



Therapeutic Revolution in Frontline CLL

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Treatment Evolution in CLL

1960s

Alkylating agents
- Chlorambucil
- Cyclophosphamide

1970s

Purine nucleosides
- Fludarabine
- Pentostatin

1980s

Purine nucleosides
and alkylators

1990s

Chemoimmunotherapy
(FCR, BR)
Alemtuzumab
Lenalidomide

2000s

2014-

BTK inhibitors (**Ibrutinib, Acalabrutinib**)
BCL-2 inhibitor (**Venetoclax**)
Novel CD20 mAb (**Obinutuzumab**)
PI3K inhibitors (**Idelalisib, Duvelisib**)

2024

CD19 CAR T (**Liso-cel**)

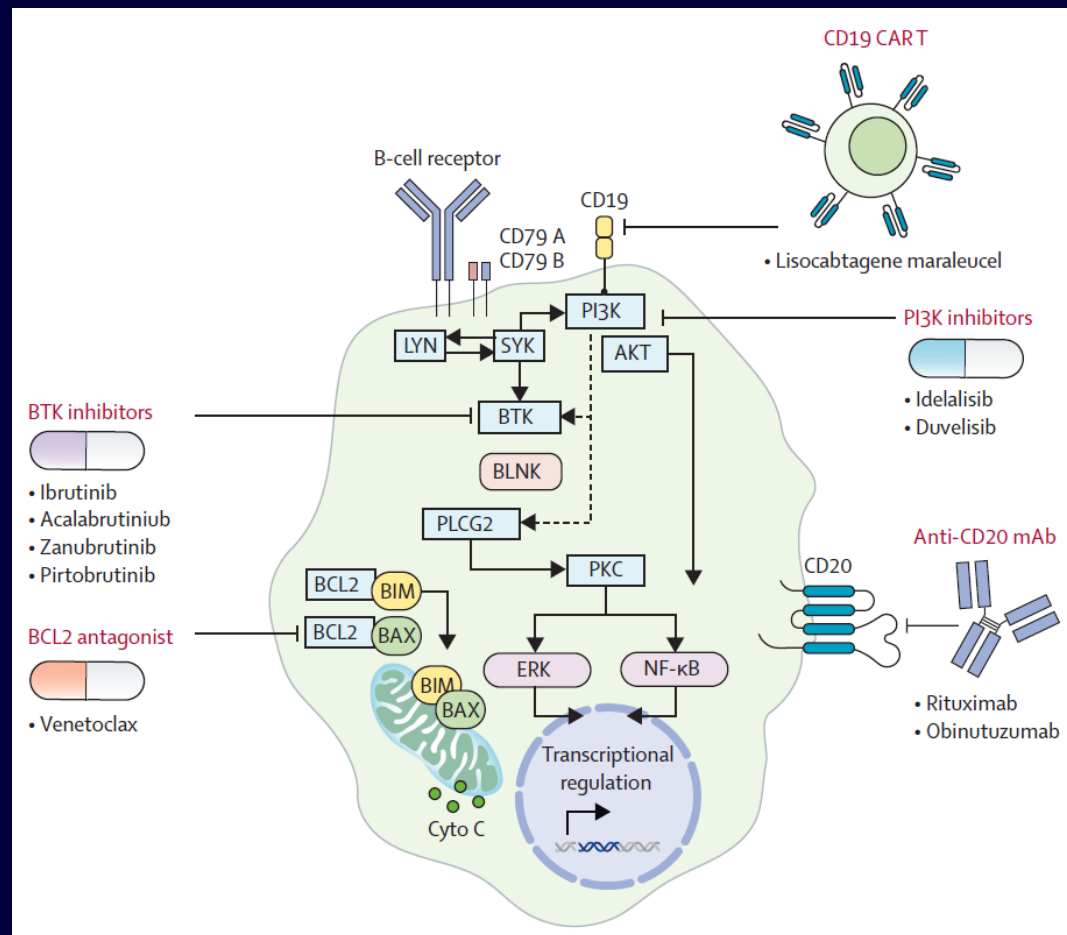
2023

BTK inhibitors
(**Zanubrutinib, Pirtobrutinib**)

2026+

BTK degraders, CD20 bispecifics,
novel BCL2i, novel BTKi, etc.

