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ASH 2022 Comes to You!

February 9, 2023

12:00 PM PT, 1:00 PM MT,
2:00 PM CT, 3:00 PM ET

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Speakers

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

Speaker
Sameer Parikh, MD
Associate Professor, Hematology
Mayo Clinic

Welcome
Robyn Brumble, MSN, RN
Director of Scientific Affairs and Research
CLL Society

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ASH 2022 Updates

Dr. Brian Koffman

February 9, 2023

Subcutaneous (SC) Epcoritamab in Richter's Syndrome (RS): Early Results from (EPCORE CLL-1)

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Background, Method and Demographics:

- 10 eligible adults with biopsy-proven transformation to CD20+ RS- large B-cell lymphoma (LBCL) with a history of CLL or SLL and no more than 1 prior line of therapy for RS. RS has no good therapies.
- Epcoritamab is a novel SC CD3xCD20 bispecific antibody that has shown clinical efficacy in R/R LBCL.
- Administered 7d in cycles 1–3, 14d in cycles 4–9, and 28d in cycles ≥10 until disease progression or toxicity.

Results:

- Median treatment duration was 2.5 months with 5 (50%) patients receiving ongoing treatment.
- The most common related treatment-emergent AEs (TEAEs) of any grade were Cytokine Release Syndrome (CRS) (90%; all mild), anemia (40%), diarrhea (40%), low phosphate (30%), injection-site reaction (30%), and low platelets (30%). No neurotoxcity (ICANS).
- Two patients died due to disease progression.
- Overall response rate was 60% and a complete response rate was 50%. Most responses are in the 1st 6 weeks.

Conclusions:

- SC epcoritamab has manageable side effects and encouraging early results though the durability of response is not known . The study is ongoing.

CAPTIVATE Study: Outcomes after uMRD with First-Line Ibrutinib (Ibr) Plus Venetoclax (Ven): Placebo Versus Continued Ibr with up to 5 Years

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Methods and Demographics:

- Pts ≤70 y with previously untreated CLL received 3 cycles of Ibr then 13 cycles of combined Ibr + Ven.
- Pts achieving uMRD in both peripheral blood and bone marrow with Ibr + Ven were then randomly assigned 1:1 to double-blinded with placebo (PBO) or single-agent Ibr.
- 164 pts were enrolled to receive combined Ibr + Ven treatment; after completion, 86 pts with uMRD were randomly assigned to PBO or single-agent Ibr.

Results:

- For uMRD pts, median time on study was 56 mo. uMRD was stable year 2 to 3 post randomization.
- The 4-y PFS was 88% and OS was 100% with PBO and 95% and 98% with continued Ibr.
- Efficacy in high-risk subgroups were consistent with the total population.

Conclusion:

- Continuing ibrutinib in those who reach uMRD added no significant benefit.
- Ibr + Ven is an all-oral, once-daily, chemotherapy-free regimen that continues to provide deep, durable clinical responses that can be stopped after a fixed duration.

ALPINE Trial: Zanubrutinib Demonstrates Superior Progression-Free Survival (PFS) Compared with Ibrutinib in R/R CLL/SLL

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Background, Methods and Demographics:

- CLL/SLL is characterized by consecutive relapses so response to therapy ultimately dictates survival.
- 652 patients from 15 countries were randomized to receive zanubrutinib (n=327) or ibrutinib (n=325)
- Demographic and disease characteristics were balanced between zanubrutinib and ibrutinib:
  - Unmutated IGHV [73.1 vs 73.5%]; del(17p) [13.8 vs 15.4%]; TP53 mutated without del(17p) [9.2 vs 7.7%]).
  - Across the study population, median age was 67 and 68 years, respectively.

Results:

- Median PFS was 35.0 months for ibrutinib pts but not reached for zanubrutinib.
- Treatment discontinuation rate was lower with zanubrutinib (26.3%) vs ibrutinib (41.2%) with most due to AEs (16.2 vs 22.8%) or progressive disease (7.3 vs 12.9%).
- Rate of atrial fibrillation/flutter was lower with zanubrutinib compared with ibrutinib (5.2% vs 13.3%).
- There were no deaths due to cardiac disorders with zanubrutinib vs 6 (1.9%) with ibrutinib.
- 48 (14.7%) pts treated with zanubrutinib and 60 (18.5%) treated with ibrutinib had died .

