CLL Global Virtual Town Hall

Thank you for your patience.
We will begin shortly.

Have questions for our panel?

Please email them to townhall@cllglobal.org

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Questions?

Please send an email to townhall@cllglobal.org

A video of today's Town Hall presentation will be available at our website www.cllglobal.org under the Upcoming Events tab

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Dr. Michael Keating

Founder
CLL Global Research Foundation

Clinical Professor, Department of Leukemia
The University of Texas MD Anderson Cancer Center

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Dr. William Wierda

President & CEO
CLL Global Research Foundation

Jane and John Justin Distinguished Chair in Leukemia
Research in Honor of Dr. Elihu Estey

Executive Medical Director
The University of Texas MD Anderson Cancer Center

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Dr. Nitin Jain

Associate Professor in the Department of Leukemia
The University of Texas MD Anderson Cancer Center

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Reports from ASH 2022 on CLL

13 January 2023

WILLIAM G. WIERDA MD,PHD

PROFESSOR OF MEDICINE

SECTION HEAD, CLL

DEPARTMENT OF LEUKEMIA

U.T. M.D. ANDERSON CANCER CENTER

HOUSTON, TX USA

Advancing Knowledge of First-line Targeted Treatments for CLL ASH 2022

- First-line ibrutinib + venetoclax (MDACC / CAPTIVATE / GLOW / FLAIR)
  - Deep remissions with IBR+VEN for most, long remissions for all uMRD
  - Higher uMRD rate for IGHV-unmutated
  - Optimal duration of treatment still unclear (longer treatment slow responders?)
- First-line BTKi + venetoclax + obinutuzumab (GiVe and AVO)
  - High uMRD rate, tolerable toxicity (individual contributions?)
- Predictors for outcomes with VEN-based combinations (CLL13/GAIA)
  - Response (ORR and uMRD) for all; independent association of U-IGHV, *NOTCH1, BRAF/NRAS/KRAS* mutations, hCKT (≥5 abberations), and chromosome translocations with PFS

Advances in Treatments for Rel/Ref CLL ASH 2022

- Combined IBR + VEN (CLARITY) highly active in R/R CLL
- Venetoclax consolidation feasible in patients on IBR ≥12 months with potential for clinical benefit (discontinue treatment, long remission)
- Pirtobrutinib effective for prior BTKi-treated CLL, including with C481 mutation
- BTK-degrader (NX-2127) tolerated with activity – novel mechanism of action
- New BCL2 inhibitors (BGB-11417 and Lisaftoclax) have activity and being combined with BTKi and CD20 mAb
- Protein kinase C-beta inhibitor (PKCβi) - MS-553 tolerated with activity in BTKi-treated CLL being evaluated alone and in combinations

Combined Ibrutinib and Venetoclax for First-Line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL) 4-Year Follow-up Data

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

Department of Leukemia
The University of Texas MD Anderson Cancer Center
ASH 2022, Abstract 95

Treatment Evolution in CLL

1960s

Alkylating agents
- Chlorambucil
- Cyclophosphamide

1970s

Purine nucleosides
- Fludarabine
- Pentostatin
- Cladribine

1980s

1990s

Purine nucleosides and alkylators

2000s

Chemoimmunotherapy (FCR, BR)
Alemtuzumab
Lenalidomide

2014-

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

2023+

BTK inhibitors (Zanubrutinib, Pirtobrutinib)
PI3K inhibitor ~~(Umbralisib)~~
CAR-T

Background

- Ibrutinib (IBR), a BTK inhibitor, and Venetoclax (VEN), a BCL2 inhibitor, approved for CLL
- VEN + Obinutuzumab is approved for first-line CLL as 1-year time-limited therapy
- Preclinical studies support combination of IBR + VEN combination
- IBR + VEN combination have been investigated in several clinical trials
- We previously reported outcomes of 80 pts enrolled on this trial of first-line IBR + VEN

  Jain et al. N Engl J Med 2019; Jain et al. JAMA Onc 2021

- We provide updated results for these 80 pts and an additional 40 first-line pts (total 120 pts) with a median follow-up of 54.3 months

Byrd et al. NEJM. 2014;371(3):213-23; Burger et al. NEJM. 2015;373(25): 2425-37; Roberts et al. NEJM. 2016;374(4):311-22; Fischer et al. NEJM. 2019;380(23):2225-2236. Cervantes-Gomez et al. CCR. 2015; 21 (16):3705-15; Wierda et al. J Clin Oncol. 2021;39(34):3853-3865; Kater et al. NEJM Evid 2022;1(7).

