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

On behalf of AbbVie and Genentech, we respectfully request the NCCN Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Guideline Panel to consider the enclosed long-term safety and efficacy data from the full publication of the CLL14 trial evaluating Venclexta® (venetoclax) with Gazyva® (obinutuzumab) (VenG) in first-line (1L) CLL and the congress presentation of the MURANO trial evaluating venetoclax with Rituxan® (rituximab) (VenR) in relapsed or refractory (R/R) CLL. New safety data from the CLL14 trial and real-world data on sequencing of CLL treatments following venetoclax are also included. This submission includes the full publication of the 3-year data for CLL14 and replaces the previous submission sent on January 6, 2020.

Specific Changes:

1. Request update of venetoclax + obinutuzumab preferred regimen to category 1, in Suggested Treatment Regimens for First-line Therapy in CLL/SLL without del(17p)/*TP53* mutation section (CSLL-D 1 of 6) based on additional VenG data in 1L CLL/SLL.
2. Consider inclusion of debulking approaches with obinutuzumab ± bendamustine in the Special Considerations for The Use of Small-Molecule Inhibitors section (CSLL-F 5 of 5).
3. Consider inclusion of data on responses to therapies post treatment with venetoclax in the Special Considerations for The Use of Small-Molecule Inhibitors section (CSLL-F 5 of 5).

FDA Clearance:

- **Venclexta® (venetoclax)** is approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with CLL/SLL.
    - Please refer to Venclexta® (venetoclax) prescribing information for full FDA-approved indications and safety information, available at: https://www.rxabbvie.com/pdf/venclexta.pdf.

- **Gazyva® (obinutuzumab) in combination with Leukeran® (chlorambucil)** is approved by the US FDA for the treatment of patients with previously untreated CLL.
    - Please refer to Gazyva® (obinutuzumab) prescribing information for full FDA-approved indications and safety information, available at: https://www.gene.com/download/pdf/gazyva_prescribing.pdf.

- **Rituxan® (rituximab)** is approved for the treatment of patients with CLL.
    - Please refer to Rituxan® (rituximab) prescribing information for full FDA-approved indications and safety information available at: https://www.gene.com/download/pdf/rituxan_prescribing.pdf

Clinical Data

Thirty-six-month follow-up data from the Phase 3 randomized, controlled CLL14 trial in adult, treatment-naïve patients with comorbidities and 1L CLL who have been off treatment for at least 2 years after 1-year fixed treatment with VenG were recently published in Lancet Oncology.[1] Results showed that after 2 years off therapy (39.6 months of median follow up), patients who received VenG had a significantly longer progression free survival (PFS) rate than patients who received chlorambucil plus obinutuzumab (GClb) (hazard ratio [HR] 0.31: 95% confidence interval [CI], 0.22 – 0.44; p<0.0001). MRD negativity rates in the peripheral blood in the intent-to-treat population 3 months after end of treatment (EOT) were achieved in 76% (163/216) of patients in the VenG arm and 35% in the GClb arm (76/216) (p<0.0001). At follow-up month 18, almost 50% of patients remained MRD undetectable in the VenG arm. Median overall survival (OS) had not been reached in either treatment group at the time of data cutoff (HR 1.03, 95% CI 0.60–1.75; p=0.92). There were no significant changes in Grade 3/4 adverse events (AEs).

Similarly, a recently presented 48-month update from the MURANO trial where patients with R/R CLL/SLL received 2 years fixed-treatment with VenR, data showed that at 2 years post-EOT, patients who received VenR (n=194) had an investigator-assessed PFS rate of 57.3% (95% CI 49.4-65.3) versus 4.6% (95% CI 0.1-9.2) in the bendamustine + rituximab (BR; n=195) arm (HR 0.19, 95% CI 0.14-0.25; p<0.0001).[2] After a median 22 months off therapy (range 1-25 months), 95 patients who completed the fixed 2 years of venetoclax therapy remained progression-free. The 24-month post treatment cessation PFS among patients who were MRD negative in peripheral blood upon completion of 2 years fixed-treatment with venetoclax was 83.9% (95% CI 72.9-94.9). OS rates were also maintained: VenR 4-year OS rate of 85.3% versus BR 66.8% (HR: 0.41, 95% CI 0.26-0.65; p<0.0001). This benefit in OS seen with VenR occurred despite a high percentage of patients (79% [81/103]) in the BR arm receiving additional novel targeted therapies post PD. No new Grade 3/4 or serious AEs were seen after 48-months follow-up.

