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NCCN Guidelines Panel: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

On behalf of Illumina, I respectfully request the NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) guideline panel to review the enclosed to support the consideration of next-generation sequencing in the context of comprehensive TP53 genetic testing in CLL/SLL.

Specific Requested Changes:

We propose consideration of next-generation sequencing in the context of genetic testing of TP53, as suggested in the Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma NCCN Guidelines v 5.2018.

FDA Clearance:

The recommendation to use an NGS-based technique is not associated with any specific FDA-cleared product/s.

Rationale:

In chronic lymphocytic leukemia (CLL), chromosomal deletion and mutation of the TP53 gene is associated with resistance to conventional chemotherapy and poor prognosis.[1-3] Consequently, current NCCN guidelines advise analyzing chromosome 17p deletions [del(17p)] using fluorescence in-situ hybridization (FISH), as well as determining TP53 mutation status prior to initiating CLL treatment.[4] A recent 2-year follow-up study of the RESONATE trial demonstrated that more than half of patients with TP53 mutations lack del(17p).[5] TP53 mutation status is an independent prognostic factor for CLL, even in the absence of del(17p).[6] Further, investigators from the European Research Initiative on CLL (ERIC) screened 3,490 CLL patients for TP53 mutations and found that TP53 mutational status predicted poor clinical outcomes independent of immunoglobulin heavy-chain variable-region (IGHV) mutational status.[7]

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, has shown efficacy in CLL patients with TP53 mutations as well as in relapsed or refractory CLL.[8] In a recent phase 2 study, Farooqui et al. reported 2-year progression-free survival (PFS) in 82% of patients with del(17p) or TP53 mutations.[9] A 5-year follow up of this study demonstrated that patients with TP53 aberrations had a long-term and durable response to ibrutinib.[10] Finally, a recent phase 2 study of 145 CLL patients with del(17p) (RESONATE-17) showed that ibrutinib was an effective treatment in this subset of CLL patients.[11] Consequently, the NCCN now recommends ibrutinib as the preferred first-line therapy for patients with del(17p)/TP53 mutation. These clinical data highlight the need for determination of TP53 mutation status as early as possible, before initiating treatment.

Conventional Sanger sequencing is reported to misclassify 5% of newly diagnosed CLL with low abundance TP53 mutant subclones.[12] In a pivotal study, Rossi et al. performed ultra-deep next-generation sequencing (NGS) on the TP53 gene in 309 newly diagnosed cases of CLL. They identified small TP53 mutant subclones in 9% of untreated CLL cases that were missed by Sanger sequencing due to their very low abundance. Notably, the patients with small TP53 mutant subclones showed the same resistance to chemotherapy and poor survival as those patients with clonal TP53 CLL.

In a similar study, NGS sequencing of 48 newly diagnosed CLL patients identified TP53 mutations in 10.6% of patients, with 4.2% of TP53 mutations being subclonal; and, these subclonal TP53 mutations predicted shorter overall survival.[13] In another recent study, NGS was used to retrospectively analyze TP53 mutations in samples from 60 relapsed CLL patients.[14] Of the 40 patients that tested wild-type for TP53 before and after chemotherapy, only 1 TP53 mutant subclone was observed in relapse. Of the 20 patients that were initially classified as TP53 wild-type, but then tested positive for TP53 mutation after relapse, NGS retrospectively identified 18 TP53 mutant subclones present at new diagnosis. These data suggest that TP53 mutant subclones can become dominant clones due to selective pressure during chemotherapy. Additionally, these data suggest that NGS is better suited to identify subclonal populations at earlier stages and with better sensitivity than Sanger sequencing.

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Proposed Changes: Figures CSLL-1, CSLL-A, and HT-1

Figures *CSLL-1*, *CSLL-A*, and *HT-1*: Informative for Diagnosis and Prognostic and/or Therapy Determination

"TP53 sequencing"
Change to:
"TP53 mutation status by next-generation sequencing"

Figure *HT-1*, addition to sub bullet "b" :
b "IGHV rearrangements involving VH3-21 carry poor prognosis even if mutated. TP53mutation status also provides additional prognostic information to FISH. NGS sequencing is the preferable method for determining mutation status and detects subclones at lower levels than Sanger sequencing"

We would like to acknowledge the contributions of NCCN panel members, who are also co-authors or co-contributors in some of these publications.

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4. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia (Version 3.2018). https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed March 21, 2018.
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6. Nabhan C., Raca G. and Wang Y. L. (2015) Predicting Prognosis in Chronic Lymphocytic Leukemia in the Contemporary Era. JAMA Oncol 1: 965-974
7. Baliakas P., Hadzidimitriou A., Sutton L. A., Rossi D., Minga E., et al. (2015) Recurrent mutations refine prognosis in chronic lymphocytic leukemia. Leukemia 29: 329-336
8. Byrd J. C., Furman R. R., Coutre S. E., Flinn I. W., Burger J. A., et al. (2013) Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. New England Journal of Medicine 369: 32-42
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12. Pospisilova S., Gonzalez D., Malcikova J., Trbusek M., Rossi D., et al. (2012) ERIC recommendations on TP53 mutation analysis in chronic lymphocytic leukemia. Leukemia 26: 1458-1461
13. Nadeu F., Delgado J., Royo C., Baumann T., Stankovic T., et al. (2016) Clinical impact of clonal and subclonal TP53, SF3B1, BIRC3, NOTCH1, and ATM mutations in chronic lymphocytic leukemia. Blood 127: 2122-2130
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Thank you for your consideration,

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