CLL Therapy Armamentarium



Jain, Wierda, O'Brien. Lancet. 2024 Aug 17; 694-706.

10 years of oral targeted Rx approval in CLL

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205552Orig2s000

Trade Name: Imbruvica

Generic Name: Ibrutinib capsules, 140 mg

Sponsor: Pharmacyclics, Inc.

Approval Date: February 12, 2014

Indications: For the treatment of patients with Chronic Lymphocytic Leukemia (CLL) who have received at least one prior therapy.

Monotherapy, Doublet, or Triplet?

Monotherapy

- **BTKi***

Doublet

- **BCL2i + CD20 mAb**
- **BTKi + BCL2i**

Triplet

- **BTKi + BCL2i + CD20 mAb**

BTKi

Covalent (ibrutinib, acalabrutinib, zanubrutinib)
Non-covalent (pirtobrutinib, nemtabrutinib)


BCL2i

Venetoclax, Sonrotoclax, Lisoftoclax

CD20 mAb

Obinutuzumab

* +/- obinutuzumab (acalabrutinib +/- obinutuzumab)



Combined Ibrutinib and Venetoclax for First-Line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL) 5-Year Follow-up Data

Nitin Jain, Michael Keating, Philip Thompson, Alessandra Ferrajoli, Jayastu Senapati, Jan Burger, Gautam Borthakur, Mahesh Swaminathan, Koichi Takahashi, Zeev Estrov, Alex Bataller, Marina Konopleva, Koji Sasaki, Tapan Kadia, Naveen Pemmaraju, Naval Daver, Elias Jabbour, Courtney DiNardo, Yesid Alvarado, Musa Yilmaz, Prithviraj Bose, Maro Ohanian, Rashmi Kanagal-Shamanna, Keyur Patel, Jeffrey Jorgensen, Sa Wang, Sameh Nassar, Naveen Garg, Hyunsoo Hwang, Xuemei Wang, Nichole Cruz, Ana Ayala, William Plunkett, Hagop Kantarjian, Varsha Gandhi, William Wierda

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ASH 2023, Abstract 4635

Treatment Schema

	C1	C2	C3	C4 --> 27 (<u>24 cycles</u> of Combined Rx)
Ibrutinib	420mg daily	420mg daily	420mg daily	420mg daily
Venetoclax	-	-	-	20mg daily 1 week; 50mg daily 1 week; 100mg daily 1 week; 200mg daily 1 week; 400mg daily continuous