Ibrutinib and Venetoclax Trial

- Investigator-initiated Phase II trial (NCT02756897)

- Patients with treatment-naïve CLL/SLL meeting 2008 iwCLL treatment criteria with at least one of the following feature:
  - Del(17p) or mutated *TP53*
  - Del(11q)
  - Unmutated *IGHV*
  - Age ≥65 years

Jain, IBR + VEN in CLL, ASH 2022, Abs 95

Treatment Schema

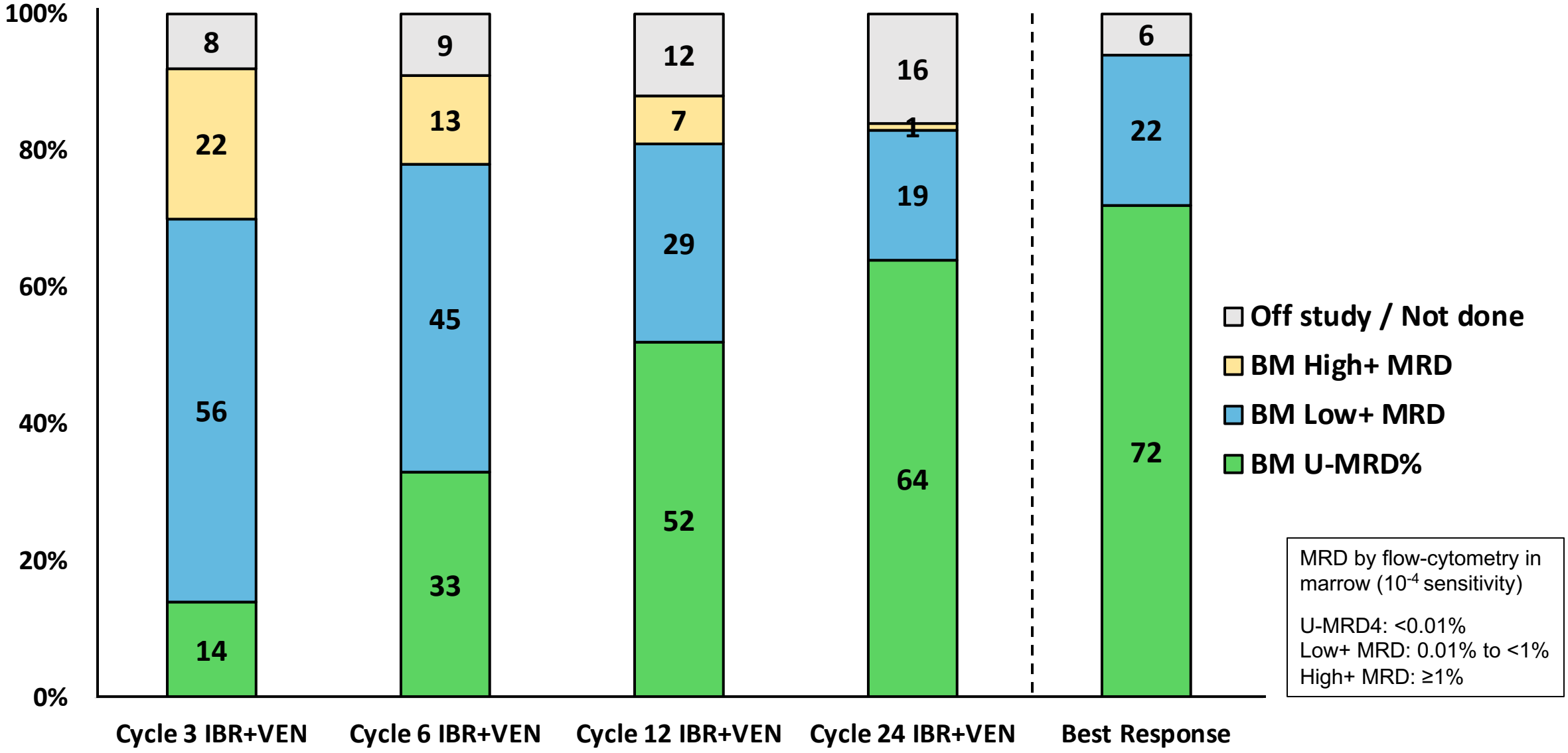
	C1	C2	C3	C4 --> 27 (24 cycles of Combined Rx)
Ibrutinib	**420mg daily**	**420mg daily**	**420mg daily**	**420mg daily**
Venetoclax	**-**	**-**	**-**	**20mg daily 1 week; 50mg daily 1 week; 100mg daily 1 week; 200mg daily 1 week; 400mg daily continuous**