Conclusions:

- First head-to-head comparison suggests zanubrutinib is more efficacious and better tolerated than ibrutinib.

Figure 1: IRC-Assessed Progression-Free Survival (ITT Population)

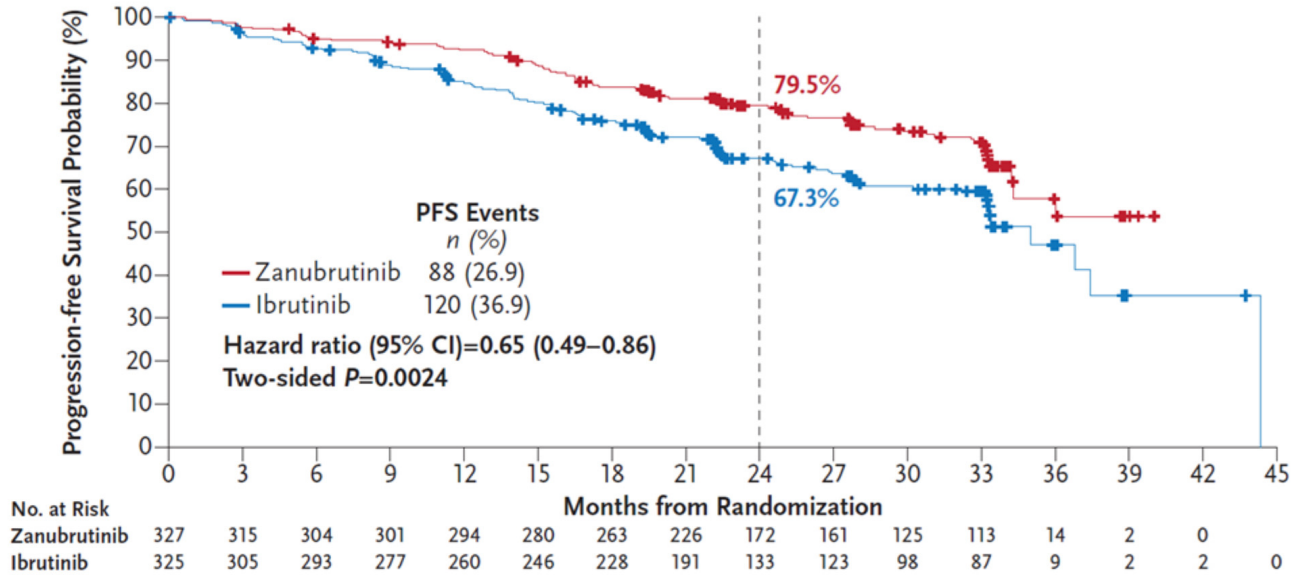
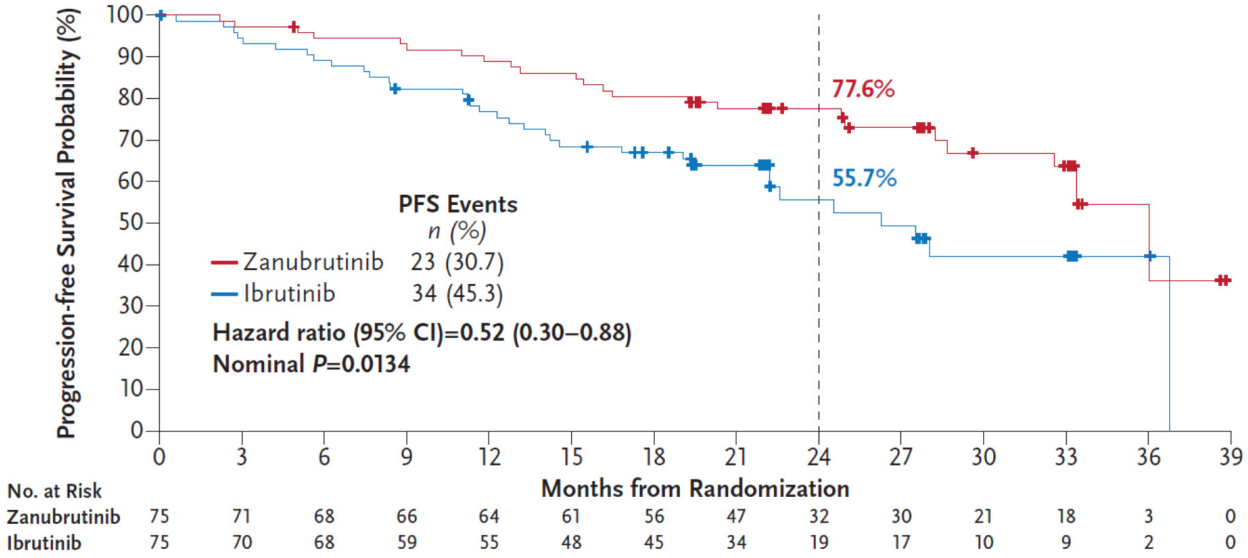