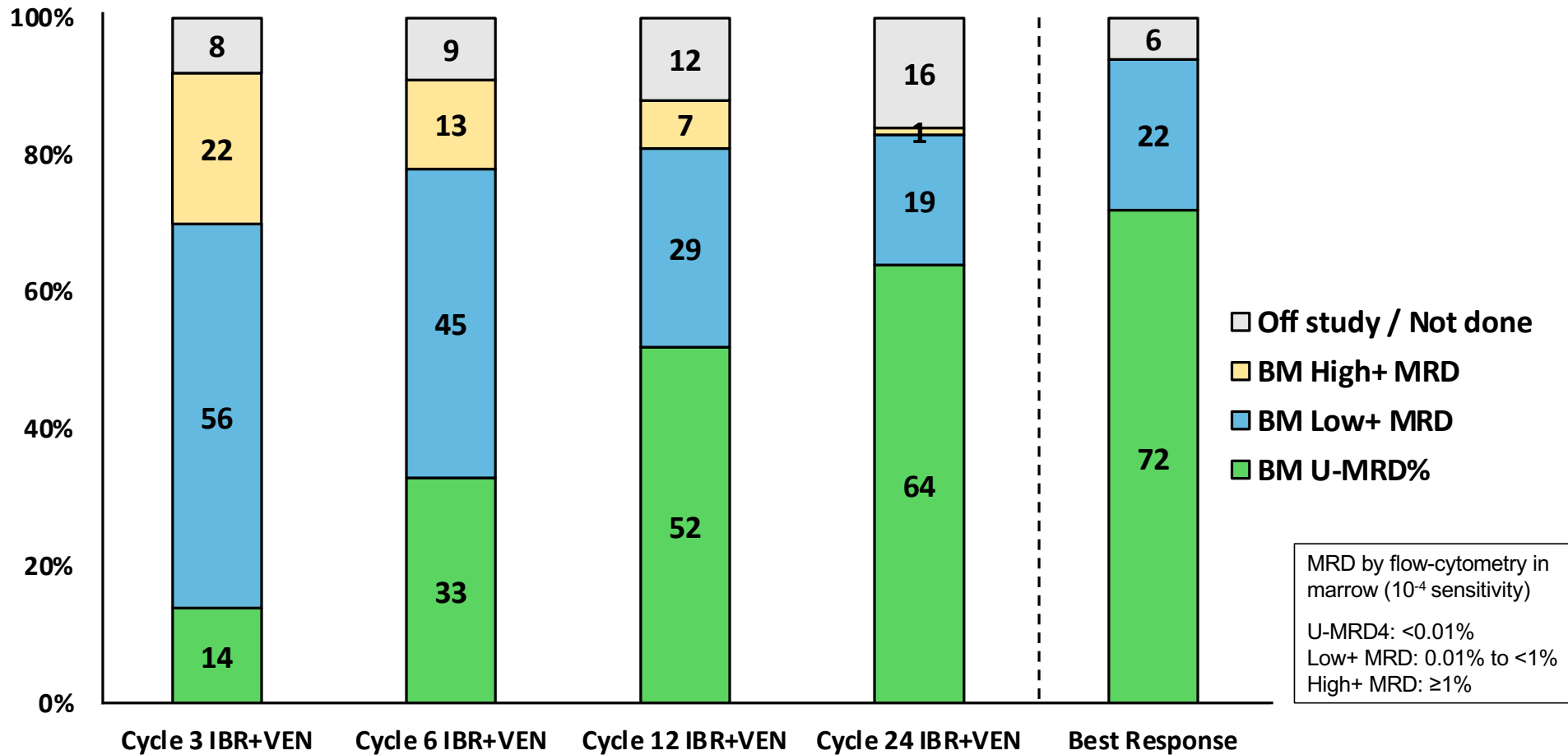
Duration of therapy: 24 cycles of combined IBR and VEN

Marrow MRD (flow cytometry) at end of cycle 24 of combined Rx

