Year in Review 2020: CLL Part 2

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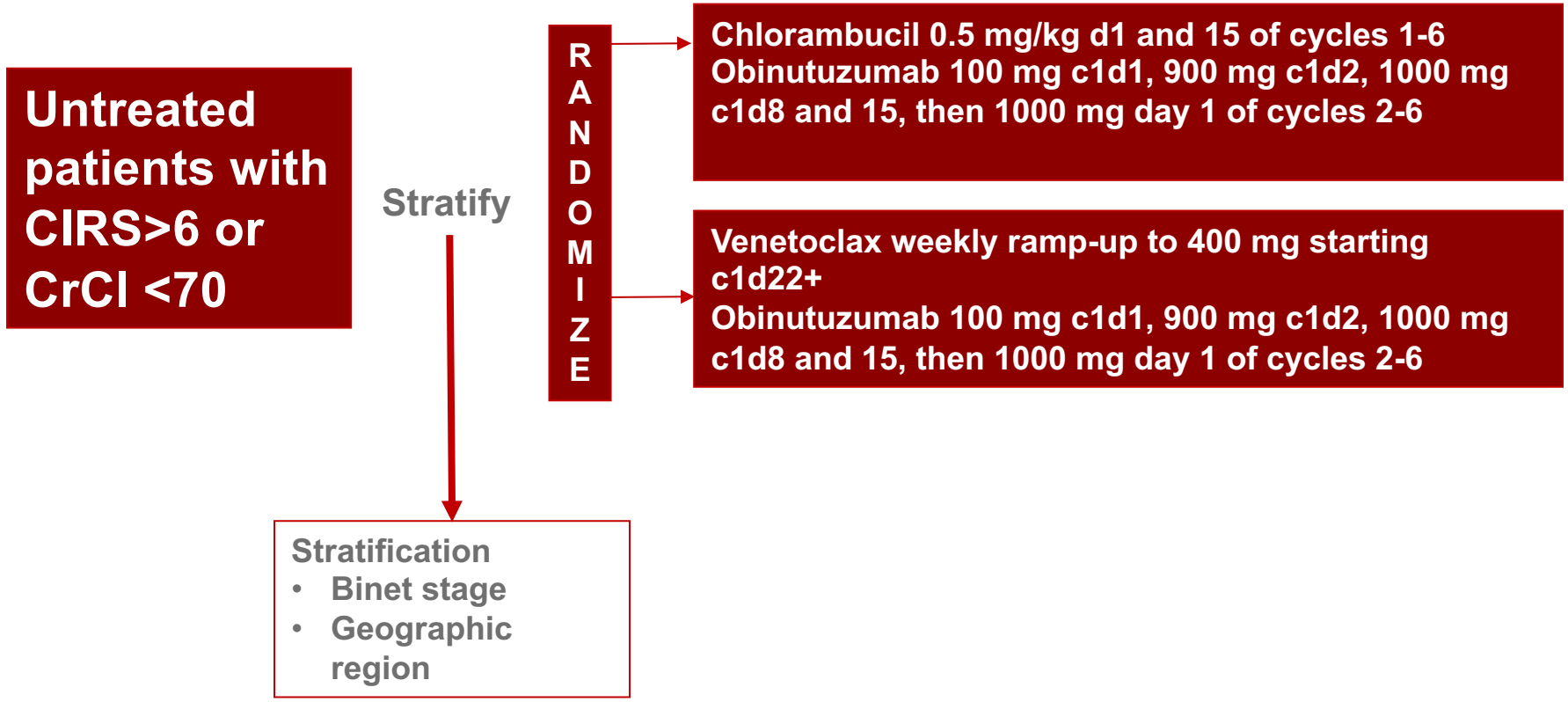
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