Duration of therapy: 24 cycles of combined IBR and VEN

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

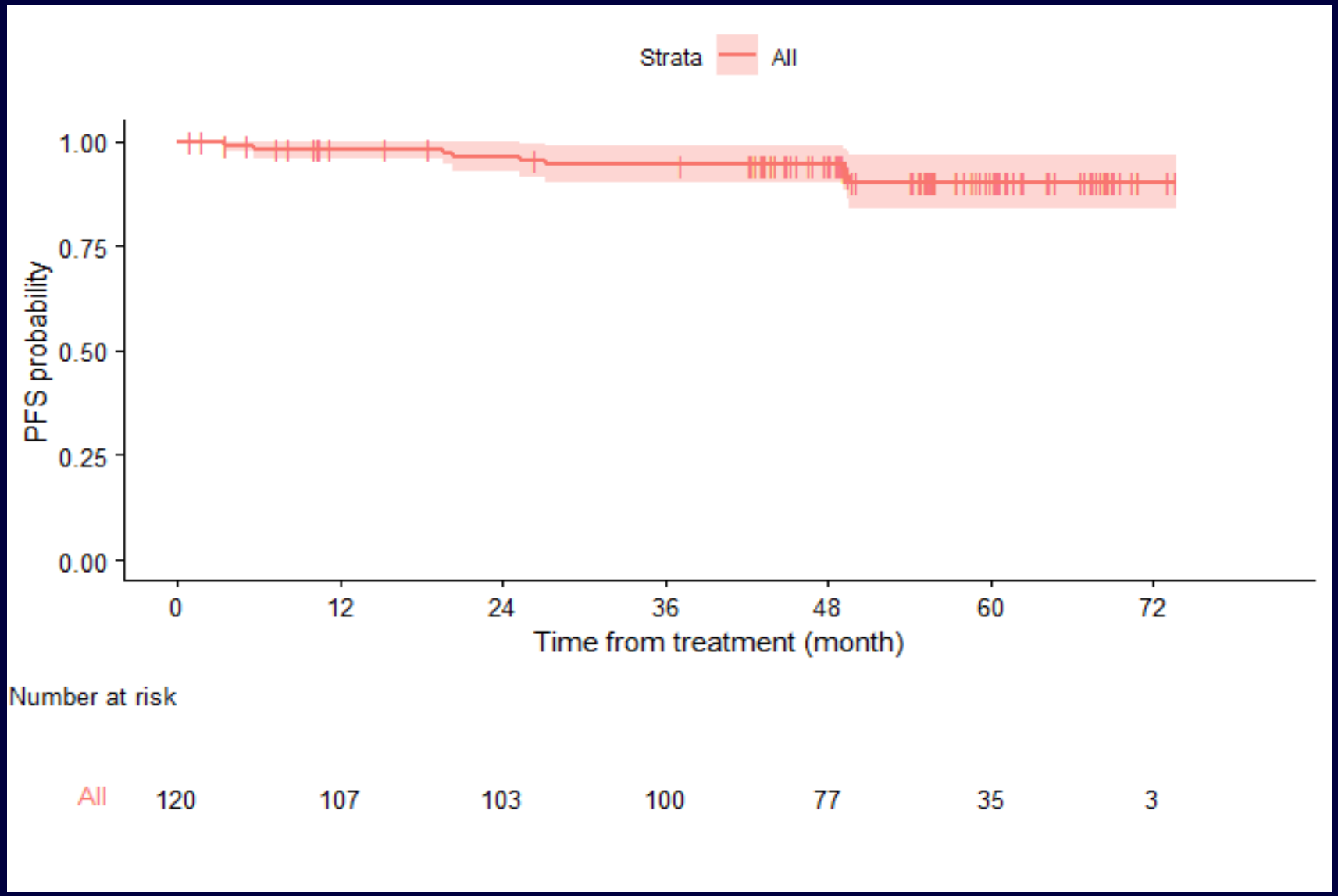
- Negative (<0.01%): Stop both IBR and VEN
- Positive (≥0.01%): Continue 12 additional cycles of IBR + VEN

