Where Science Becomes Hope

IS MRD AN IMPORTANT CLINICAL ENDPOINT IN FRONTLINE MANAGEMENT OF CLL?

Jean Louise Koff, MD, MSc

Associate Professor, Hematology and Medical Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

Disclosures

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FRONTLINE MANAGEMENT OF CLL: BTK INHIBITOR OR VENETOCLAX-BASED[1]

Venetoclax + Obinutuzumab[2]

Fixed duration

Excellent responses: 5-year PFS = 62.6%
= 40.6% in del(17p)/*TP53*m
mPFS = 76.2 months

Side effects of note: tumor lysis risk, neutropenia, infections, diarrhea

Zanubrutinib[3] or Acalabrutinib +/- Obinutuzumab[4]

Continuous treatment until progression or intolerance

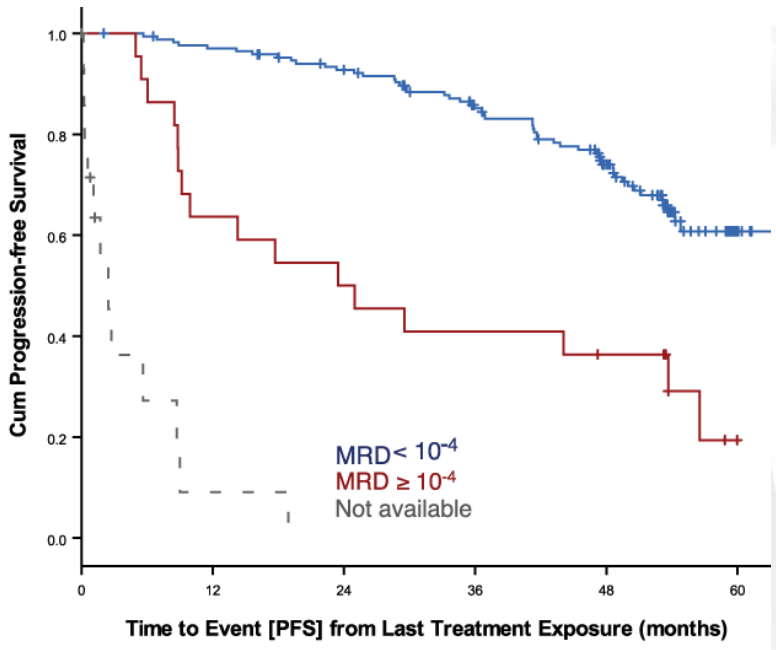
Excellent responses: Zanu mPFS = NR at median f/u 44 mos
42-mo PFS = 82.4%
= 79.4% in del(17p)
A +/- O mPFS = NR at median f/u 74 mos
= 73.1 mo/NR in del(17p)/*TP53*m
6-year PFS = 78% / 62%
= 56% in del(17p)/*TP53*m

Side effects of note: neutropenia, thrombocytopenia, hemorrhage, arthralgias, headache, hypertension, arrhythmias, rash

1. NCCN Guidelines: CLL/SLL. Version 3.2024. 2. Al-Sawaf O, *et al. Nat Comm.* 2023. 3. Munir T, *et al*. EHA/*Hemasphere.* 2023. 4. Sharman JP, *et al.* ASH/*Blood.* 2023.

IS MRD ASSOCIATED WITH OUTCOMES IN FRONTLINE CLL TREATMENT?

Venetoclax + Obinutuzumab[1]



BTKi

CR is not necessary for durable disease control.

Zanu: CR/CRi =17.4% (14.5% in del(17p)[2]

uMRD not reported

A +/- O: CR/CRi 37% / 19%[3]

uMRD (only tested in patients with CR/CRi) = 13%[4]

1. Al-Sawaf O, *et al. Nat Comm.* 2023. 2. Munir T, *et al*. EHA/*Hemasphere*. 2023.
3. Sharman JP, *et al.* ASH/*Blood.* 2023. 4. Sharman JP, *et al. Lancet.* 2021.

IS MRD ASSOCIATED WITH OUTCOMES IN FRONTLINE CLL TREATMENT?