BCL2 Inhibitors

Courtesy of Jennifer Woyach, MD

Phase 3 CLL14 Follow-Up



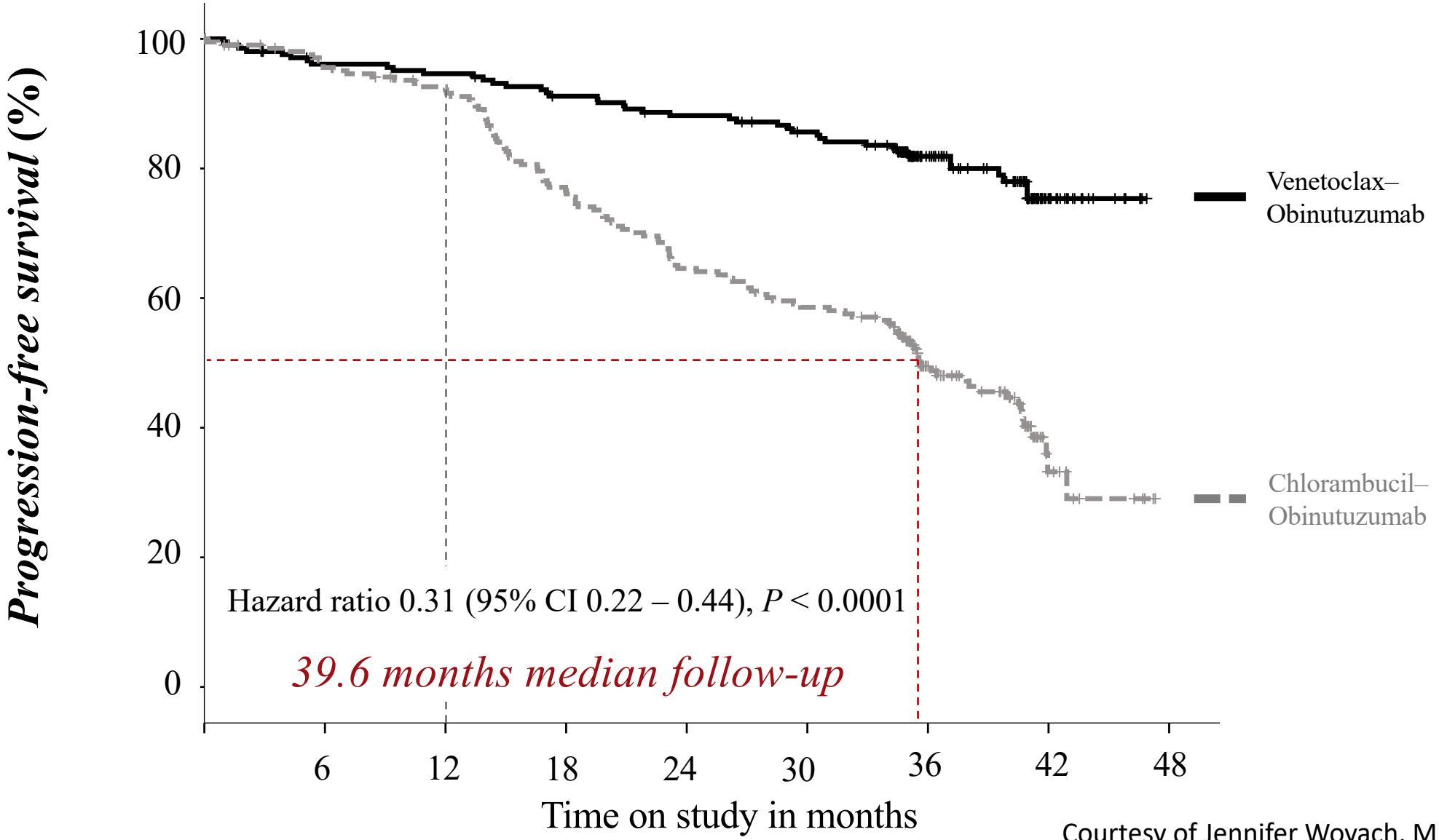
Key Points

- Median age 72
- 7-9% del(17p), 8-11% TP53 mutated
- 60% IGHV unmutated

Al-Sawaf O et al, Lancet Oncol 2020

Courtesy of Jennifer Woyach, MD

Phase 3 CLL14 Follow-Up



36 month PFS: 82% vs 50%

OS: no difference

uMRD peripheral blood 76% 3 months post-tx; 47% 18 months post-tx

Al-Sawaf O et al, Lancet Oncol 2020

Courtesy of Jennifer Woyach, MD