Figure 2: IRC-Assessed Progression-Free Survival in Patients with del(17p)/TP53 mutation



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Contribution of Obinutuzumab (O) to Acalabrutinib (A) to Progression Free Survival (PFS) & Overall Survival (OS) in Treatment-Naïve CLL

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Background, Methods and Demographics:

- Understanding when adding O to A offers benefits is critical as more drugs can mean more toxicity.
- Retrospective analysis: PFS and OS compared between the A+O (197 pts) and A alone (179 pts).

Results:

- PFS improved with A+O vs A in pts
  - with uIGHV (hazard ratio [HR] 0.51).
  - without del(17p)/*TP53*mutated (*TP53*m) (HR 0.38).
  - with mutated IGHV (HR 0.39).
  - with no Complex Karyotype (CK) abnormality (HR 0.43).
- OS was improved with A+O vs A in pts
  - with uIGHV (HR 0.44).
  - without del(17p)/*TP53*m (HR 0.44).
  - with no CK abnormality (HR 0.41) .
- No significant improvement was noted in pts with del(17p)/*TP53*m (HR 0.55) or in pts with CK (HR 0.69).

Conclusions:

- Pts with uIGHV or without del(17p)/*TP53*m or CK abnormalities benefited from adding O to A monotherapy.
- It is unclear if there is any benefit in del(17p)/*TP53*m pts leaving a significant unmet need.

Other ASH Abstracts of Note

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- Initial Results from a Phase 1/2 Dose Escalation and Expansion Study Evaluating MS-553, a Novel and Selective PKCβ Inhibitor, in Patients with CLL/SLL
- Breakthrough COVID-19 Infections in Patients with Hematologic Malignancies during the Omicron (B.1.1.529) Surge- Data from the Patient-Reported Leukemia & Lymphoma Society National Registry
- The Outcomes of Covid-19 in Patients with CLL during the Omicron Sub-Variants Surge
- Targeting Inflammatory Pathways to Reverse Immunosuppressive Tumor Microenvironment in Chronic Lymphocytic Leukemia
- Racial/Ethnic, Sex, and Income Disparities in Overall Survival (OS) in Chronic Lymphocytic Leukemia (CLL) Patients in the Era of Targeted Therapy- Surveillance, Epidemiology, and End Results (SEER) Registry Analysis

