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NCCN Guidelines Panel: B-Cell Lymphomas (BCL) Panel

Based on the NCCN open unsolicited request for data, on behalf of TG Therapeutics, Inc., I respectfully request the NCCN B-Cell Lymphomas Panel to review the enclosed clinical data and recent FDA approval for the inclusion of UKONIQ™ (umbralisib), in addition to the prior submission of clinical data on 1/22/2021, for the treatment of relapsed or refractory Marginal Zone Lymphoma (MZL) in the BCL Guidelines.

FDA Clearance: We are pleased to inform you that on 2/5/2021 umbralisib was FDA approved for the following indications:

- The treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen
- The treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy

Both indications are approved under accelerated approval based on overall response rate (ORR); continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Specific Changes: We respectfully request consideration of the following changes:

v1.2021 BCL Guidelines

In **MZL-A 2 of 4** (page 46)	Second-line and Subsequent Therapy	Add "**Umbralisib**" under "**Preferred regimens**"
	Second-line and Subsequent Therapy for Elderly or Infirm	Add "**Umbralisib**" under "**Preferred regimens"**

Rationale: Umbralisib is the first and only kinase inhibitor of PI3Kδ and CK1ε and is approved by the FDA in R/R MZL. Umbralisib has a more than 1000-fold greater selectivity for PI3Kδ compared to the α- and β- isoforms, and is more than 200-fold more selective for PI3Kδ relative to PI3Kγ. CK1ε has been implicated in the pathogenesis of cancer cells, including lymphoid malignancies, and is an important regulator of oncogene translation (c-myc, Cyclin D1 and Bcl-2) [please see references #3 Deng, et al and #4 Maharaj, et al for additional information on the mechanism of action of umbralisib]. In kinase profiling, umbralisib is highly and uniquely specific for the delta isoform of PI3K in contrast to other PI3k inhibitors (copanlisib, duvelisib, and idelalisib) currently not approved for R/R MZL [please see references #1 Zinzani, et al].

The safety and efficacy of umbralisib were evaluated in a single-arm cohort of UNITY-NHL, an open-label, multi-cohort phase 2b study. The MZL cohort evaluated umbralisib 800 mg in 69 patients with MZL who had received at least one prior anti-CD20 containing regimen (extranodal (N=38), nodal (N=20), and splenic (N=11)). Median age was 67 (34-88), and median prior number of therapies was 2 (1-6). With a median follow-up of 20.3 months (15 – 28.7), the primary endpoint of ORR by Independent

Review Committee (IRC) was 49% with 16% CR and 33% PR. Median duration of response was not reached (9.3 – NE). The median time to response was 2.8 months (1.8 - 21.2). ORR was 44.7%, 60.0%, and 45.5% for the three MZL sub-types (extranodal, nodal, and splenic, respectively).

The Prescribing Information does not contain a boxed warning; selected Warnings and Precautions include infections, neutropenia, diarrhea/non-infectious colitis hepatotoxicity, and severe cutaneous reactions.

The safety of umbralisib was evaluated in a pooled safety population that included 221 patients with MZL (37%) and FL (63%) enrolled in four clinical trials, including the UNITY-NHL trial, who received umbralisib 800 mg. Among these 221 patients, 60% were exposed for 6 months or longer and 34% were exposed for greater than one year. Serious adverse reactions occurred in 18% of patients, of which those that occurred in ≥2% of patients were diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Fatal adverse reactions occurred in <1% of patients who received umbralisib. Permanent discontinuation of umbralisib due to an adverse reaction occurred in 14% of patients and dose interruptions due to an adverse reaction occurred in 43% of patients. The most common (≥15%) adverse reactions, including laboratory abnormalities, were increased creatinine, diarrhea-colitis, fatigue, nausea, neutropenia, transaminase elevation, musculoskeletal pain, anemia, thrombocytopenia, upper respiratory tract infection, vomiting, abdominal pain, decreased appetite, and rash. For additional information on the safety profile of umbralisib please see reference #5 Davids, et al, for a separate integrated safety analysis of umbralisib across hematologic clinical trials.

The following manuscripts, congress presentations, and FDA Prescribing Information are submitted in connection with this request.

1. Zinzani, P L, et al. “Umbralisib, a PI3Kδ/CK1ε dual inhibitor demonstrates marked clinical activity in patients with relapsed or refractory indolent non-Hodgkin lymphoma: Results from the Phase 2 global UNITY-NHL trial”. Abstract 2934, ASH Annual Meeting 2020.
2. UKONIQ (umbralisib) package insert. Edison, NJ: TG Therapeutics, Inc. 2021.
3. Deng, Changchun et al. “Silencing c-Myc translation as a therapeutic strategy through targeting PI3Kδ and CK1ε in hematological malignancies.” Blood vol. 129,1 (2017): 88-99. doi:10.1182/blood-2016-08-731240
4. Maharaj, Kamira et al. “The dual PI3Kδ/CK1ε inhibitor umbralisib exhibits unique immunomodulatory effects on CLL T cells.” Blood advances vol. 4,13 (2020): 3072-3084. doi:10.1182/bloodadvances.2020001800
5. Davids MS, et al. “Long Term Integrated Safety Analysis Of Umbralisib (TGR-1202), A PI3Kδ/Ck1εInhibitor With A Differentiated Safety Profile, In Patients With Relapsed/Refractory Lymphoid Malignancies.” 23rd European Hematology Association Congress; June 14-17, 2018; Stockholm, Sweden.

Thank you for the consideration, if you have any questions please do not hesitate to reach out.

Sincerely,
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