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NCCN Guidelines® Panel: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

On behalf of AbbVie and Genentech, I respectfully submit a request to the NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Guideline panel to evaluate existing guidelines based on the data and rationale provided.

Specific Changes:

- In Section CSLL-F of version 5.2018 guidelines regarding dosage of Venetoclax, the guideline states: Venetoclax 5 weeks ramp-up should be followed, as described in the Venclexta® package insert. *Initiation and accelerated ramp up of Venetoclax (20 mg to 400 mg over 3-weeks) with close inpatient TLS monitoring can be done in the subgroup of patients with high tumor burden and where there was a concern for rapid disease progression on or following BTK-inhibitor therapy (Coutre, 2018a; Jones, 2018a).* This accelerated schedule has been explored in a small number of patients and they were hospitalized and received intensive monitoring and prophylaxis. Please consider the publications and rationale below.
- In Section CSLL-F of version 5.2018 guidelines regarding concurrent initiation of Venetoclax with Ibrutinib, the guideline states *continued BTK-inhibition concurrent with initiation and escalation of Venetoclax with discontinuation of BTK-inhibitor when up to the Venetoclax 400 mg daily dose can be considered. These agents can be given together safely.* Ibrutinib and Venclexta® have only been studied at the initiation of therapy. Please consider the rationale below.

FDA Clearance:

- Venclexta® is a BCL-2 inhibitor indicated for the treatment of patients with CLL or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy (Venclexta PI).
    - Please refer to the product prescribing information for the full FDA-approved indications and safety information.
    - Full Venclexta® prescribing information available at: http://www.rxabbvie.com/pdf/venclexta.pdf

Rationale:

Jones, et al., and Coutre, et al., recently published data for use in patients with R/R CLL in B-cell receptor inhibitor failure (Coutre, 2018a; Coutre, 2018b; Jones, 2018a; Jones, 2018b). A small number of the study population that were considered high-risk and showing clinical signs of disease progression were allowed to participate in an accelerated ramp up schedule from 20 mg to 400 mg daily by Week 3, Day 1. Additionally, the Venclexta® prescribing information recommends dosing according to a weekly ramp-up

schedule over 5 weeks to gradually reduce tumor burden and decrease the risk of tumor lysis syndrome (Venclexta PI). We respectfully request the statement surrounding accelerated ramp up be clarified and expanded on the recommended ramp up period and stronger wording surrounding the FDA-approved dosing for Venclexta®.

Ibrutinib and Venclexta® combinations have only been studied at initiation of therapy and not in the context of BTKi progression. During the clinical study evaluating patients who had been previously treated with and progressed on or after ibrutinib or idelalisib, patients were required to have at least 3 days washout period before initiating Venclexta® therapy (Coutre, 2018b; Jones, 2018b). In addition, recent pharmacokinetic studies have suggested that there is increased exposure to venetoclax in combination with ibrutinib (Data on file, Venetoclax IB). We ask that you evaluate your recommendations given that there may be unknown risks to a post-BTKi progressing patient initiating Venclexta®.

Cited References:

Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. Blood 2018a; doi: 10.1182/blood-2017-06-788133. [Epub ahead of print].

Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy [supplement]. Blood 2018b; doi: 10.1182/blood-2017-06-788133. [Epub ahead of print].

Data on file, Venetoclax Investigator's Brochure, Edition 9, March 8, 2018, AbbVie.

Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2018a;19(1):65-75.

Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial [supplement]. *Lancet Oncol*. 2018b;19(1):65-75.

Venclexta® [package insert]. AbbVie, Inc. 2018.

Respectfully submitted,

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