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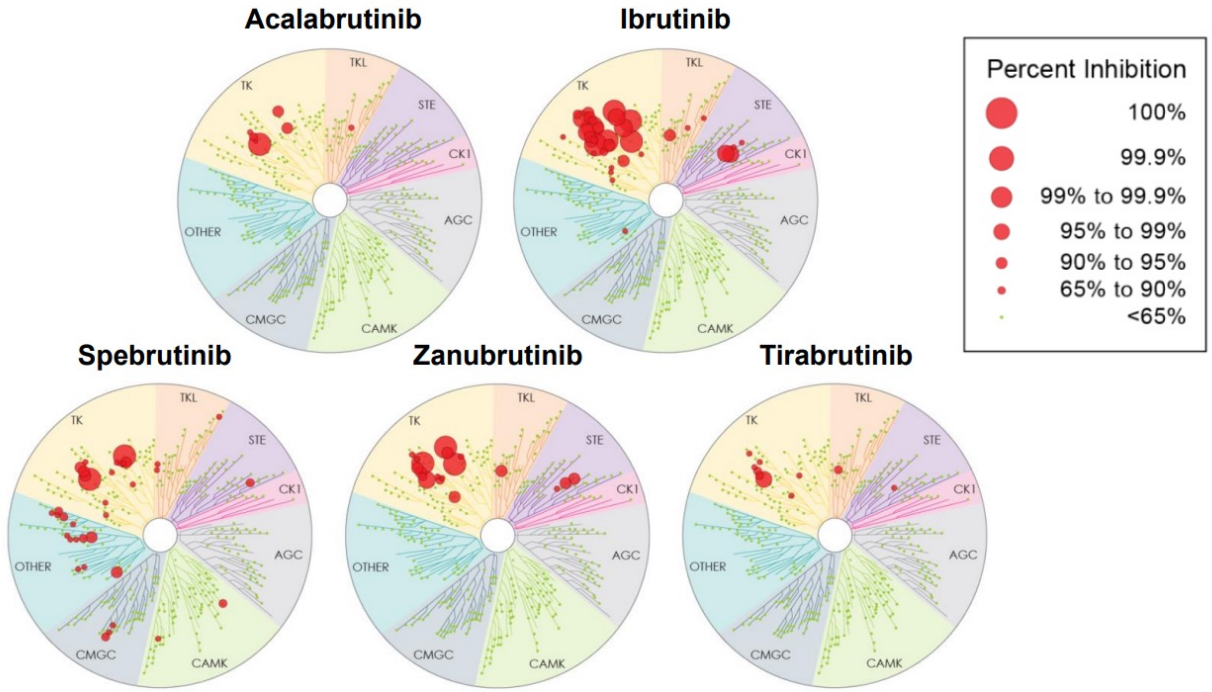
ASH 2022 Updates

Sameer A. Parikh
Mayo Clinic

February 9, 2023

BTK Inhibitors in CLL

- Many BTK inhibitors are now available to treat CLL:
  - FDA approval for ibrutinib, acalabrutinib and zanubrutinib



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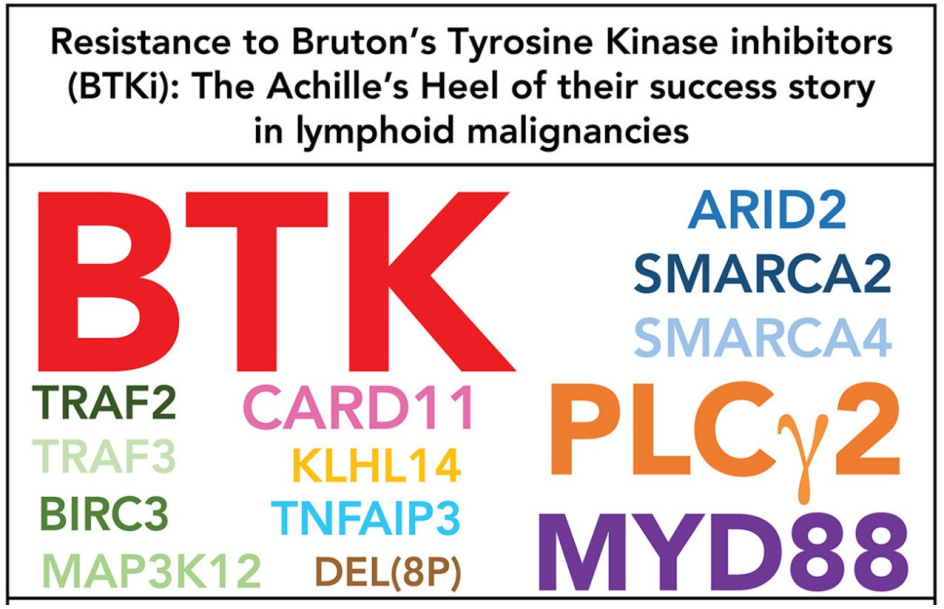
- Unfortunately, continuous treatment with a BTK inhibitor often leads to resistance



How Can We Get Past Resistance to BTK inhibitors?