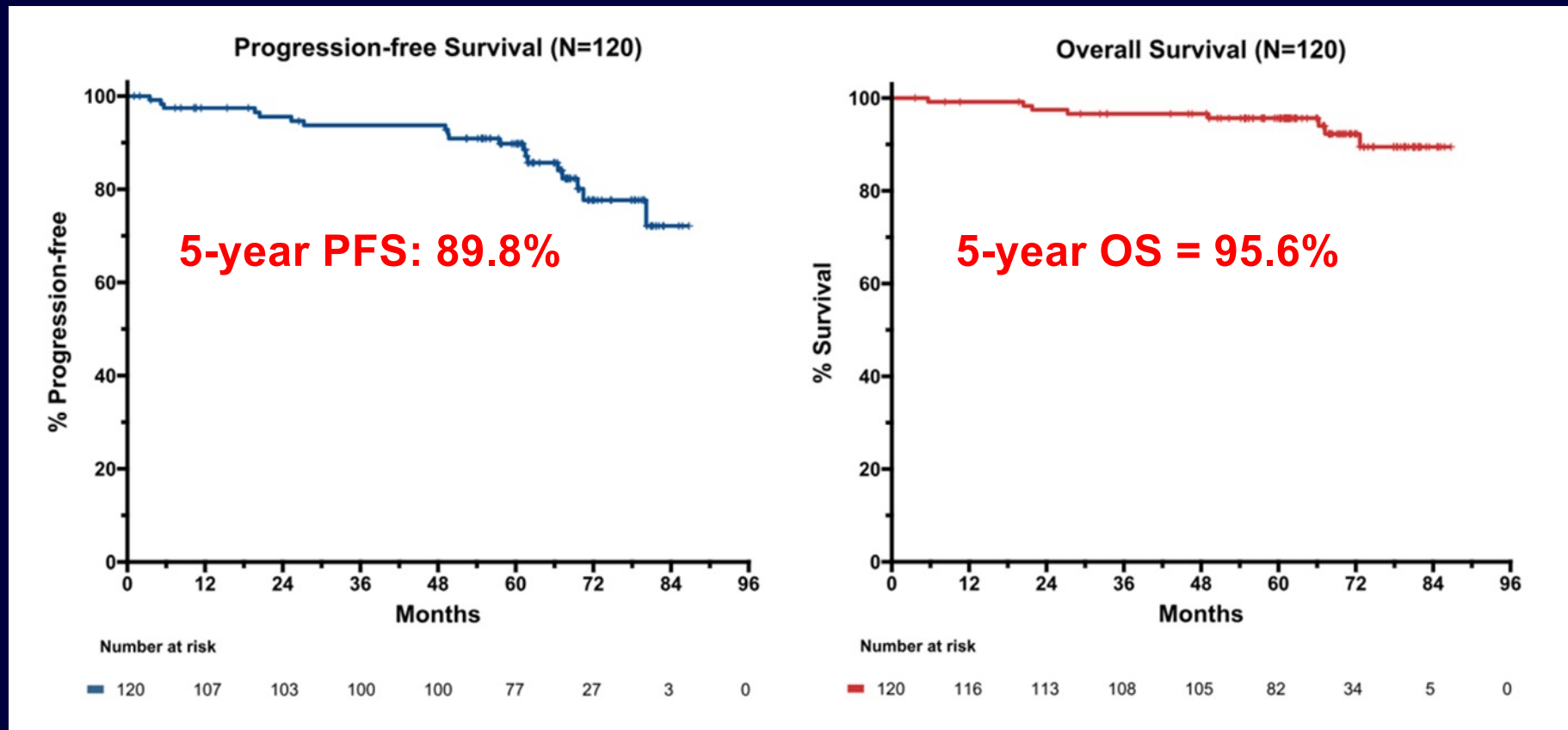
- Negative (<0.01%): Stop both IBR and VEN
- Positive (≥0.01%): Continue 12 additional cycles of IBR + VEN


