ASH 2023 Comes to You!

January 29, 2024

1:00 PM PT, 2:00 PM MT
3:00 PM CT, 4:00 PM ET
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Speakers

**Speaker**
Nicole Lamanna, MD
Associate Professor of Clinical Medicine, Department of Medicine, Division of Hematology Oncology
Columbia University Medical College

**Moderator and Speaker**
Brian Koffman, MDCM (retired), MS Ed
Executive Vice President and Chief Medical Officer
CLL Society

**Welcome**
Robyn Brumble, MSN, RN
Director of Scientific Affairs and Research
CLL Society
First-in-Human Phase 1 Trial of NX-2127

First-in-Human Phase 1 Trial of NX-2127, a First-in-Class Bruton's Tyrosine Kinase (BTK) Dual-Targeted Protein Degrader with Immunomodulatory Activity, in Patients with Relapsed/Refractory B Cell Malignancies (Dr. Alexey Danilov)

• BTK inhibitors (BTKi) have revolutionized the treatment of CLL, but emerging BTK resistance mutations as well as the importance of scaffolding function of BTK, present a need for new approaches

• NX-2127 is an oral, first-in-class, dual-function small molecule degrader that combines BTK degradation with the immunomodulatory activity
First-in-Human Phase 1 Trial of NX-2127

How BTKi and Degraders Work

Covalent BTK inhibitor
Examples are acalabrutinib, ibrutinib, and zanubrutinib

BTK inhibitor blocks signaling by nonvariant BTK
BTK inhibitor does not block signaling by variant BTK

Noncovalent BTK inhibitor
Pirtobrutinib is a noncovalent BTK inhibitor that binds reversibly to the ADP-binding pocket

Noncovalent BTK inhibitor inhibits both nonvariant (C) and variant (S) BTK

BTK degrader
Linker (drug)
Ubiquitin ligase
Polyubiquitination
Proteasome degradation

n engl j med 389;1 nejm.org July 6, 2023
First-in-Human Phase 1 Trial of NX-2127

• 47 patients were treated with NX-2127 at once-daily doses of 100 mg (n=28), 200 mg (n=10), and 300 mg (n=9)
• 66% were male. Median age of 74 (range 50–92) years
• 29 patients were treated for CLL/SLL
• Heavily pretreated CLL/ SLL with median of 5 prior therapies
  • 100% prior BTKi, 76% BCL2i, most resistant to BTKi

Adverse events:
• Fatigue (48.9%) low neutrophils (38.3%), hypertension (14.9%), anemia (12.8%), confusion (17.7%), atrial fibrillation (12.8%)
First-in-Human Phase 1 Trial of NX-2127

CLL Results:
• 9 partial remissions, 11 stable disease and 4 progressive disease

Conclusions:
• Go forward dose is 100mg for CLL and 300 mg for MCL & DLBCL.
• Promising in a difficult to treat population, but trial is on a partial hold now not due to safety but due to manufacturing issues
• NX-5948 is a similar degrader in open trials with only BTK activity that now has FDA fast track designation for CLL/SLL
Clinical Outcomes with Venetoclax-Based Treatment Regimens in CLL

Clinical Outcomes with Venetoclax-Based Treatment Regimens in Patients with Chronic Lymphocytic Leukemia (CLL) (Dr. Paul Hempel)

- Goal was to identify factors that impact outcomes of venetoclax for patients with CLL treated at a tertiary center (Mayo Clinic)

- Studied:
  - Frontline use
  - Relapsed with no prior BTKi exposure
  - Relapsed with prior BTKi exposure
Clinical Outcomes with Venetoclax-Based Treatment Regimens in CLL

Results:

• 155 patients were identified between 2012 and 2023 at Mayo:
  • 55 front line therapy (in combination with obinutuzumab)
  • 100 relapsed CLL
    • 17 had relapsed/BTKi-naïve CLL
    • 83 had previously received BTKi, 55 with progression after BTKi, relapsed/BTKi-exposed

• The median treatment free survival (TFS) for the overall cohort was 39.0 months. The median overall survival (OS) was 54.6 months.