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- Non-covalent BTK inhibitors:
  - Pirtobrutinib (now approved for mantle cell lymphoma)
  - Nemtabrutinib

- BTK degraders:
  - NURIX (NX-2127)

Pirtobrutinib in CLL

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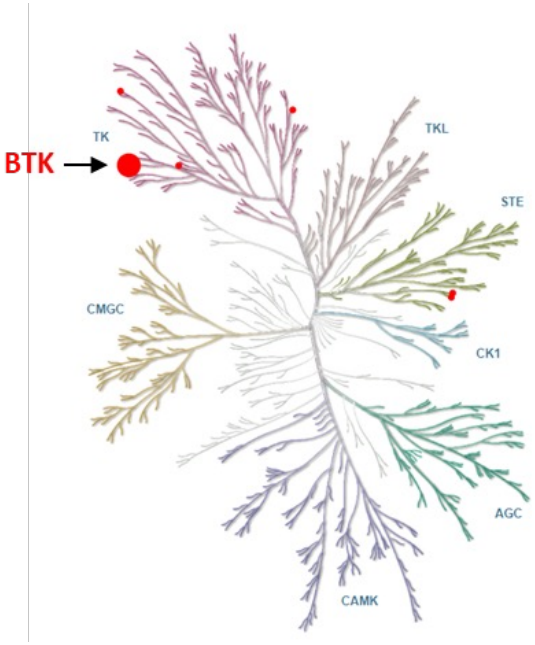
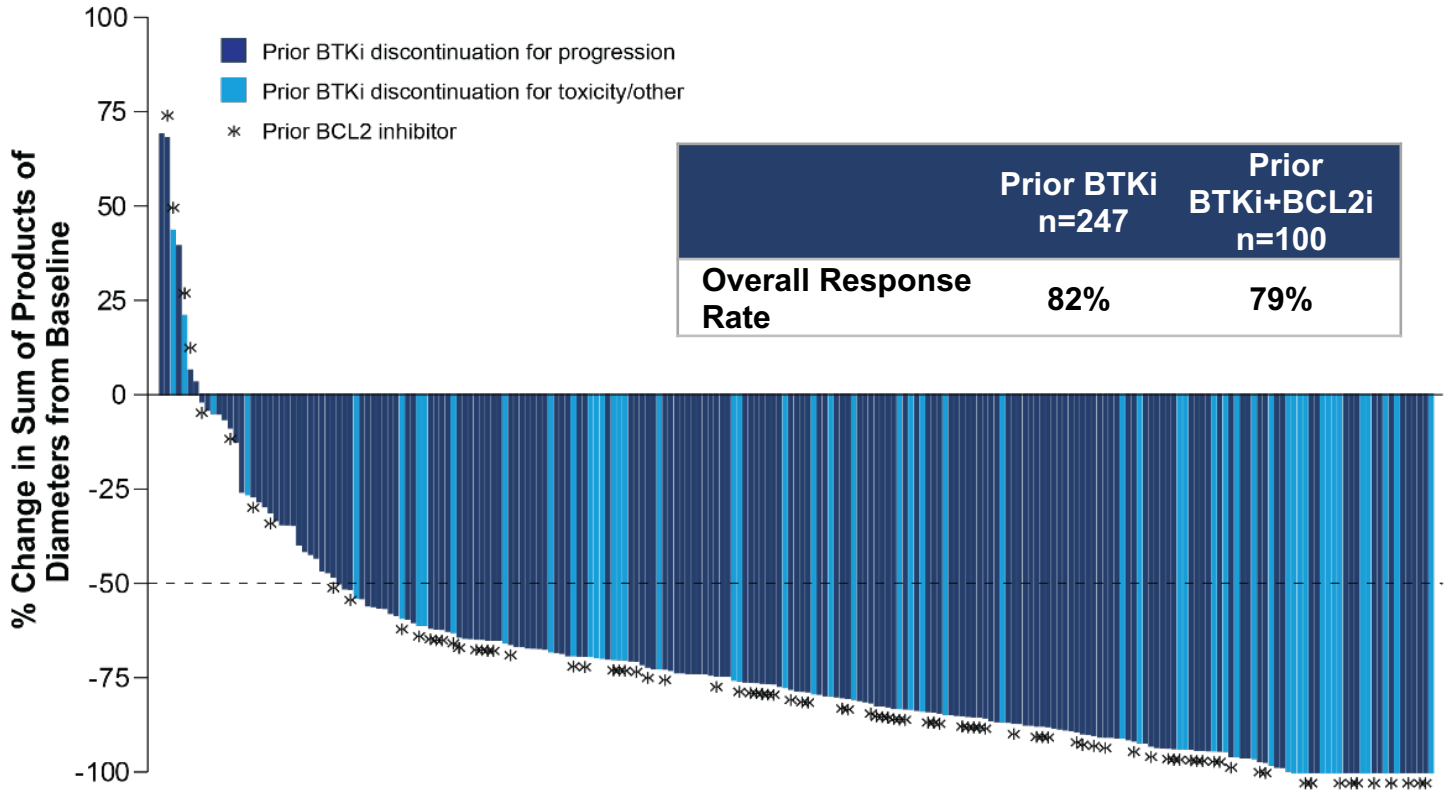
Highly Selective Non-Covalent (Reversible) BTK Inhibitor