Jain N et al. N Engl J Med. 2019 May 30;380(22):2095-2103.
Jain N et al. JAMA Oncol. 2021 Aug 1;7(8):1213-1219.

Marrow MRD Response at Serial Time-Points Intent-to-Treat (N=120)



PFS and OS for all Patients (N=120)



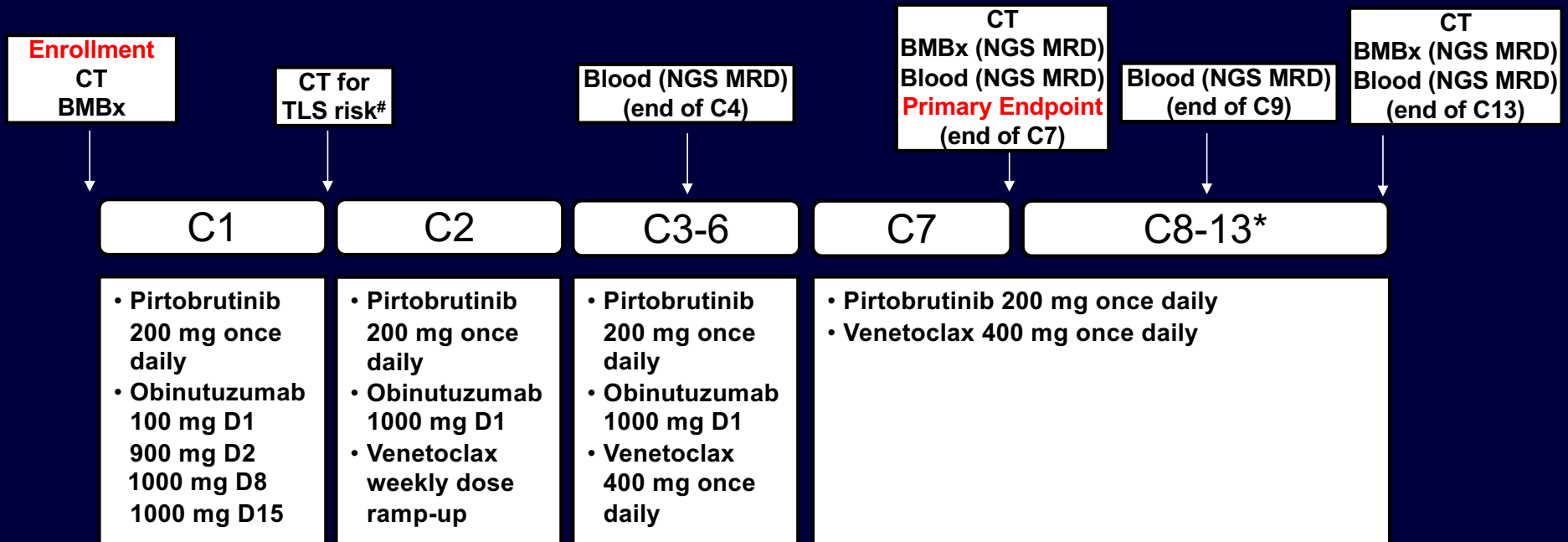


Combined Pirtobrutinib, Venetoclax, and Obinutuzumab As First-Line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL)

Nitin Jain, MD, Alessandra Ferrajoli, MD, Mahesh Swaminathan, MD, Patrick K. Reville, MD, MPH, Jan A. Burger, MD, PhD, Vanthana Bharathi, MD, Himachandana Atluri, MD, Hua-Jay J Cherng, MD, Alex Bataller, MD, PhD, Elias Jabbour, MD, Tapan M. Kadia, MD, Gautam