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



Jain, IBR + VEN in CLL, ASH 2022, Abs 95

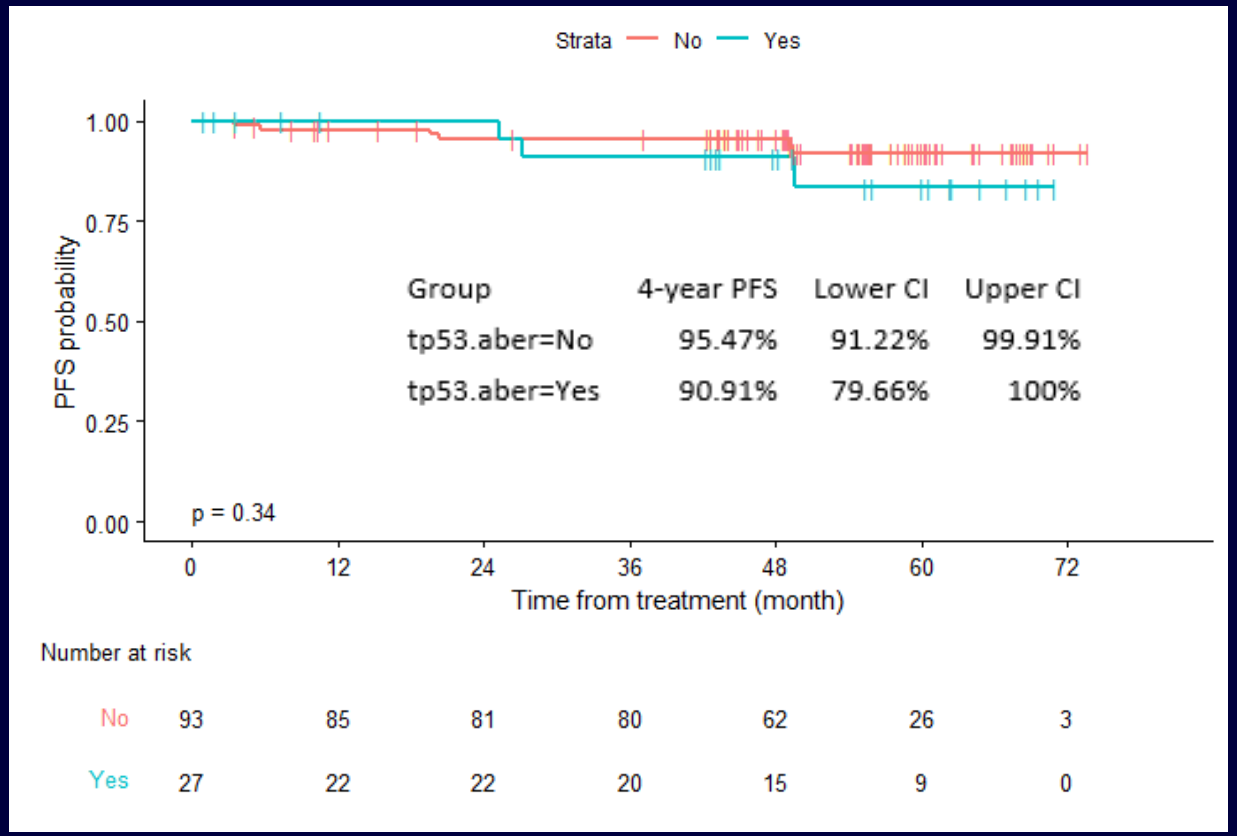
PFS for all Patients (N=120)