Further evaluation of VenG and TLS prevention and management was assessed in a Phase 3b trial in an outpatient community setting.[3] The impact of obinutuzumab ± bendamustine debulking before venetoclax treatment was evaluated for reduction of tumor burden and TLS risk in patients with 1L CLL/SLL who had a medium to high tumor burden. During the debulking stage, patients were permitted to receive up to 6 28-day cycles; disease restaging was conducted every 2 cycles. As of September 19, 2019, 79 patients completed the debulking regimen and were dosed with venetoclax: 71% (68/96) of patients debulked with obinutuzumab, and 29% (28/96) received obinutuzumab + bendamustine. After 2 cycles of debulking with obinutuzumab ± bendamustine, TLS risk decreased in the majority of evaluable patients, 68/78 (87%) of which had a low TLS risk (obinutuzumab only, n=51; obinutuzumab + bendamustine, n=17). Furthermore, after 2 cycles of debulking, 100% (79/79) of evaluable patients had an absolute lymphocyte count reduced to <25 x 10^9/L. In the obinutuzumab arm, an additional 4 patients were downgraded to low-risk TLS after cycle 4, and another patient after cycle 6. In the obinutuzumab + bendamustine arm, an additional 2 patients were downgraded to low-risk TLS after cycle 4. Eight AEs of TLS were reported during the debulking phase, 6 of which were clinical TLS (obinutuzumab alone, n=2; obinutuzumab +

bendamustine, n=4). One report of clinical TLS was observed during the venetoclax phase in a low-risk patient who, at baseline, had high TLS risk and renal insufficiency, underlining the importance of multifactorial risk assessment prior to venetoclax initiation. The study demonstrated that debulking with obinutuzumab ± bendamustine prior to initiating venetoclax decreased the TLS risk burden and reduced the need for hospitalization.

Sequencing Post Venetoclax

Outcomes to therapy post-venetoclax were included in the 48-month update from the MURANO trial.[2] Patients in the VenR arm who received subsequent therapy (eg, BTKi, PI3Ki, Ven, CIT) after progression achieved an objective response rate (ORR) of 64.3% (complete response [CR]/CR with incomplete bone marrow recovery [CRi]=7.1%; partial response [PR]/nodal partial response [nPR]=57.1%). In those evaluable patients who received ibrutinib post venetoclax, the response rate was 100% (10/10).

In addition, recently published real-world studies evaluated treatment sequencing patterns and responses to treatments following venetoclax in patients with CLL and/or SLL.[4,5] Both studies included patients who received either mono- or combination therapy with venetoclax. In the study by Mato and colleagues, 101/355 patients (28.5%) received venetoclax in at least one line of therapy.[4] In patients who had a subsequent line of therapy following venetoclax (n=23), the overall response was 60.8% (CR, 21.7%; PR, 39.1%). In a second study, by Brown and colleagues, investigators focused on the use of ibrutinib post-venetoclax in ibrutinib-naïve patients, evaluating efficacy and safety outcomes (N=27).[5] Best response in patients treated with venetoclax in any line of therapy was 88.5% (CR, 15.4%; PR, 73.1%). In patients treated with ibrutinib post-venetoclax, the ORR was 56% (CR, 4.0%; PR, 52.0%). There were no new safety signals for ibrutinib when used following venetoclax.

In summary, fixed-treatment duration venetoclax-based regimens demonstrated a sustained PFS with deep and durable responses off treatment for up to 2 years, across lines of therapy. Debulking, together with standard risk mitigation measures decreased TLS risk and the need for hospitalization. Furthermore, use of venetoclax in earlier lines of therapy showed positive outcomes for patients who received subsequent therapy to venetoclax.

References

1. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21:1188-1200.
2. Seymour JF, Kipps TJ, Eichhorst BF, et al. Four-year analysis of MURANO study confirms sustained benefit of time-limited venetoclax-rituximab (VenR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Presented at the 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL. Oral presentation.
3. Sharmon J, Andorsky D, Melear J, et al. Debulking eliminates need for hospitalization prior to initiating frontline venetoclax therapy in previously untreated CLL patients: a phase 3b study. Poster presented at the 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL.
4. Mato AR, Sail K, Yazdy MS, et al. Treatment sequences and outcomes of patients with CLL treated with venetoclax and other novel agents post introduction of novel therapies. Poster presented at the 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL.

5. Brown JR, Davids, MS, Chang JE, et al. Outcomes of ibrutinib (Ibr) therapy in Ibr-naïve patients with chronic lymphocytic leukemia (CLL) progressing after venetoclax (Ven). Poster presented at the 61st American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL.

Respectfully submitted,

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