Borthakur, MD, Koichi Takahashi, MD, PhD, Kelly S. Chien, MD, Musa Yilmaz, MD, Naveen Pemmaraju, MD, Naval Daver, MD, Fadi G. Haddad, MD, Yesid Alvarado Valero, MD, Jo Ishizawa, MD, PhD, Guillermo Montalban-Bravo, MD, Naveen Garg, MD, Hyunsoo Hwang, MS, Wei Qiao, PhD, Cameron Garcia, RN, Anna Evangelio, RN, Ana Ayala, RN, Deepa Sampath, PhD, Varsha Gandhi, PhD, Michael J. Keating, MBBS, Hagop M. Kantarjian, MD, William G. Wierda, MD, PhD

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ASH 2024, Abstract 1011

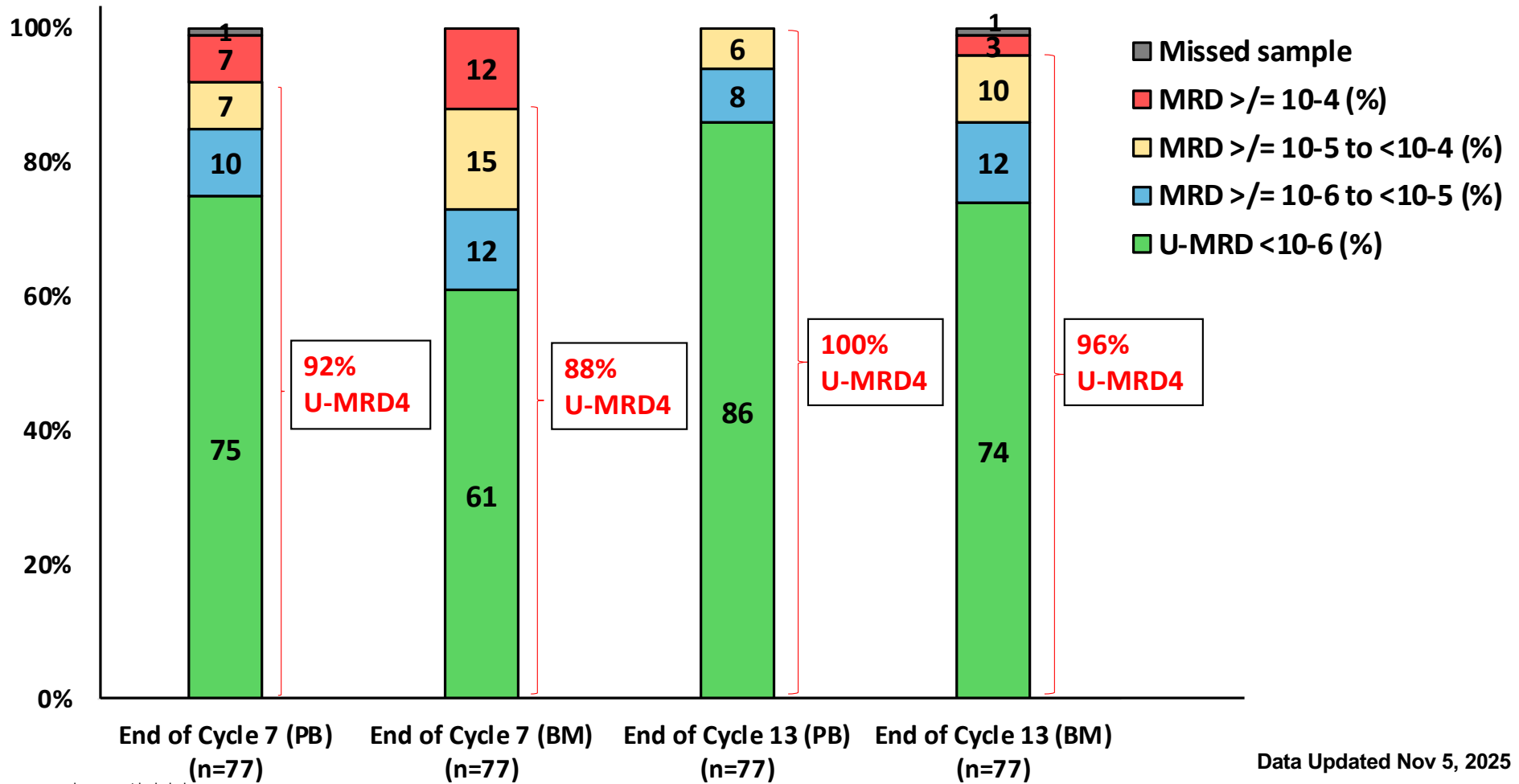
Pirtobrutinib, Venetoclax, Obinutuzumab Trial Treatment Schema