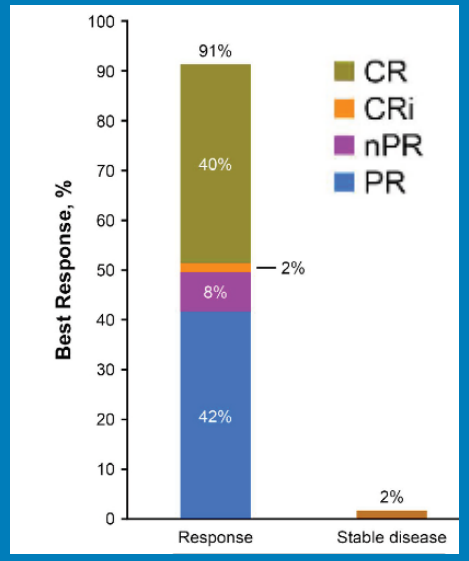
BTKi

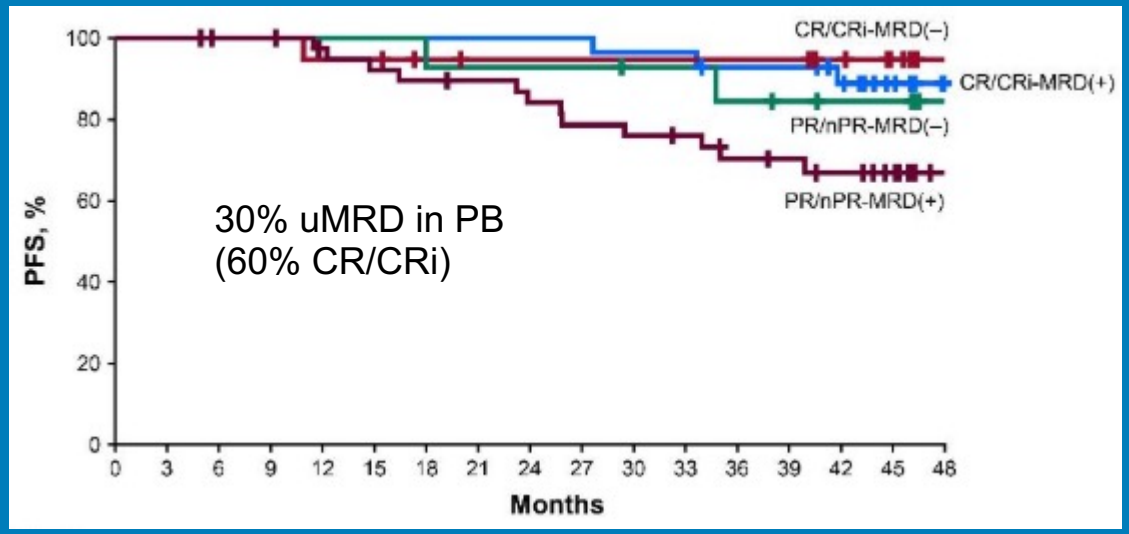
Do not frequently induce uMRD as single agents… or with anti-CD20

E1912: Ibrutinib + Rituximab[1]

uMRD at 12 months: 8.3 % 5-year PFS = 78%

iLLUMINATE: Ibrutinib + Obinutuzumab[2]

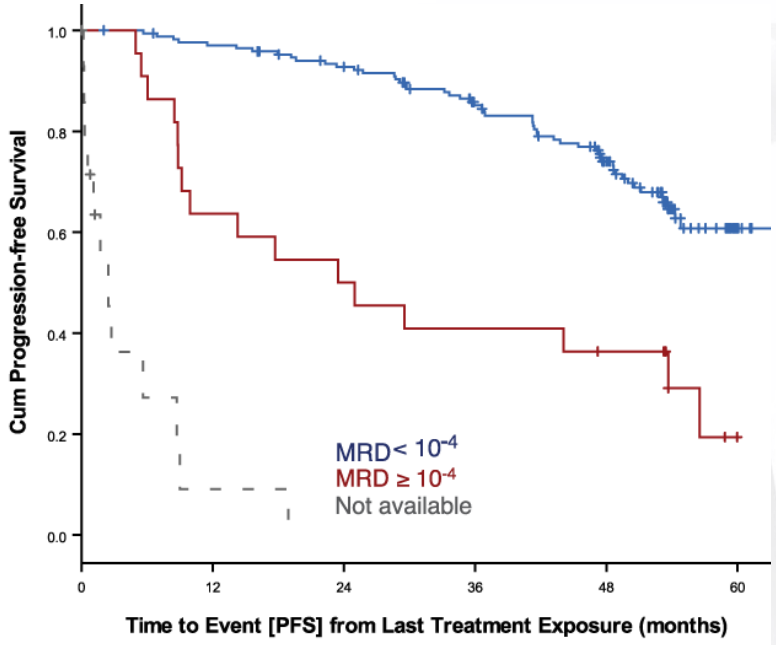




1. Shanafelt TD, *et al. Blood.* 2022. 2. Moreno C, *et al. Haematologica.* 2022.

DOES MRD TESTING CHANGE MANAGEMENT AFTER FRONTLINE CLL TREATMENT?