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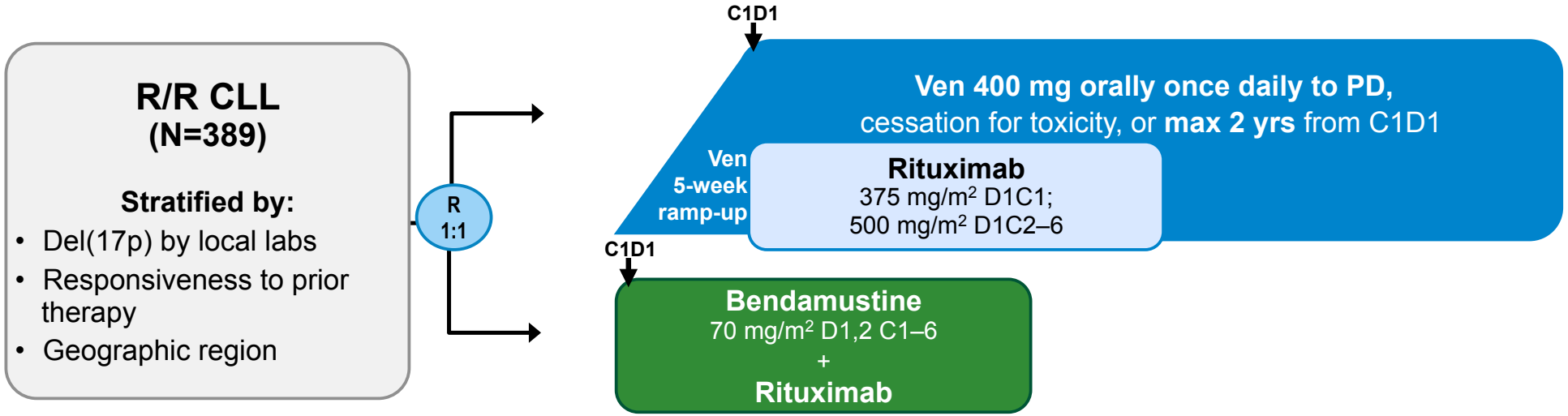
Conclusions

- **Clinical Implications**
  - Venetoclax/Obinutuzumab is a standard of care frontline regimen and ideal for patients who desire fixed duration therapy
  - Long term outcomes and potential side effects remain under investigation
- **Future Directions**
  - Median PFS not yet reached
  - Study planned (CLL17) to investigate ven/obin vs ibrutinib vs ibrutinib/ven