[#]CT imaging is repeated for TLS risk assessment only if baseline CT had nodes ≥ 5 cms

- Each cycle is 28 days
- NGS MRD assessed by clonoSEQ assay (Adaptive Biotechnologies) with 10^{-6} sensitivity
- All pts monitored by PB NGS MRD q3 mos for first 12 mos off therapy, and then q6 mos
- *For pts who are MRD+ at $\geq 10^{-5}$ in either PB or BM at end of C13 can continue pirtobrutinib + venetoclax for an additional 12 cycles

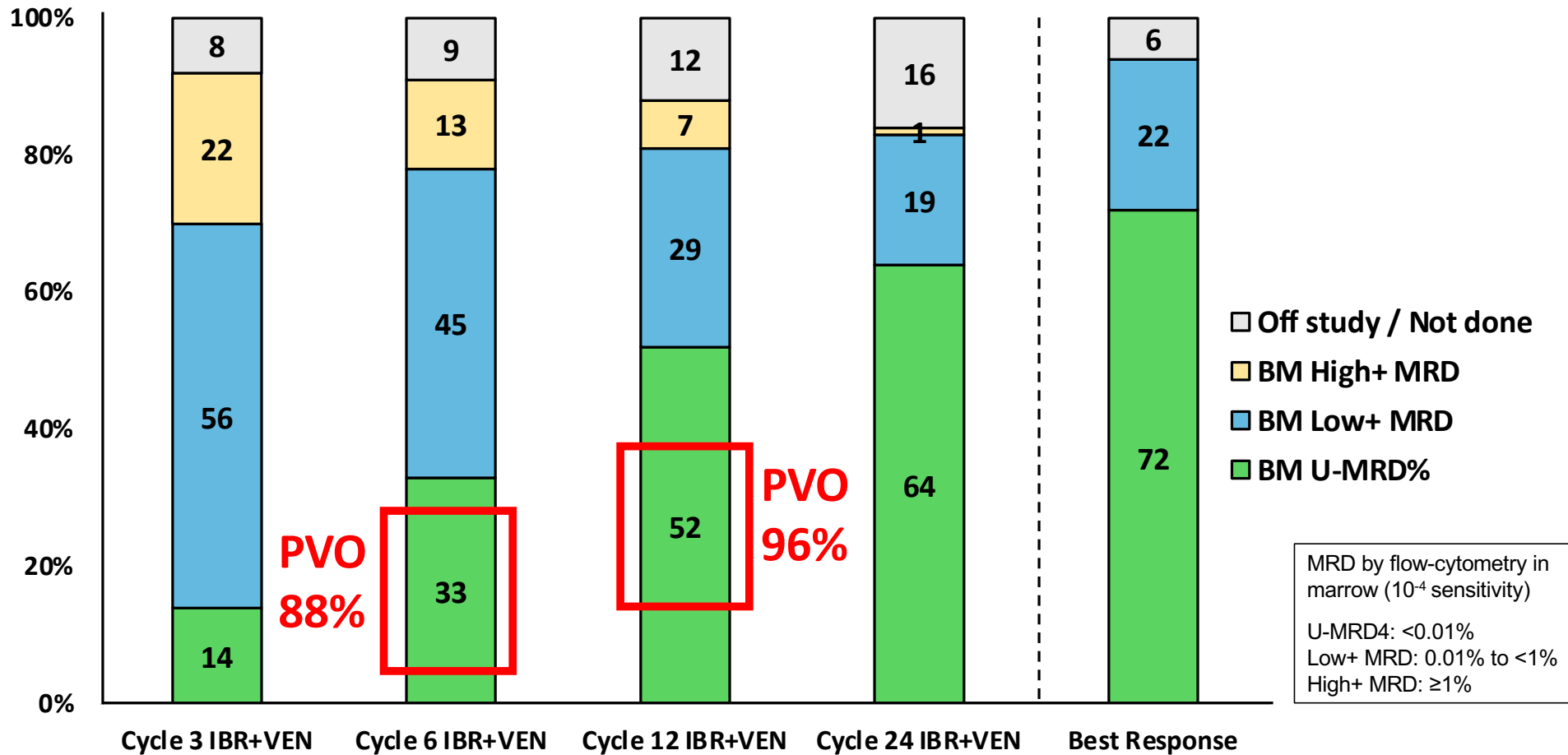
PVO trial: NGS MRD in Blood and Marrow



Data Updated Nov 5, 2025

3 pts off study for non progression are not included

Ibrutinib + Venetoclax Marrow MRD Response at Serial Time-Points Intent-to-Treat (N=120)

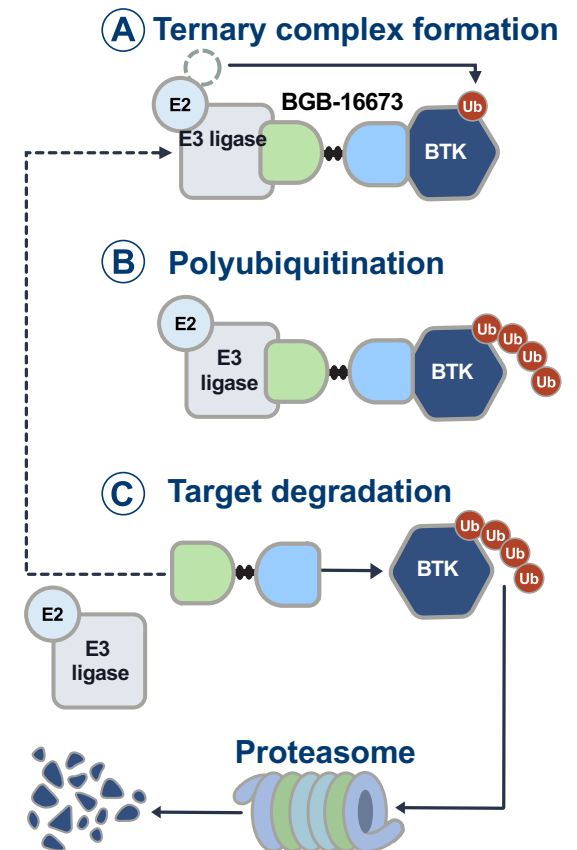


What new targets in CLL?