Venetoclax + Obinutuzumab



When your now-asymptomatic patient fails to achieve uMRD after treatment with VenO, do you…?

A. Serially monit[illegible]RD to de[illegible]ine when they will next need treatme[illegible]

B. Immediately [illegible]erapy since VenO didn't work

C. Counsel patient that average PFS is still ~2 years, so the plan is for active surveillance with (re)treatment upon meeting iwCLL criteria again

Al-Sawaf O, *et al. Nat Comm.* 2023.

WHAT ABOUT OTHER FIXED-DURATION REGIMENS IN FRONTLINE CLL?

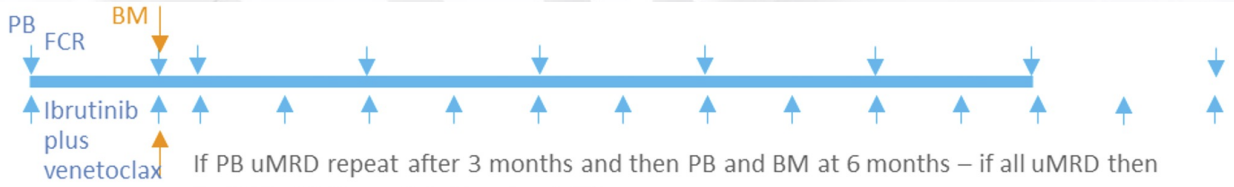
- FCR?

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL Without del(17p)/*TP53* Mutation
(alphabetical by category)

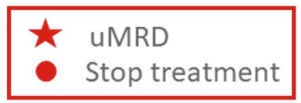
FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Acalabrutinib[f,g,*] ± obinutuzumab (category 1) • Venetoclax[f,h] + obinutuzumab (category 1) • Zanubrutinib[f,g,*] (category 1)	• Ibrutinib [f,g,i,*] (category 1) • Ibrutinib[f,g,*] + obinutuzumab (category 2B) • Ibrutinib[f,g,*] + rituximab[j] (category 2B) • Ibrutinib[f,g,*] + venetoclax[f,h] (category 2B)	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ‣ FCR (fludarabine, cyclophosphamide, rituximab)[k,l] • Consider when BTKi and venetoclax are not available or contraindicated or rapid disease debulking needed ‣ Bendamustine[m] + anti-CD20 mAb[n,o] ‣ Obinutuzumab ± chlorambucil[p] ‣ High-dose methylprednisolone (HDMP) + anti-CD20 mAb[n] (category 2B; category 3 for patients <65 y without significant comorbidities)

FLAIR: I+VenO vs. VenO vs. VenR vs. BR/FCR

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



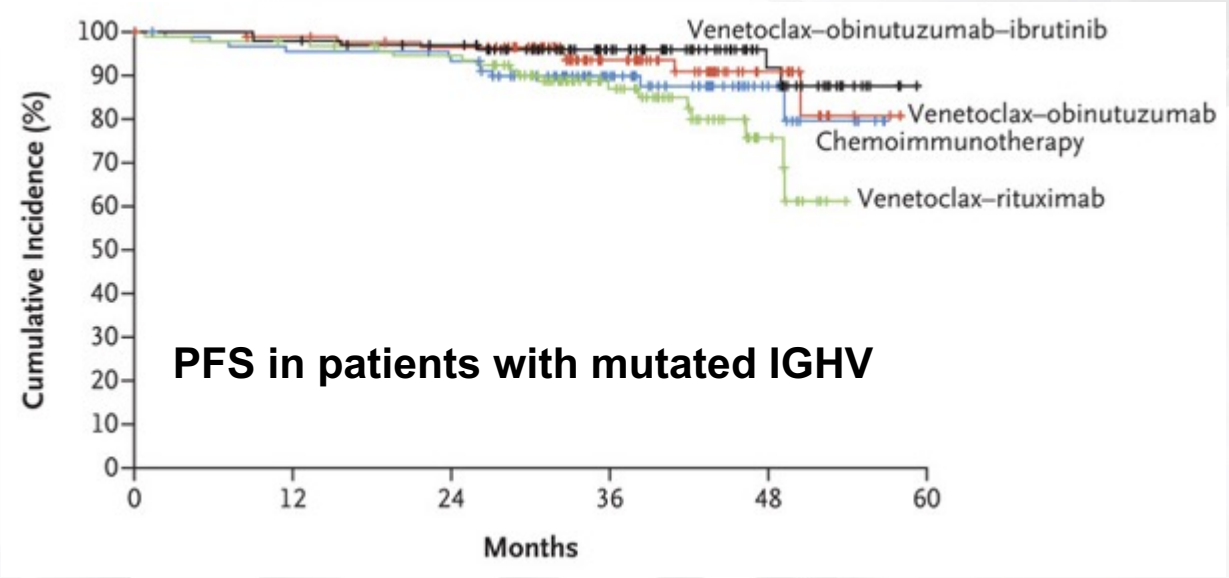
Stopping rules
2 to 6 years ibrutinib plus venetoclax
Double time after uMRD