Courtesy of Jennifer Woyach, MD

Phase 3 MURANO Study 5 Year Follow-Up

MURANO study design



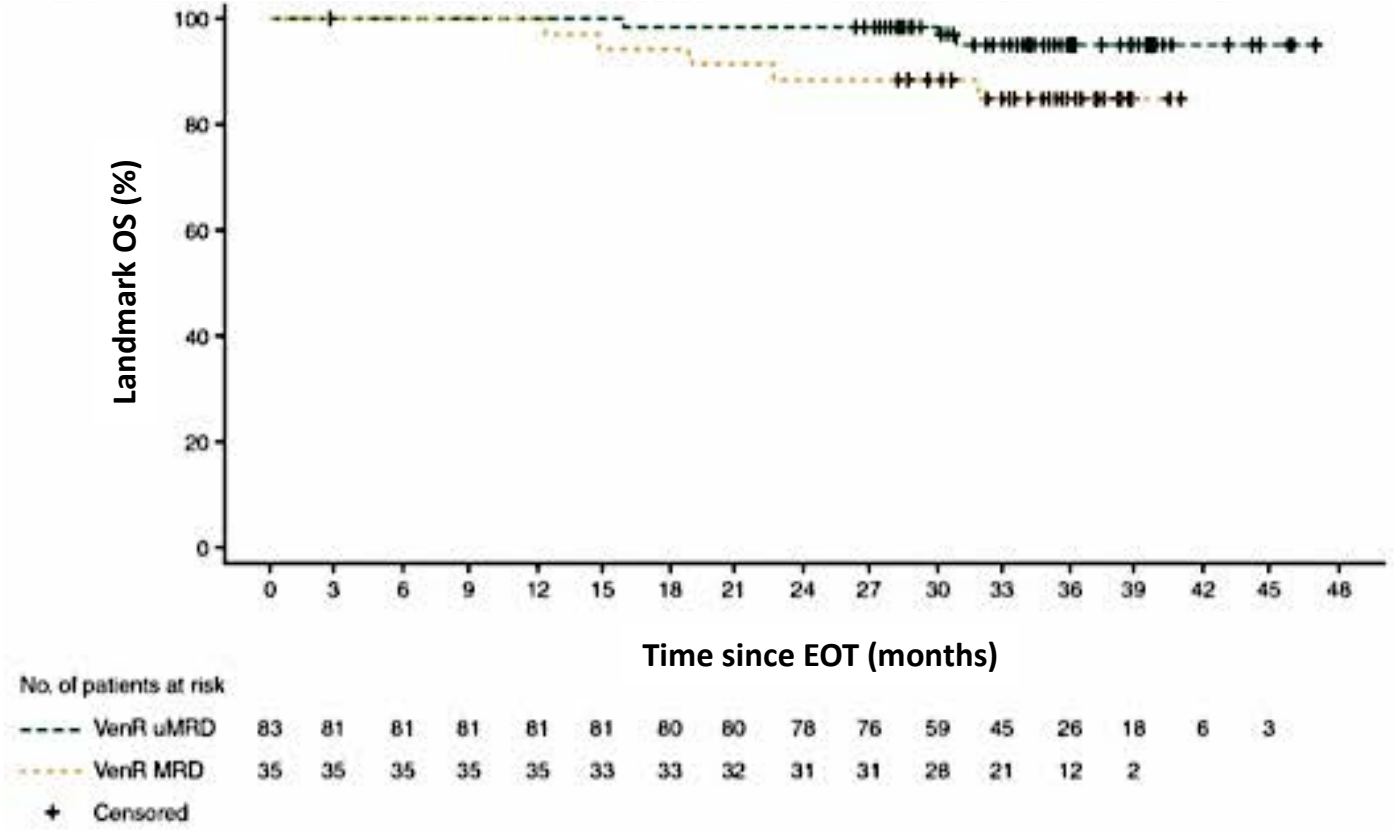
- Primary endpoint: investigator-assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD)

Kater et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Phase 3 MURANO Study 5 Year Follow-Up

Figure 1: Landmark OS by PB MRD status in pts that completed Ven Tx without PD.



EOT, end of treatment; MRD, minimal residual disease; OS, overall survival; PB, peripheral blood; PD, progressive disease; pts, patients; Tx, therapy; uMRD, undetectable minimal residual disease; Ven, venetoclax.

- Median PFS for VenR 53.6 months
- 5 year OS 82%
- Of 83 pts with uMRD at EOT, 38.5% remained uMRD. Unmutated IGHV and del17p were risk factors
- 25 months was average time from MRD conversion to requirement for therapy