• Among patients treated with venetoclax as first-line therapy (n=55), the 2-year TFS and 2-year OS rates were both 91%

• MRD testing was performed in 28 patients and was uMRD in 23 (82%) patients (only PB assessed, n=7; only BM assessed, n=2; PB and BM assessed, n=14)
Clinical Outcomes with Venetoclax-Based Treatment Regimens in CLL

Results:

• Patients treated with venetoclax in the relapsed/BTKi-naïve setting (n=17), the 2-year TFS rate was 73% and the 2-year OS rate was 100%. MRD testing was performed in 7 patients and was uMRD in all 7.

• Among relapsed/BTKi-exposed venetoclax-treated patients (n=83), the median TFS was 26.9 months and the median OS was 39.4 months.

• The median TFS for patients with (n=55) and without (n=28) prior disease progression on prior BTKi were 22.3 and 42.3 months, respectively. Median TFS with venetoclax monotherapy (n=30) was 24.0 months, venetoclax in combination with rituximab (n=37) was 26.9 months, and venetoclax in combination with obinutuzumab (n=16) was 39.0 months.
Clinical Outcomes with Venetoclax-Based Treatment Regimens in CLL

Results:

• TP53 disruption, unmutated IGHV genes, older age, complex karyotype (CK; defined as more than 3 chromosomal aberrations on CpG stimulated karyotype), and disease progression on prior BTKi were associated with shorter TFS in the overall cohort. TP53 disruption, older age, CK, and disease progression on prior BTKi were associated with shorter OS in the overall cohort.

Conclusions:

• Patients with BTKi-exposed CLL, particularly those with prior disease progression on BTKi, had worse outcomes. CK as one of the most important baseline predictors of adverse TFS and OS.
CAR-T for Richter’s Transformation: A Retrospective Study

Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy for Richter’s Transformation: An International Multicenter Retrospective Study (Dr. Adam S Kittai)

- CAR-T has drastically improved outcomes for patients with diffuse large B-cell lymphoma (DLBCL), but Richter’s Transformation (RT) has been mostly excluded from trials
- RT is when CLL transforms into a more aggressive lymphoma, usually DLBCL
CAR-T for Richter’s Transformation: A Retrospective Study

Results:

• 62 patients were included. Median age was 65
• Median prior therapies for both CLL and RT was 2 each
• 84% had received a prior BTKi or a BCL2i (venetoclax)
• Ki-67 was 80% which means the cancer was growing very fast
• Medium SUV was 15: this is a high measure of metabolic activity seen on PET scan. Median lymph node size was 3.8 cm
• Median wait from apheresis (special blood draw to get the T cells) to receiving CD19 CART infusion was 33 days
• 84% had “bridging therapy” or treatment to control CLL while waiting
CAR-T for Richter’s Transformation: A Retrospective Study

Results:

• Overall response rate was 65%, with 29 (47%) and 11 (18%) pts attaining complete response (CR) and partial response (PR), respectively

• After a median follow up of 24.1 months (mos) from CD19 CART infusion, the median progression free survival (PFS) was 4.7 mos and median overall survival (OS) was 8.5 mos

• Median duration of response was 14.5 mos with a median not reached (NR) for pts who achieved a complete remission (CR), but only 2.3 mos for pts who achieved a partial remission (PR)
CAR-T for Richter’s Transformation: A Retrospective Study

Results and Adverse Events:

• 39 pts died:
  • 28 (72%) died due to progression of disease (PD)
  • 11 (28%) died for other reasons including
    • 8 infections (4 COVID)
    • 1 septic shock
    • 1 stroke
    • 1 respiratory failure

• 3 pts in a CR underwent allogeneic stem cell (bone marrow transplant from someone else (ASCT), 2 were alive at last known follow up, 1 died post transplant of progressive disease

• 55 (89%) pts had CRS, with 9 (15%) grade ≥3 events. 43 (69%) pts had neurotoxicities (ICANS), with 23 (38%) grade ≥3 events
CAR-T for Richter’s Transformation: A Retrospective Study

Conclusions:

• Largest cohort studied with RT who received CD19 CART
• Earlier use of CD19 CART in the RT might yield better results
• Follow-up with transplant seems to improve outcomes
• CART combinations with novel agents are in trials now
• RT remains a major unmet need, though these results are better than historical results with chemoimmunotherapy
Pirtobrutinib in Richter Transformation