NCCN Guidelines: CLL/SLL. Version 3.2024.
Munir T, *et al. New Eng J Med.* 2024.

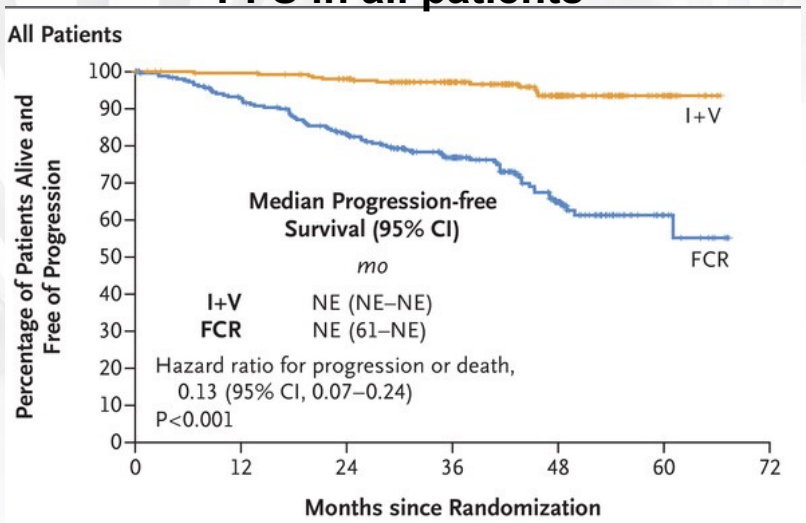
WHAT ABOUT OTHER FIXED-DURATION REGIMENS IN FRONTLINE CLL?

