Discussion of zanubrutinib (BRUKINSA®) for Adult Patients with CLL/SLL

Presenter: Kirollos S. Hanna, PharmD, BCPS, BCOP, FACCC | Minnesota Oncology

I. The BRUKINSA® Difference

1. Demonstrated efficacy safety across 5 B-cell malignancies
2. Consistent benefit across patient subgroups
3. High potency and affinity for Bruton's tyrosine kinase (BTK), resulting in sustained inhibition over 24 hours
4. Unmatched dosing flexibility with once-daily (QD) or twice-daily (BID) options
5. BRUKINSA® is an oral treatment for long-term management of chronic lymphocytic leukemia (CLL)

II. Important Safety Information

Warnings and Precautions

- **Hemorrhage**
  - ≥ Grade 3 hemorrhagic events occurred in < 3.8% of patients
  - Not contraindicated in patients receiving anti-platelet or anti-coagulation; however, closer monitoring for bleeding or bruising is required
  - For surgical or dental procedures, hold BRUKINSA® for 3-7 days pre- and post- procedure to allow adequate washout and platelet recovery
- **Infections**
  - ≥ Grade 3 infections occurred in 26% of patients; pneumonia was most common (7.9%)
  - No widely adopted standard for infectious prophylaxis
  - Certain aggressive B-cell malignancies or prior treatment history may increase infection risk
  - In CLL, most patients are not preemptively placed on prophylaxis
- **Cytopenias**
  - Neutropenia (21%)
  - Thrombocytopenia (8%)
  - Anemia (8%)
- **Second Primary Malignancies**
  - Occurred in 14% of patients; majority were non-melanoma skin cancers (8%)
- **Cardiac Arrhythmias**
  - Class-related toxicity due to off-target kinase activity
  - Atrial fibrillation/flutter were reported in 4.4% of patients
  - ≥ Grade 3 atrial arrhythmias occurred in 1.9%
  - ≥ Grade 3 ventricular arrhythmias reported in 0.3%
  - Monitor for signs and symptoms of cardiac arrhythmias and manage appropriately
  - Pre-existing cardiac arrhythmias are not a contraindication; ensure rhythm and rate are well controlled and that patients remain adherent to cardiac therapies
- **Hepatotoxicity**
  - Typically Grade 1 or 2
  - Monitor hepatic function during treatment
- **Embryo-Fetal Toxicity**
  - Use effective contraception while on therapy and for one week after the last dose
- **Adverse Reactions**
  - Most common adverse reactions (≥30%), including laboratory abnormalities:
    - Decreased neutrophil count (51%)
    - Decreased platelet count (41%)
    - Upper respiratory tract infection (38%)
    - Hemorrhage (32%)
    - Musculoskeletal pain (31%).

- **Drug Interactions:**
  - **CYP3A Inhibitors:**
    - Strong CYP3A4 inhibitors → reduce dose to 80mg QD
    - Moderate CYP3A inhibitors → reduce BRUKINSA® dose to 80mg BID
  - **CYP3A Inducers:**
    - Avoid strong or moderate CYP3A inducers
    - Dose adjustment may be required with moderate CYP3A inducers
- **Specific Populations**
  - **Severe hepatic impairment:** Recommend 80mg orally BID

III. BTK Pathway

- B-cell receptor (BCR) is a transmembrane receptor that control B-cell development and regulation
- BCR signaling activates downstream signaling pathways via BTK
- BTK signaling promotes survival of both normal and malignant B-cells

IV. Pharmacokinetic & Pharmacodynamic Differences Among BTK Inhibitors (BTKis)

BTK Inhibition

- BRUKINSA®:
  - QD dosing:
    - 100% BTK inhibition in peripheral blood mononuclear cells (PBMCs) over 24 hours
    - 94% BTK inhibition in lymph nodes over 24 hours
  - BID dosing:
    - 100% BTK inhibition in PBMCs and lymph nodes over 24 hours
      - *Clinical significance of 100% inhibition has not been established*
- Ibrutinib
  - QD dosing: >90% BTK inhibition in PBMCs over 24 hours
- Acalabrutinib
  - BID dosing: ≥ 95% BTK inhibition in PBMCs over 12 hours

BTK Binding Affinity (IC_{50}, nM)

- IC_{50} (nM) reflects the mean inhibitory concentration required to achieve 50% BTK inhibition
  - BRUKINSA®: 0.5 ± 0.0
  - Ibrutinib: 1.5 ± 0.2
  - Acalabrutinib: 5.0 ± 1.0
- BRUKINSA® demonstrates the highest affinity for BTK receptor in comparison to ibrutinib and acalbrutinib

Sustained BTK Coverage

- BRUKINSA® maintains concentration levels above IC_{50} for 24 hours with either QD or BID dosing
  - Ibrutinib (QD): ~17 hours below IC_{50}
  - Acalabrutinib (BID): ~19 hours below IC_{50}