Kater et al, ASH 2020

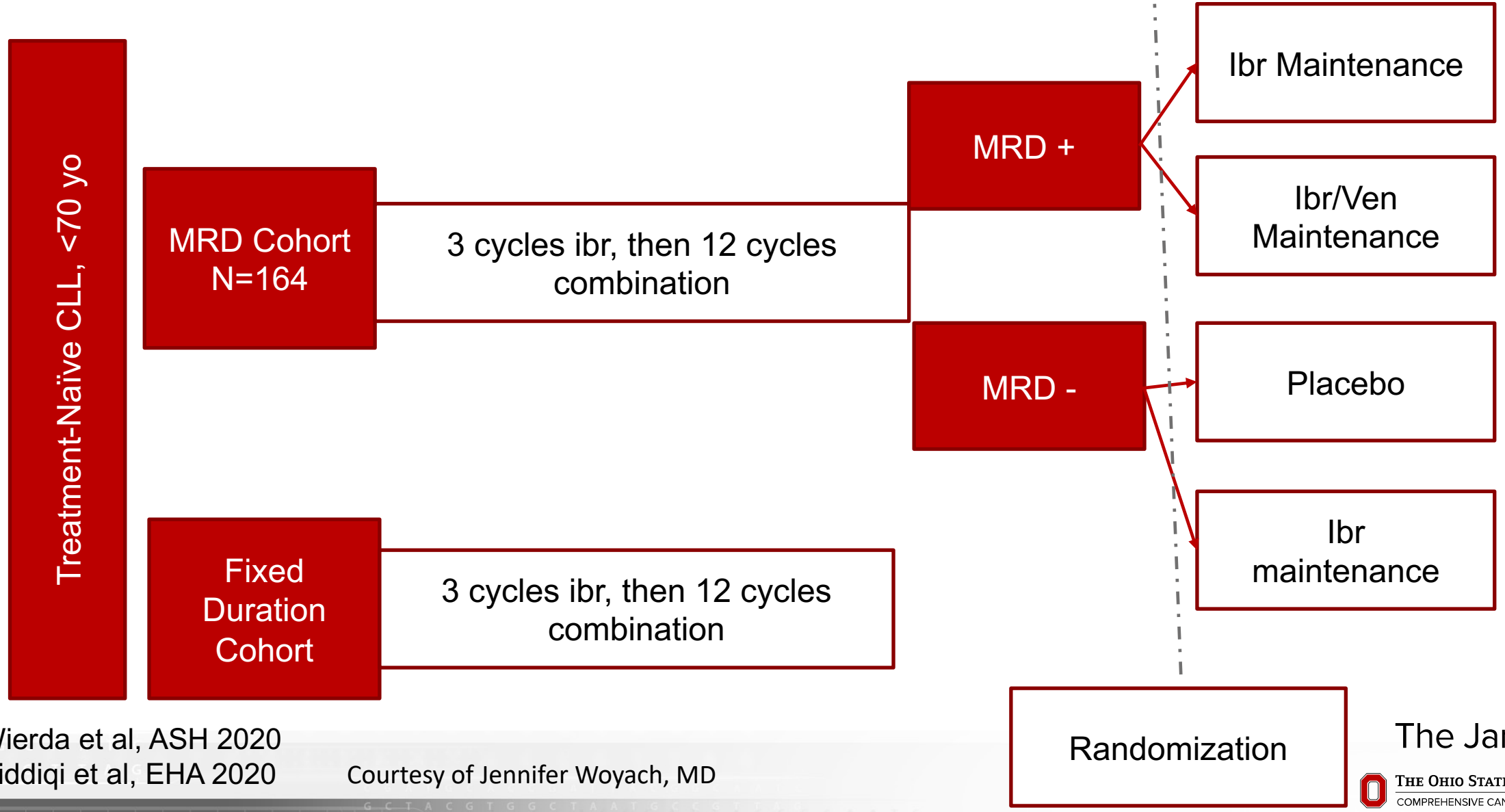
Courtesy of Jennifer Woyach, MD

Conclusions

- **Clinical Implications**
  - Venetoclax/Rituximab demonstrates durable remissions in relapsed CLL
  - Patients with del17p, genomic complexity, unmutated IGHV have higher risk of relapse
- **Future Directions**
  - Whether some patients would benefit from longer/shorter treatment course has not yet been explored
  - Benefit of higher sensitivity MRD assays (ClonoSeq) yet to be established