	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate	82%	79%

Mato, ASH Abstracts, 2022

Pirtobrutinib in CLL

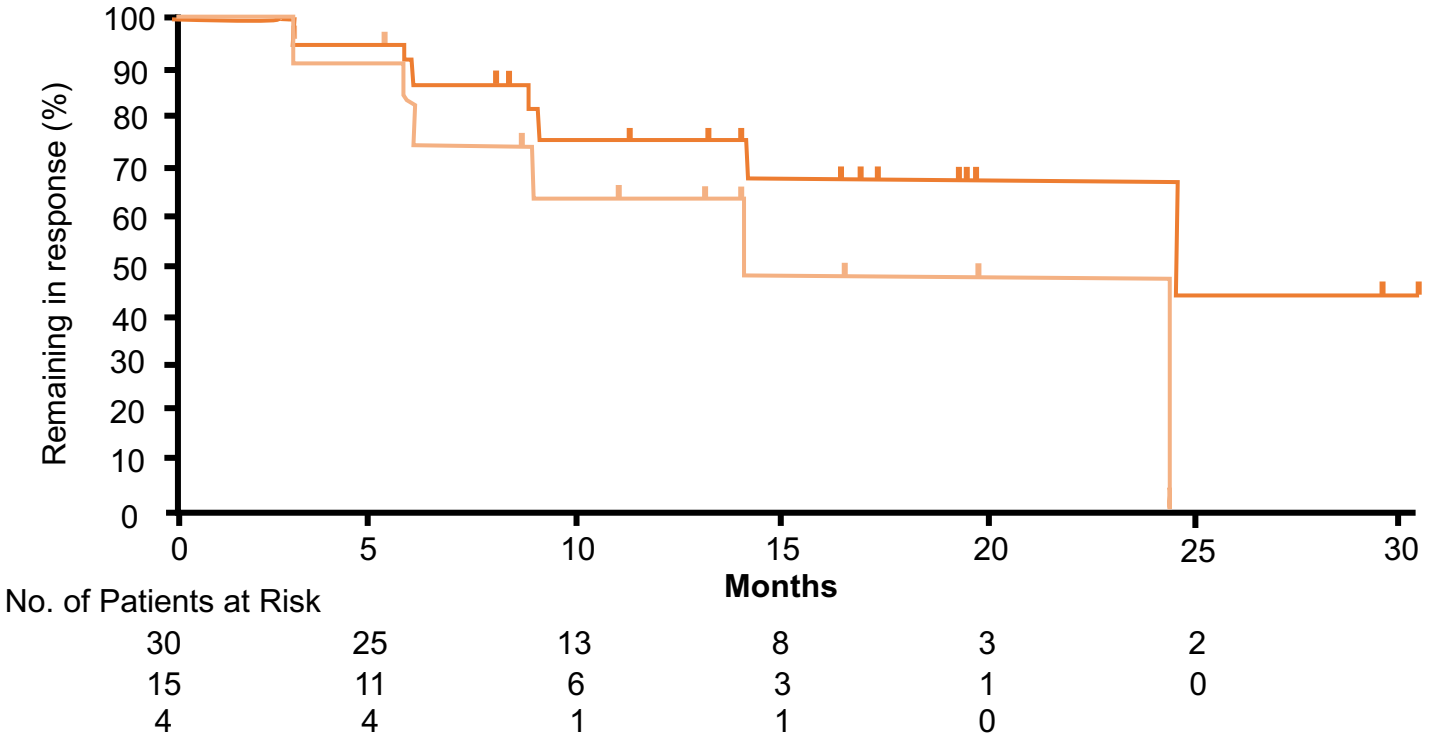
- Average length of time for which pirtobrutinib works after other BTK inhibitors have stopped working is about 18-24 months
- Pirtobrutinib works regardless of the presence or absence of *BTK* mutations such as C481S
- Side effect profile appears similar to other BTK inhibitors (less frequent?)