Pirtobrutinib in Richter Transformation: Updated Efficacy and Safety Results with 18-Month Median Survival Follow-up from the Phase 1/2 BRUIN Study (Dr. William G. Wierda)

• Richter transformation (RT) occurs in up to 10% of CLL patients

• Poor prognosis with no standard of care so often a clinical trial is the best option

• Updated data from the Bruin trial on use of pirtobrutinib in RT
Pirtobrutinib in Richter Transformation

Results:

• Among all pts with RT (N=82) the median age was 67 and the median total number of lines of prior therapy was 4
• Overall response rate (ORR) was 50.0% including complete (13.4%, n=11) and partial (36.6%, n=30) responses
• For 61 pts who received prior covalent BTKi (cBTKi) such as ibrutinib, acalabrutinib, and zanubrutinib), the ORR was 45.9%
• At median follow-up time of 9.7 months, the median duration of response (DoR) for all 82 RT pts was 7.4 months
• Eight pts stopped pirtobrutinib to pursue a ASCT (bone marrow transplant from someone else) with the intent to cure
Pirtobrutinib in Richter Transformation

Adverse Events:
• Low neutrophil count (29.3%, n=24), fatigue (24.4%, n=20) and diarrhea, shortness of breath, low platelet count, and fever (18.3% each, n=15)
• Only 3 had hypertension and 1 had atrial fibrillation
• No one stopped pirtobrutinib due to an adverse event

Conclusions:
• Pirtobrutinib is well tolerated and has some activity in RT
• Better treatments for RT are needed
ASH 2023 Comes to You!

Nicole Lamanna, MD
January 29, 2024
Abstracts:


• 325 Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-up and Subgroup Analysis With/Without Prior BCL2i from the Phase 1/2 BRUIN Study. Woyach J, et al.

Targeted Therapy: FDA Approvals

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Status in CLL/SLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib&lt;sup&gt;1&lt;/sup&gt;</td>
<td>BTK (covalent)</td>
<td>Approved</td>
</tr>
<tr>
<td>Acalabrutinib&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>Approved</td>
</tr>
<tr>
<td>Zanubrutinib&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>Approved</td>
</tr>
<tr>
<td>Venetoclax&lt;sup&gt;4&lt;/sup&gt;</td>
<td>BCL2</td>
<td>Approved</td>
</tr>
<tr>
<td>Pirtobrutinib&lt;sup&gt;5&lt;/sup&gt;</td>
<td>BTK (noncovalent)</td>
<td>December 2023: Approved for patients receiving ≥prior lines of therapy, including a BTKi and a BCL2i</td>
</tr>
</tbody>
</table>
Summarizing the Safety Experience With BTKi

What Are the Implications of Covalent and Noncovalent BTKi Selectivity for Off-Target Effects?

Potential off-target effects include:

- **TEC**
  - Bleeding
  - Cardiac toxicity

- **EGFR**
  - Rash
  - Diarrhea
  - Arthralgia

Less selective BTK inhibitors (eg, ibrutinib) have more off-target effects, which contribute to more toxicity compared with more selective agents. 

CLL SOCIETY
Abstract 202: Alpine Follow-Up Zanubrutinib

ALPINE Study Design

R/R CLL/SLL with ≥1 prior treatment (N=652)

Key Inclusion Criteria
- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- Requires treatment per iwCLL

Key Exclusion Criteria
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

Zanubrutinib 160 mg BID

Ibrutinib 420 mg QD

Stratification factors:
Age, geographic region, refractoriness, del(17p)/TP53

Treatment until disease progression or unacceptable toxicity


Abbreviations: BID, twice daily; CT, computed tomography; MRI, magnetic resonance imaging; QD, once daily; R, randomized.
Patient Disposition At Extended Follow-Up

Randomized (N=652)

Zanubrutinib (n=327)
- Not treated (n=3)
- Discontinued (N=130)
  - AE (n=69)
  - PD (n=51)
  - Withdrawal by patient (n=7)
  - Lost to follow-up/other (n=3)
- Treatment ongoing (n=194; 59%)
  Median Follow-up: 40.3 months

Ibrutinib (n=325)
- Not treated (n=1)
- Discontinued (N=172)
  - AE (n=88)
  - PD (n=62)
  - Withdrawal by patient (n=15)
  - Physician decision (n=6)
  - Lost to follow-up/other (n=1)
- Treatment ongoing (n=152; 47%)
  Median Follow-up: 38.7 months

AE = Adverse Events
PD = Progressive Disease

Zanubrutinib Demonstrates Sustained PFS Benefit Over Ibrutinib

Across arms, median study follow-up was 39 months

Progression Free Survival (PFS): refers to the time from randomization or initiation of treatment to the occurrence of disease progression or death.