V. National Comprehensive Cancer Network® (NCCN®) Recommendations

- **NCCN® preferred treatment option for patients with CLL is BRUKINSA®:**
  - **CLL without del(17p)/TP53**
    - First-line: Category 1
    - Second-line: Category 1
  - **CLL with del(17p)/TP53**
    - First-line: Category 2A
      - *Category 2A represents the highest recommendation currently available in this setting*
    - Second-line: Category 1

VI. Key Clinical Trials: ALPINE and SEQUOIA

SEQUOIA (Study 304)

- Global Phase 3, randomized, open-label, multicenter trial in treatment-naïve CLL/SLL
- Sustained progression free survival (PFS) at ~5 years in patients regardless of del(17p) status

Cohort 1 (without del[17p], n=479):

- BRUKINSA® 160mg BID vs bendamustine + rituximab (BR) (≤6 cycles)
- Lower rates of nausea, fatigue, dose reductions and discontinuations due to adverse events (AEs)
- ≥ Grade 3 infection rates remined consistent over time
- Low and stable rates of atrial fibrillation/flutter
- 70% of patients remained on BRUKINSA® at 5 years

Cohort 2 (with del[17p], n=110):

- BRUKINSA® 160mg BID until progressive disease or unacceptable toxicity
- Consistent PFS outcomes
- Dose reductions (10%) and discontinuations (5%) due to AEs
- 62% of BRUKINSA® patients remained on treatment at 5 years

ALPINE (Study 305)

- Phase 3, randomized, open-label, multicenter trial conducted in relapsed/refractory CLL/SLL who received ≥1 prior systemic therapy
- Long-term follow-up: ~3.5 years

Study Design

- BRUKINSA® 160mg BID (n=327) vs ibrutinib 420mg QD (n=325)

Key Outcomes

- Superior overall response rate (ORR): 92% vs 86% at 1 year
- Superior PFS regardless of mutation status
- Comparable rates of hypertension
- Lower dose reductions and discontinuations due to AEs
- Fewer cardiac events; no fatal cardiac events with BRUKINSA® vs six with ibrutinib

VII. Tolerability in BTKi-Intolerant Patients (Study 215)

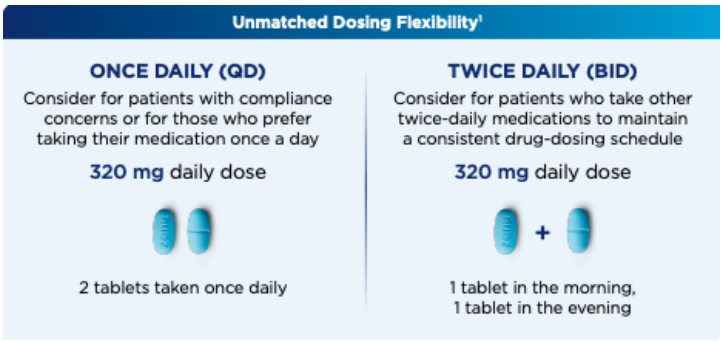
- Ongoing Phase 2 exploratory study (n=92), with data from long-term update of only patients with CLL/SLL (n=71)
- Patients intolerant to acalabrutinib (n=27) or ibrutinib (n=44) were given BRUKINSA® 160mg BID or 320mg QD
- ~Two-thirds of prior intolerance events did not recur with BRUKINSA®
- No AEs occurred at a higher grade
- 94% or patients with BRUKINSA® maintained or improved response

VIII. Additional FDA Approved Indications

- **Waldenstrüm Macroglobulinema (WM):** Category 1 preferred treatment option for front-line and previously treated WM
- **R/R Mantle Cell Lymphoma (MCL):** Category 2A preferred treatment option for second line and subsequent therapy for MCL
- **R/R Marginal Zone Lymphoma (MZL):** Category 2A preferred treatment option for second line and subsequent therapy after at least one prior anti-CD20 mAB-based regimen for MZL
- **R/R Follicular Lymphoma (FL):** In combo with obinutuzumab, is a Category 2A recommended treatment option for third line and subsequent therapy for FL

IX. Dosing & Administration

- Only BTKi with flexible QD or BID dosing
- Reformulated from 80mg capsules to 160mg tablets
- 50% reduction in pill burden
- No dose exchange or new prescription required for dose reductions



Adverse Reactions Requiring Dose Modification

- ≥ Grade 3 non-hematological toxicities
- Grade 3 febrile neutropenia
- Grade 3 thrombocytopenia with significant bleeding
- Grade 4 neutropenia or thrombocytopenia lasting >10 consecutive days

Dose Modifications for ≥ Grade 3 Adverse Reactions

Starting Dose	1st Occurrence	2nd Occurrence	3rd Occurrence	4th Occurrence
Start at 320mg Total dose (Two 160mg tablets)	No dose change	Reduce to 160mg total dose	Reduce to 80mg total dose	Discontinue

**Resume therapy once toxicity has resolved to ≤ Grade 1 or baseline*

X. myBeOne Support

- Assisting in providing support for eligible patients after BRUKINSA has been prescribed: [myBeOneSupport]
  - Simplifying access
  - Educating patients and caregivers about their treatment and disease
  - Connecting patients to independent organization that offer day-to-day living support

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