AEs of Special Interest[b]	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%
Rash[d]	12.7%	0.5%
Arthralgia	14.4%	0.6%
Hemorrhage/Hematoma[e]	11.4%	1.8%
Hypertension	9.2%	2.3%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%

- Pirtobrutinib now approved for mantle cell lymphoma – and hence we can prescribe it in an "off-label" indication for relapsed CLL

Nemtabrutinib in CLL

Overall response rate = 56%



All patients at 65 mg QD N = 112	
Treatment-related AEs ≥5%, n (%)	
Abnormal taste	23 (21)
Neutrophil count decreased	22 (20)
Fatigue	14 (13)
Platelet count decreased	13 (12)
Nausea	13 (12)
Hypertension	11 (10)
Diarrhea	11 (10)
Rash	6 (5)

NX-2127: BTK Protein Degrader in CLL

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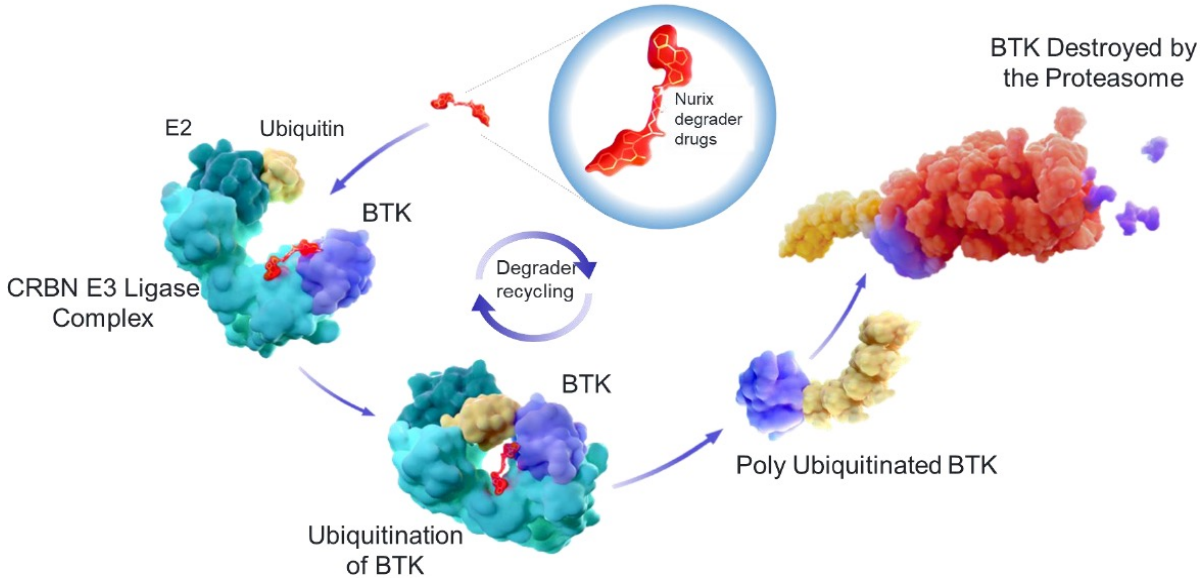
Utilizing the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in hematological malignances