FLAIR: I+V vs. VenO vs. VenR vs. BR/FCR



PFS in patients with mutated IGHV

PFS in all patients

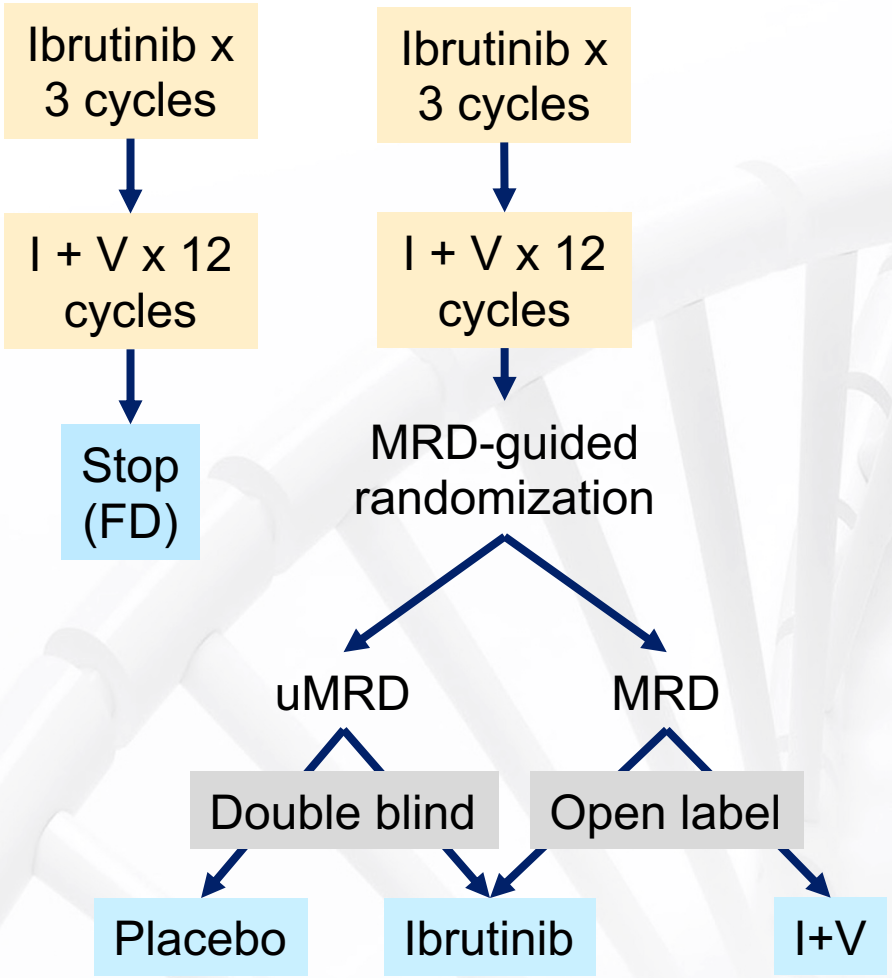


MRD-directed I+VenO showed similar PFS to VenO, regardless of subtype

Munir T, *et al. New Eng J Med.* 2024.

WHAT ABOUT NOVEL FIXED-DURATION REGIMENS IN FRONTLINE CLL?

CAPTIVATE: phase 2, I+V fixed vs MRD-guided



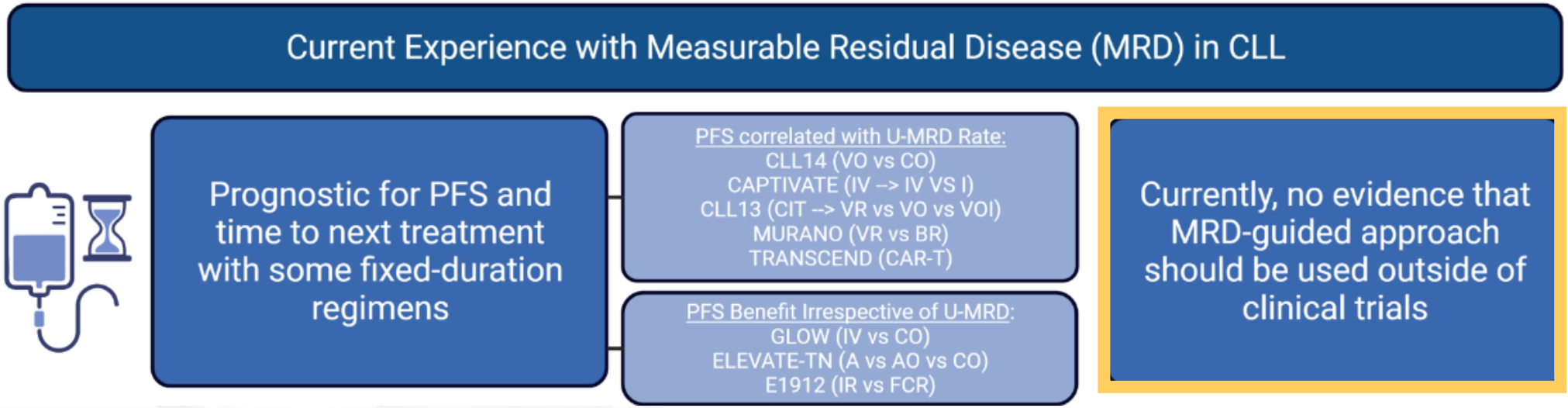
- In FD arm, uMRD associated with better PFS
- In MRD-guided arms, MRD status could help determine best treatment strategy
- Until BTKi + Ven approved as frontline approach, this strategy is not applicable in routine clinical management

Wierda W, *et al.* ASCO 2024.
Tam C, *et al. Blood.* 2022.

CONCLUSIONS

- **MRD testing does not guide routine clinical management in frontline CLL treatment… yet.**
- uMRD is *not* an important clinical endpoint with continuous frontline cBTKi therapy.
- Achieving uMRD after fixed-duration VenO therapy is prognostic… but does not currently inform changes in management.

- **MRD testing is an essential component of ongoing and future trials in CLL**:
  - Clarify relationship between clinical response and end-of-treatment MRD status in a treatment-specific context
  - Examine uMRD as a potential surrogate endpoint
  - Identify candidates for MRD-driven changes in treatment duration or switches in therapy



QUESTIONS?