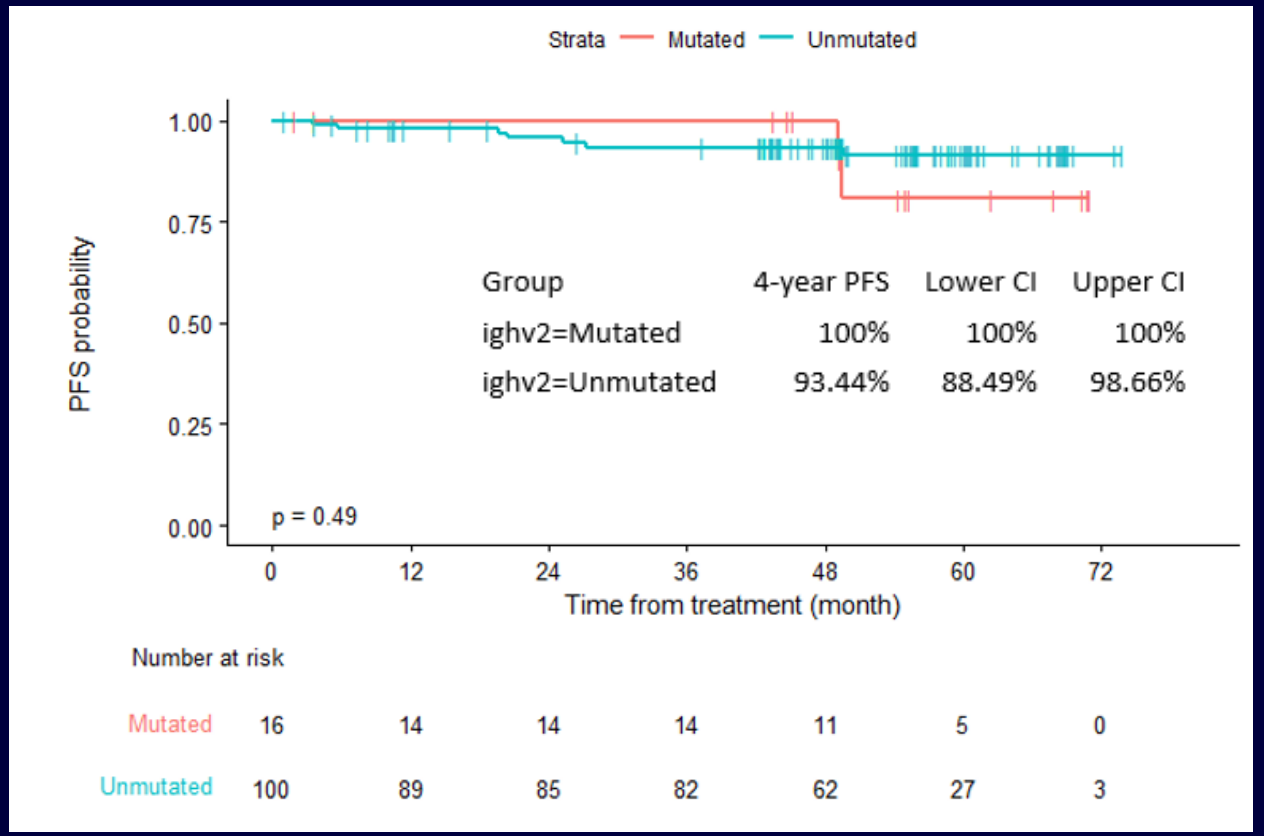
4-year PFS = 94.5%
(95% CI, 90.3-98.9%)

Jain, IBR + VEN in CLL, ASH 2022, Abs 95

PFS by Genomic Subgroups



TP53 aberrant status



IGHV mutation status

Jain, IBR + VEN in CLL, ASH 2022, Abs 95

Conclusions

- Combined ibrutinib and venetoclax is an effective chemotherapy-free oral regimen for patients with high-risk untreated CLL
- Best marrow U-MRD4 remission: 72%
- 4-year PFS is 94.5% and is independent of *IGHV*, FISH and *TP53* aberrant status
- Continuation of combined therapy among pts with marrow MRD+ disease for the second and the third year led to achievement of U-MRD remission in a subset of pts

Jain, IBR + VEN in CLL, ASH 2022, Abs 95

Current CLL Trials at MDACC

Firstline CLL

- Acala + VEN +/- Obin
- VEN + Obin + Atezolizumab (PD-L1 mAb)
- LOXO-305 + Obin + VEN (Jan 2023)
- Acala + Obin
- Zanu + Rituxan

Consolidation CLL

- VEN added to Ibrutinib
- Pirto added to VEN

R/R CLL

- Acala + VEN +/- Obin
- VEN + R +/- LOXO-305
- BTK PROTAC (Nurix)
- MS-553 (PKCβ inhibitor)
- FT819 (allogeneic CD19-CART)
- Ipilimumab + Nivolumab + Ibrutinib
- Mosenutuzumab (CD20 bispecific)
- ROR1 CAR T

RT

- VEN + Obin + Atezolizumab
- R-CHOP + VEN
- LOXO-305 + Obin + VEN
- MS-553
- FT819 (allogeneic CD19-CART)
- Ipilimumab + Nivolumab + Ibrutinib
- Epcoritamab (CD20 bispecific)

Q&A

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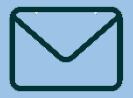

Sam Pace
townhall@cllglobal.org
(713) 745-1861

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CLL Global Research Foundation
P.O. Box 301402, Unit 428
Houston, Texas 77230