Improved PFS Was Demonstrated With Zanubrutinib in Patients With del(17p)/TP53\textsuperscript{mut}

- PFS Events:
  - Zanubrutinib: 31 (41.3%)
  - Ibrutinib: 46 (61.3%)

- HR = 0.52 (95% CI: 0.33, 0.83)

- 2-sided descriptive \( P = 0.0047 \)

Most Common Adverse Events (AE)

- COVID-19 Related\(a,b,c\)
- Neutropenia\(^a\)
- Hypertension\(^a\)
- Upper Respiratory Tract Infection
- Diarrhea
- Arthralgia
- Anemia\(^a\)

\(a\) Pooled MedDRA preferred terms
\(b\) Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.
\(c\) COVID-related deaths (grade 5 AE): 13 (4.0%) with zanubrutinib and 15 (4.6%) with ibrutinib.

Zanubrutinib Continues to Demonstrate a Favorable Cardiac Safety Profile

- Serious cardiac adverse events were lower with zanubrutinib vs ibritinib
  - Atrial fibrillation/flutter (3 vs 13)
  - Ventricular fibrillation/supraventricular tachycardia (0 vs 4)
  - MI/ACS (2 vs 3)

- Fatal cardiac events:
  - Zanubrutinib, n=0 (0%)
  - Ibrutinib, n=6 (1.9%)

<table>
<thead>
<tr>
<th>Cardiac adverse events</th>
<th>Zanubrutinib (n=324)</th>
<th>Ibrutinib (n=324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious cardiac adverse events</td>
<td>11 (3.4)</td>
<td>31 (9.6)</td>
</tr>
<tr>
<td>Cardiac adverse events leading to treatment discontinuation</td>
<td>3 (0.9)</td>
<td>15 (4.6)</td>
</tr>
<tr>
<td>Ventricular extrasystoles</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>1 (0.3)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Cardiac failure acute</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Congestive cardiomyopathy</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; CHF, congestive heart failure; MI, myocardial infarction.

Conclusions:

• Zanubrutinib continues to demonstrate sustained progression free survival (PFS) superiority over ibrutinib in patients with R/R CLL/SLL with over 39 mos of follow-up

• This advantage also seen in patients with 17p del/TP53 mut

• Although similar rates of hypertension between zanubrutinib and ibrutinib, there was still lower rates of other serious adverse events and fewer adverse events leading to treatment discontinuation or dose reduction

• Similar to ELEVATE-RR study (acalabrutinib vs ibrutinib), less cardiac issues and likely that most patients initiating a BTKi for first time will likely be started on one of these newer BTKis over ibrutinib
How Noncovalent BTK Inhibitors Overcome Resistance

Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, and Zanubrutinib) Require WT BTK for Activity

Noncovalent BTK Inhibitors (Pirtobrutinib/Nemtabrutinib) Are Potent Against Both WT and C481-Mutated BTK

Ibrutinib Covalently bound to C481

C481 Does not require C481 to bind to the kinase domain

BTK inhibition, regardless of BTK mutation

WT = wild type or no mutations
Pirtobrutinib: Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment

MCL = mantle cell lymphoma
cBTKi = covalently binding BTKi (ibrutinib, acalabrutinib and zanubrutinib)
BCL2i (only venetoclax now)
BRUIN: Longer (~30 Month) Follow-Up Demonstrates Durable Efficacy of Pirtobrutinib After cBTKi Therapy

... regardless of prior BCL2i status

ORR for all post-cBTKi patients: 72%

Median follow-up 22 months

ORR of 83.1% for BCL2i-N patients

Median follow-up 15.9 months

ORR of 79.7% for BCL2i-E patients

ORR = overall response rate

Pirtobrutinib PFS with Prior cBTKi, with or without Prior BCL2i

**BCL2i-N (naïve)**
- Median Follow-up: 23.0 months
- 95% CI: 19.6-28.4
- Median 79/154
- Events/Total: 87.1%

**BCL2i-E (exposed)**
- Median Follow-up: 15.9 months
- 95% CI: 13.6-17.5
- Median 91/128
- Events/Total: 82.2%

Conclusions:

