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NCCN Guidelines Panel: B-Cell Lymphomas

BeiGene, Ltd., respectfully requests that the NCCN B-Cell Lymphomas Guidelines Panel review the enclosed materials and consider revising the Guidelines.

We appreciate the thoughtful collective efforts required to update the NCCN B-Cell Lymphoma Guidelines and the inclusion of BRUKINSA™ (zanubrutinib) as a preferred second-line therapy option for the treatment of mantle cell lymphoma.

We observed in your recent update that the NCCN recommends considering infection prophylaxis with the use of zanubrutinib. There is, however, no mention of infection risk or the potential need for prophylaxis in the listings for other Bruton's tyrosine kinase (BTK) inhibitors, although the warning about infection risk is class labeling. We have received feedback that the difference in emphasis in the guidelines is creating a misperception of differences in actual clinical risk and resulting in varying levels of clinical concern for the risk of infection across the BTK inhibitor class.

Specific Change

We respectfully request one of the following changes:

(1) The addition to the Guidelines of the rates of infection and the need to consider prophylaxis for all three BTK inhibitors, for parity in risk communication across the class.

OR

(2) The removal of the following information from the zanubrutinib listing under Special Considerations for the Use of Small Molecule Inhibitors (NHODG-E):

Infections: Grade 3 or higher infections occurred in 23% of patients treated with zanubrutinib monotherapy. Consider prophylaxis for herpes simplex virus, PJP, and other infections according to standard of care in patients who are at increased risk for infections.

FDA Clearance

On November 14, 2019, zanubrutinib was approved by the Food and Drug Administration (FDA) for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.[1] This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Rationale

Infection risk and the need to consider infection prophylaxis is a class warning that applies to all BTK inhibitors according to their respective FDA-approved labels; the full prescribing information is cited in the NCCN B-Cell Lymphoma Guidelines as the reference for the Special Considerations for the Use of Small Molecule Inhibitors.

The prescribing information for each of the three current FDA-approved BTK inhibitors includes a warning/precaution regarding the risk of infection and need to consider infection prophylaxis in select patients. The Special Considerations for the Use of Small Molecule Inhibitors section of the B-Cell Lymphoma Guidelines

lists infection as a risk only for zanubrutinib and not for other drugs in the BTK inhibitor class. For your reference, the completed infection warning from each BTK inhibitor label is excerpted below (**bold** emphasis added).

Ibrutinib[2]	Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA in clinical trials [see Adverse Reactions (6.1, 6.2)]. **Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jirovecii pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.** Monitor and evaluate patients for fever and infections and treat appropriately.
Acalabrutinib[3]	Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE. Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. **Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, Pneumocystis jiroveci pneumonia, Epstein-Barr virus reaction, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for infections.** Monitor patients for signs and symptoms of infection and treat promptly.
Zanubrutinib[1]	Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred. **Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections.** Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Questions from healthcare professionals to BeiGene suggest that the difference in the description of infection risk in the Guidelines is interpreted in clinical practice as a true difference in clinical risk between drugs in the BTK inhibitor class. Anecdotal reports suggest that this misperception may be inadvertently propagated in institutional practice guidelines, formulary restrictions, and clinical pathways. Please consider the potential risk of inadequate infection prophylaxis and inadequate clinical suspicion for infection in patients treated with BTK inhibitors other than zanubrutinib that could result.

References

1. Brukinsa (zanubrutinib) [package insert]. BeiGene USA, Inc; San Mateo, CA. November 2019.
2. Imbruvica (ibrutinib) [package insert]. Pharmacyclics LLC; Sunnyvale, CA. November 2019.
3. Calquence (acalabrutinib) [package insert]. AstraZeneca Pharmaceuticals LP; Wilmington, DE. November 2019.