, et al. A phase 2 study of Rituximab-Bendamustine and Rituximab-Cytarabine for transplant-eligible patients with mantle cell lymphoma. British Journal of Haematology. 2016;173(1):89-95. PMID: 26729345