Courtesy of Jennifer Woyach, MD

Phase 2 CAPTIVATE MRD Cohort

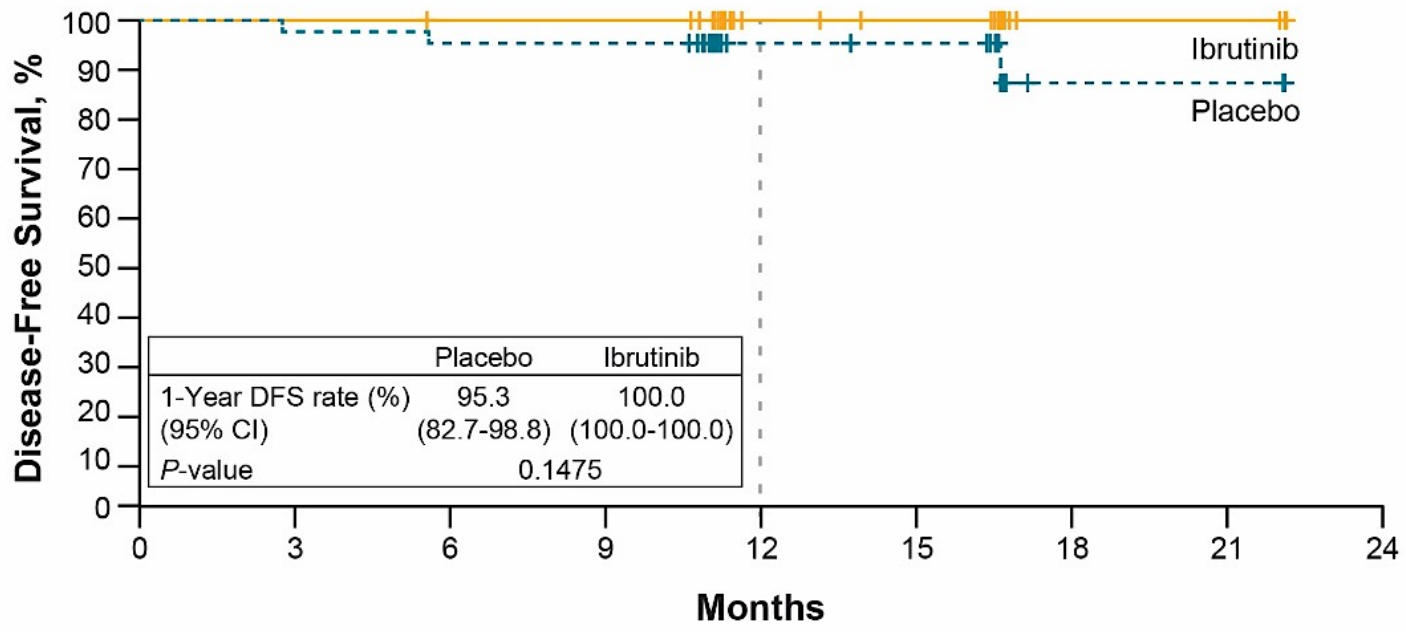


Wierda et al, ASH 2020
Siddiqi et al, EHA 2020

Courtesy of Jennifer Woyach, MD

Phase 2 CAPTIVATE MRD Cohort

Figure. DFS by Randomized Treatment Arm in Confirmed uMRD Group[a]



Patients at Risk

Placebo	43	42	41	41	22	21	3	3	0
Ibrutinib	43	43	42	42	25	23	5	5	0

[a]The 3 DFS events in placebo arm were disease progression in 2 patients and MRD relapse in 1 patient.

