Submitted by: Audrey Schnell, PharmD, Medical Affairs Manager
Name: Ilan Kirsch, MD, SVP, Translational Medicine
Company/Organization: Adaptive Biotechnologies
Address: 1551 Eastlake Ave East, #200 Seattle, WA 98102
Phone: (202) 693-2160
Email: lkirsch@adaptivebiotech.com
Date of request: May 18, 2018
NCCN Guidelines Panel: T-cell Lymphoma

On behalf of Adaptive Biotechnologies, we respectfully request that the NCCN T-cell Lymphoma Guideline Panel review the enclosed data for the addition of content within the following sections of the Guidelines. Most of the data contained within this submission focuses on mycosis fungoides (MF)/Sezary syndrome (SS), but may be applicable to other T-cell lymphomas. There have now been a series of peer-reviewed published papers that support the application of next generation sequence based analysis of patients with MF/SS as an aid in diagnosis, prognosis, and evaluation of response to therapy.

Specific Changes (to Version 2.2018):

1. On page 24 (MFSS-1): Add the underlined phrase under *Essential Diagnosis*: "Multiple biopsies may be necessary to capture the pathological variability of disease at diagnosis, including identification of a common dominant TCR sequence(s)".
2. On page 24 (MFSS-1): Footnote E speaks specifically about TCR-PCR. Please add the following regarding NGS: "In direct comparisons between NGS and TCR-PCR, sequencing has been demonstrated to be as or more sensitive and specific than TCR-PCR at identifying clonal populations".
3. On page 28 & 29 (MFSS-5 & MFSS-6) under *Primary Treatment*: Add "Assessment of TCR gene rearrangements by next generation sequencing (NGS) to identify patients at high risk for progression".
4. Pages 28-31 (MFSS-5 – MFSS-9): In every instance of a CR assessment, add: "Residual disease determination by NGS". We would also suggest adding a footnote to this text stating, "Ensure diagnostic sample is available to enable subsequent NGS MRD assessment".
5. The end of this request lists recent evidence in CTCL related to TCR gene assessment by NGS, including baseline clonality and serial MRD assessment. We ask that you please consider adding reference to these data into the *'Discussion'* section of the Guidelines.

Rationale:

Request #1: Thurber et al. showed that assessing the gene rearrangements of two skin biopsies at diagnosis was highly specific at differentiating MF from inflammatory dermatoses. This clonality assessment is also useful in determining if the expanded T-cell clones are present in both samples, indicating that the disease is related.

Request #2: As both TCR-PCR and NGS can be utilized for detection of TCR gene rearrangements, we felt that there needs to be additional context in footnote E regarding NGS. Specifically, that NGS is more sensitive and specific at identifying TCR gene rearrangements than TCR-PCR. Kirsch et al. assessed 39 samples by NGS and TCR-PCR at diagnosis. The study demonstrated that T-cell clones were identified in all samples by NGS, and in 27/39 (70%) samples by TCR-PCR. The authors conclude that NGS is more

sensitive and specific than TCR-PCR. Rea et al. showed the diagnostic specificity of NGS versus TCR-PCR was 100% versus 88%, demonstrating that NGS is more specific at distinguishing CTCL from reactive and indeterminate histology than TCR-PCR.

Request #3: Typically, stage 1A-1B CTCL is a chronic, indolent disease. However, a small subset of patients will develop progressive disease. It is therefore important to identify patients who are at a high risk of progression. deMasson et al. demonstrated that "in early-stage patients [N=208], a tumor clone frequency of >25% [at diagnosis as determined by NGS analysis] was a stronger predictor of progression than any other established prognostic factor (stage IB versus IA, presence of plaques, high blood lactate dehydrogenase concentration, large-cell transformation, or age)." This highlights the importance of assessing TCR gene rearrangements at diagnosis by NGS, as NGS can identify potential progressors early during treatment.

Request #4: In every instance of assessing a patient for CR, we would suggest that an MRD assessment also be completed to understand the molecular depth of response. Rook et al. assessed patients with stage IA-IIA CTCL to monitor the efficacy of a topical therapy of skin lesions. TCR analysis by NGS was done and showed that there was a decrease in the malignant T-cell population in 90% of patients. The study also showed the ability to assess immune reconstitution post-treatment by NGS. Weng et al. assessed MRD post-transplant in late-stage CTCL patients. Patients were assessed for 'molecular remission' in blood between +30 and +540 days post-transplant. The authors conclude the NGS is useful in monitoring response to therapy in this population and is more sensitive and specific at identifying circulating Sezary cells than routine flow cytometry. Kirsch et al. assessed residual disease in patients with all stages of CTCL. The authors conclude that NGS accurately assessed response to treatment as well as facilitated diagnosis of disease recurrence using both skin and blood samples.

Request # 5: 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 gene rearrangement assessment. For example, on page 124 (MS-50) of the discussion, information could be added about the utility of NGS to more accurately establish diagnosis than TCR-PCR.

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

1. Thurber S, et al. T-cell clonality analysis in biopsy specimens from two different skin sites shows high specificity in the diagnosis of patients with suggested mycosis fungoides. *Journal of the American Academy of Dermatology*. 2007;57(5):782-90.
2. Kirsch IR, et al. TCR sequencing facilitates diagnosis and identifies mature T cells as the cell of origin in CTCL. *Science Translational Medicine.* 2015;7(308):308ra158.
3. Rea B, et al. Role of high-throughput sequencing in the diagnosis of cutaneous T-cell lymphoma. 2018. pii: jclinpath-2018-205004.
4. de Masson A, et al. High-throughput sequencing of the T cell receptor B gene identifies aggressive early-stage mycosis fungoides. *Science Translational Medicine.* 2018;10(440). pii: eaar5894.
5. Rook AH, et al. Topical resquimod can induce disease progression and enhance T-cell effector functions in cutaneous T-cell lymphoma. *Blood.* 2016;126(12):1452-61.
6. Weng W, et al. Minimal Residual Disease Monitoring with High-Throughput Sequencing of T-cell Receptors in Cutaneous T Cell Lymphoma. *Science Translational Medicine.* 2013;5(214):214ra171.