Dose escalation

Objectives:

- Assess safety and tolerability
- Identify maximum tolerated dose (MTD)/ biologically active dose
- Evaluate PK/PD

Dose level 3 300 mg

Dose level 2 200 mg

Dose level 1 100 mg

Dose level –1 50 mg

Oral daily dosing

Dose expansion options

CLL failed 2 or more prior treatments including a BTK inhibitor and regardless of baseline BTK mutation status (up to 40)

– INITIATED –

DLBCL (up to 20)

MCL, MZL, WM (up to 20)

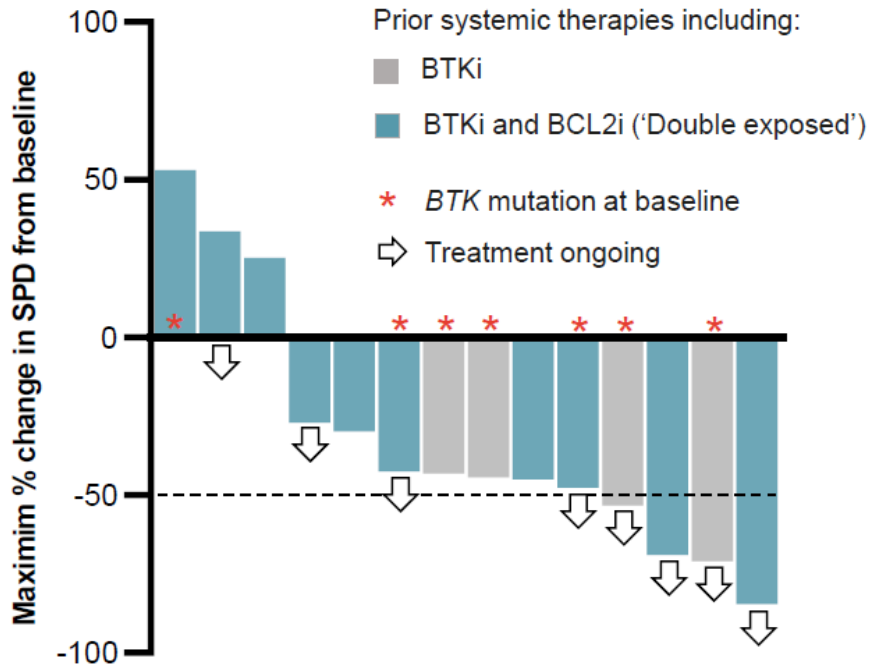
FL (up to 20)

NX-2127: BTK Protein Degrader in CLL

- The overall response rate was 33% in heavily pretreated patients with relapsed/refractory CLL with median follow up of 5.6 months:
  - Response was independent of prior CLL treatment

- Side effect profile similar to BTK inhibitors:
  - Blood count abnormalities, atrial fibrillation, etc.

- More patients with longer follow up planned
  - Other BTK degraders are in the clinic



Conclusion

- Newer classes of drugs are being developed to treat CLL patients who experience disease progression on BTK inhibitors:
  - Standard of care remains venetoclax and CD20 monoclonal antibody (if not previously received venetoclax)

- Clinical trial participation is key to advancing these drugs and get them to FDA approval:
  - Non-covalent BTK inhibitors – such as pirtobrutinib and nemtabrutinib
  - BTK degraders
  - CAR-T therapy, among many others

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Thank You for Attending!

Please take a moment to complete our **post-event survey**, your feedback is important to us

If you're question was not answered, please feel free to email asktheexpert@cllsociety.org

Join us on March 22nd for our next **Ask Me Anything Event Featuring Dr. Brian Hill and Jeff Folloder**

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