- Confirmed uMRD 30 month PFS
  - 95.3% placebo
  - 100% ibrutinib
- Without confirmed uMRD 30 month PFS
  - 95.2% ibrutinib
  - 96.7% ibr/ven

Courtesy of Jennifer Woyach, MD

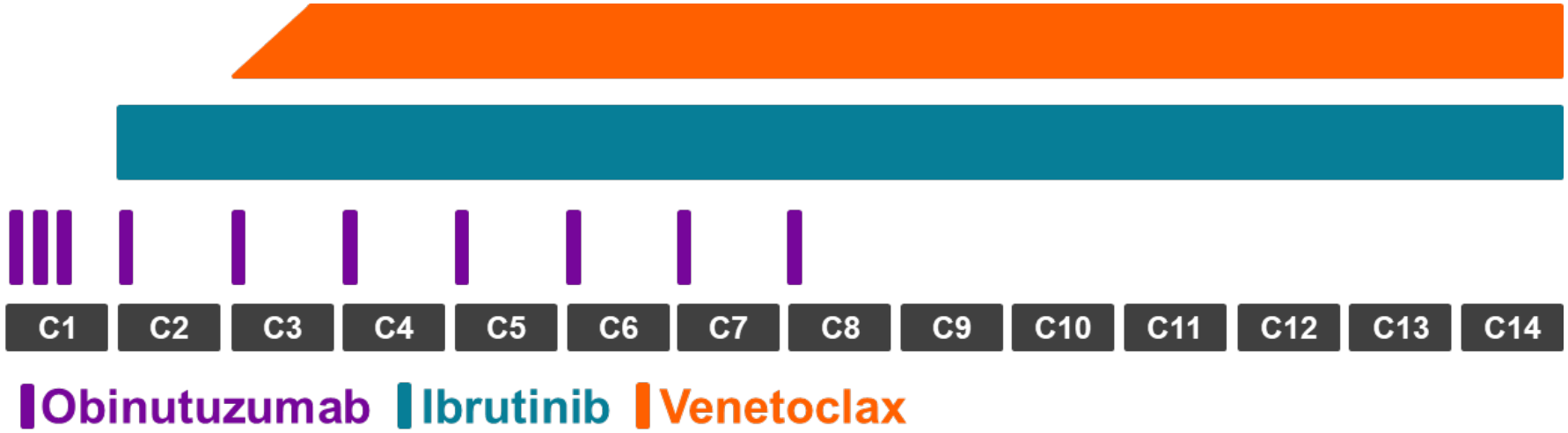
Conclusions

- **Clinical Implications**
  - For patients with no detectable MRD after 1 year treatment, further ibrutinib does not prolong PFS after an additional year
  - This is not currently standard practice
  - This follow-up is not necessarily predictive of final study outcome
- **Future Directions**
  - This study will ultimately show fixed duration vs MRD driven endpoint with ibrutinib/ven as well as utility of maintenance in uMRD

Courtesy of Jennifer Woyach, MD

Phase 2 Ibrutinib/Venetoclax/Obinutuzumab 3 year follow-up

- Phase 2 study of 1 year fixed duration ibr/ven/obin
- 25 treatment-naïve and 25 relapsed/refractory patients



Rogers et al, J Clin Oncol 2020

Courtesy of Jennifer Woyach, MD

Phase 2 Ibrutinib/Venetoclax/Obinutuzumab 3 year follow-up

- 67% of TN and 50% RR patients developed uMRD in blood and marrow
- At approximately 2 years post-completion of therapy, one patient in TN cohort died of infection, and one in RR cohort relapsed
- T and NK cells remain suppressed 1 year after completion of therapy