• Pirtobrutinib is a very active agent in patients previously exposed to prior covalent BTK inhibitors
• Efficacy also seen in patients who received *both* covalent BTK inhibitors as well as BCL2 inhibitors
• Now FDA approved for this indication
• Very well tolerated with longer follow-up with low rates of cardiac events
• New studies combining pirtobrutinib with BCL2 inhibitors and CD20-monoclonal antibody combinations and in earlier lines of therapy are ongoing
FLAIR: FCR vs I+V: Trial Design

Primary end-point:
To assess whether I+V is superior to FCR in terms of PFS

Key secondary end-points:
Overall survival (OS)
Response incl. MRD
Safety and toxicity

Key Inclusion Criteria:
• Previously untreated CLL requiring therapy by IWCLL criteria
• Considered fit for FCR
• ≤75 years old

Key Exclusion Criteria:
• Prior therapy for CLL; History of Richter’s transformation;
• >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent)
• Symptomatic cardiac failure or angina

Hillmen P, et al. ASH 2023, Abstract #631
Stopping Rules for Ibrutinib + Venetoclax

Testing schedule (Central lab, MRD flow, MRD negative <1 CLL cell in 10^4)

- PB
- B
- FCR
- M

If PB MRD negative repeat after 3 months and then PB and BM at 6 months – if all MRD negative then first PB MRD negative result is time to MRD negativity

Defining treatment duration
- 2 to 6 years Ibrutinib or both ibr+venetoclax
- Double time after MRD negative

Restart Ibrutinib + Venetoclax if becomes MRD positive prior to Year 6

Hillmen P, et al. ASH 2023, Abstract #631
FLAIR: Improved Outcomes With MRD-Directed Ibrutinib-Venetoclax Over FCR in Untreated CLL

Ibrutinib Plus Venetoclax Significantly Improved PFS and OS Compared With FCR in Untreated CLL

In I + V after 2 mo of I, V was added with a 4-week dose escalation and then I + V was given for up to 6 years; duration of I + V was defined by MRD (<1 CLL cell in 10,000 using flow)

PB MRD was assessed regularly

If all were MRD negative, then the duration of I + V was double the time between start of I + V and the initial MRD-negative PB (I + V duration: 2 to 6 years)

Using MRD to direct the duration of I + V maximizes outcome with a PFS of 97.2% at 3 years
iwCLL Response and MRD Stopping Rules

Time to attaining MRD stopping rules in I+V group

<table>
<thead>
<tr>
<th></th>
<th>Complete Response/CRi</th>
<th>Overall Response</th>
<th>BM uMRD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 months</td>
<td>Anytime</td>
<td>9 months</td>
</tr>
<tr>
<td>FCR</td>
<td>49%</td>
<td>71.5%</td>
<td>76.4%</td>
</tr>
<tr>
<td>I+V</td>
<td>59.2%</td>
<td>92.3%</td>
<td>86.5%</td>
</tr>
</tbody>
</table>

Kaplan–Meier estimates of the percentage of patients who had stopped treatment by specific time points are as follows:
- by 24 months, 28.9%
- by 36 months, 58.0%
- by 60 months, 78.4%

Five patients restarted ibrutinib–venetoclax and were alive and progression-free at the last follow-up.

Hillmen P, et al. ASH 2023, Abstract #631
Conclusions:

• MRD-guided ibrutinib–venetoclax was superior to FCR with respect to progression-free survival (97.2% vs. 76.8% at 3 years)

• Overall survival also favored ibrutinib–venetoclax over FCR (98.0% vs. 93.0% at 3 years)

• These results appear better than those in previous studies of ibrutinib monotherapy or venetoclax, as monotherapy or in combination with anti-CD20

• This study raises more questions about what is “time-limited” when utilizing MRD guided approaches to individualize patient care/outcomes. More work to be done….
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Join us for our next webinar on integrative medicine taking place on March 19th.

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