- **BTK degraders**
- **CD20 (CD19) bispecifics**
- **CD19 CAR T**

BGB-16673: A Chimeric Degradation Activating Compound (CDAC)

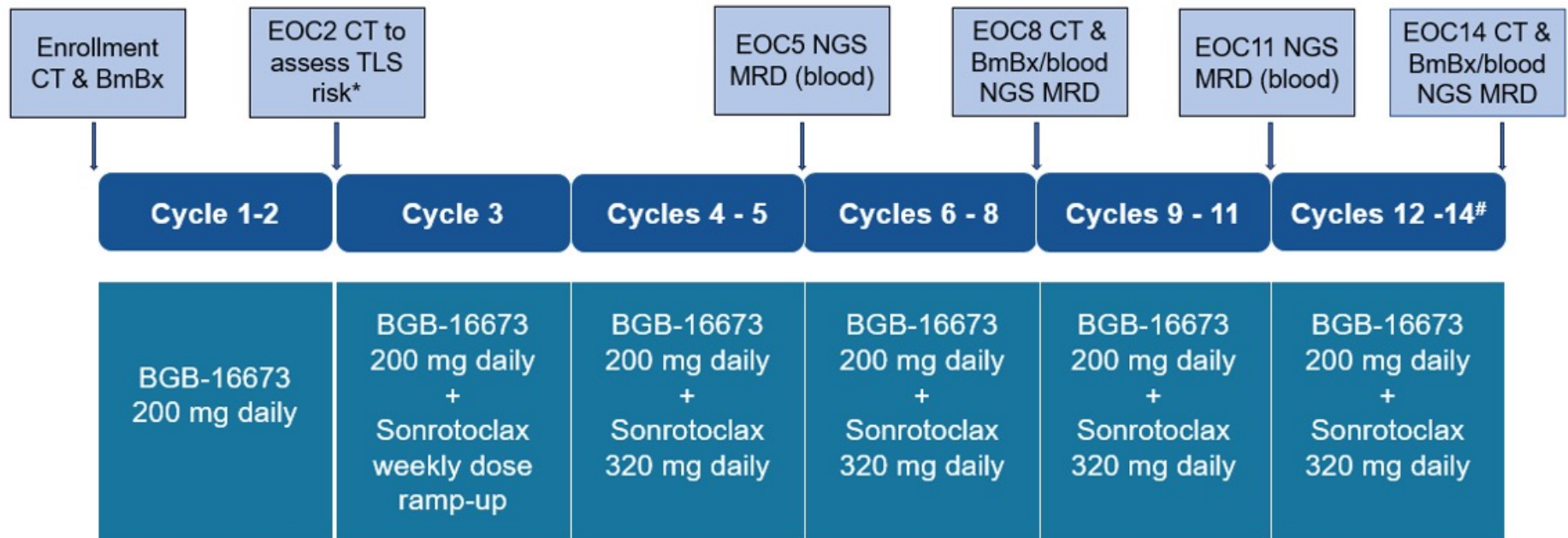
- Many patients with CLL/SLL experience disease progression with BTK inhibitors, which can be caused by resistance mutations in BTK¹⁻³
- BGB-16673 is an orally available protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression⁴
- In preclinical models, BGB-16673 showed CNS penetration and degraded both wild-type and mutant BTK resistant to cBTK (C481S, C481F, C481Y, L528W, T474I) and ncBTK inhibitors (V416L, M437R, T474I, L528W)^{4,5}
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue⁶
- Here, updated safety and efficacy results in patients with R/R CLL/SLL in phase 1 of CaDAnCe-101 are presented



BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CNS, central nervous system; ncBTK, noncovalent Bruton tyrosine kinase; R/R, relapsed/refractory; ub, ubiquitin.

1. Moreno C. *Hematol Am Soc Hematol Educ Program*. 2020;2020:33-40; 2. Woyach JA, et al. *N Engl J Med*. 2014;370:2286-2294; 3. Wang E, et al. *N Engl J Med*. 2022;386:735-743; 4. Feng X, et al. EHA 2023. Abstract P1239; 5. Wang H, et al. EHA 2023. Abstract P1219; 6. Seymour JF, et al. ASH 2023; Abstract 4401.

Planned IST
 BGB-16673 + sonrotoclax in Firstline CLL



*For patients who had lymph nodes ≥ 5 cm on baseline CT

At end of cycle 14, patients with MRD 10^{-5} or higher either in BM or PB can continue BGB-16673 and sonrotoclax for an additional 12 cycles

Firstline Investigator initiated CLL Trials

- **Pirto + Ven + Obin**
 - Amending to increase accrual from 120 to 160 pts
- **BGB-16673 + Sonrotoclax (n=40)**
 - 2 oral drugs
- **Zanubrutinib + Sonrotoclax + Obin (last 6 months) (n=40)**
 - Evaluating late obin

Thank you!

@NitinJainMD