Rogers et al, J Clin Oncol 2020

Courtesy of Jennifer Woyach, MD

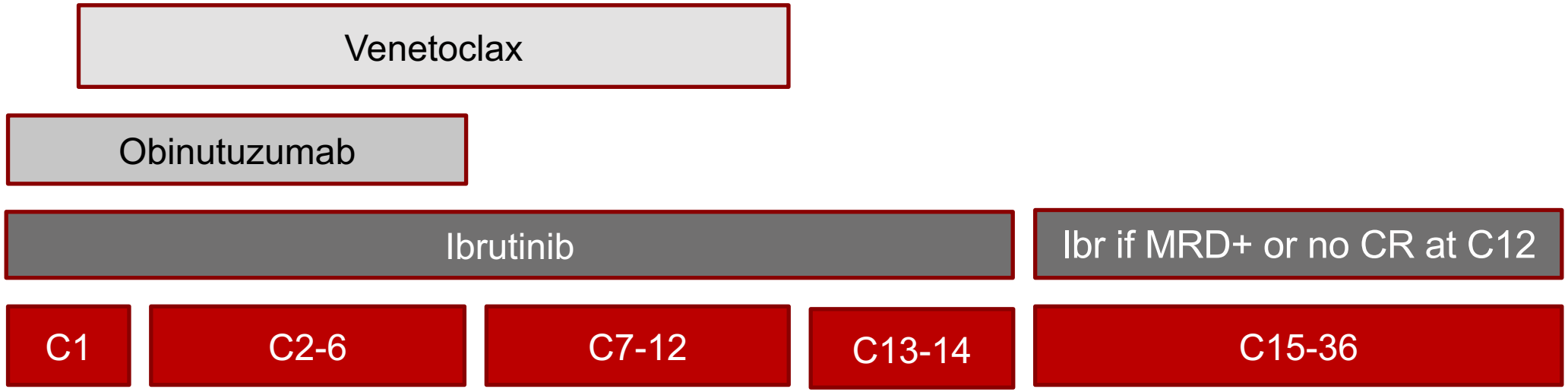
Conclusions

- **Clinical Implications**
  - IVO with 1 year fixed duration results in durable remissions of at least 2 years in almost all patients, including those MRD+ or without CR
- **Future Directions**
  - In current cohort, residual lymph node biopsy is planned at EOT to determine whether uMRD PR really represents residual disease
  - EA9161 and A041702 are phase 3 studies investigating IVO vs IO as frontline therapy

Courtesy of Jennifer Woyach, MD

Phase 2 CLL2-GIVe Study

- Included 41 patients with treatment-naïve CLL and del17p (26) and/or TP53 mutation (39)



Huber et al, EHA 2020

Courtesy of Jennifer Woyach, MD

CLL2-GIVe Study

- Median follow-up 18.6 months
  - CR 58.5%
  - Peripheral blood uMRD 80.5%
  - Only 6 patients continued ibrutinib beyond C15

Courtesy of Jennifer Woyach, MD

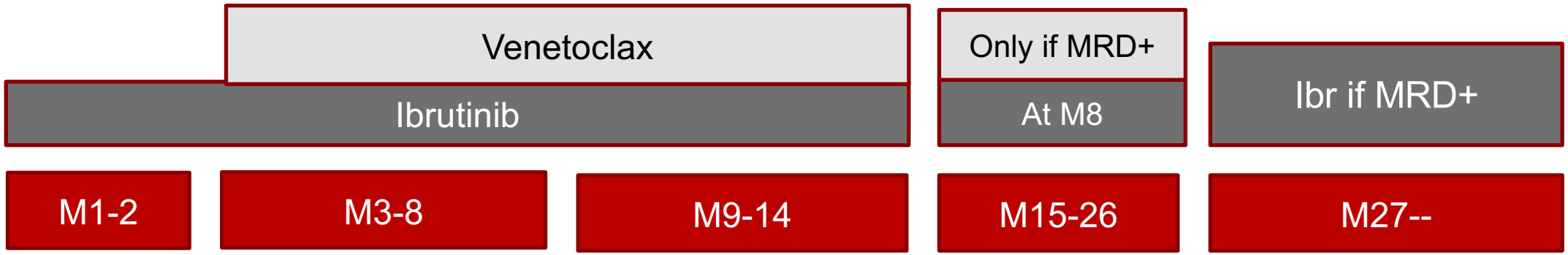
Conclusions

- **Clinical Implications**
  - IVO induces deep remissions regardless of genomic risk disease
- **Future Directions**
  - Issue with TP53 abnormalities usually is not inability to achieve remission, it is short remission duration, so this study will be more impactful in a couple of years

Courtesy of Jennifer Woyach, MD

Phase 2 CLARITY Trial

- 50 patients with relapsed/refractory CLL
- MRD in blood/marrow determined duration of therapy

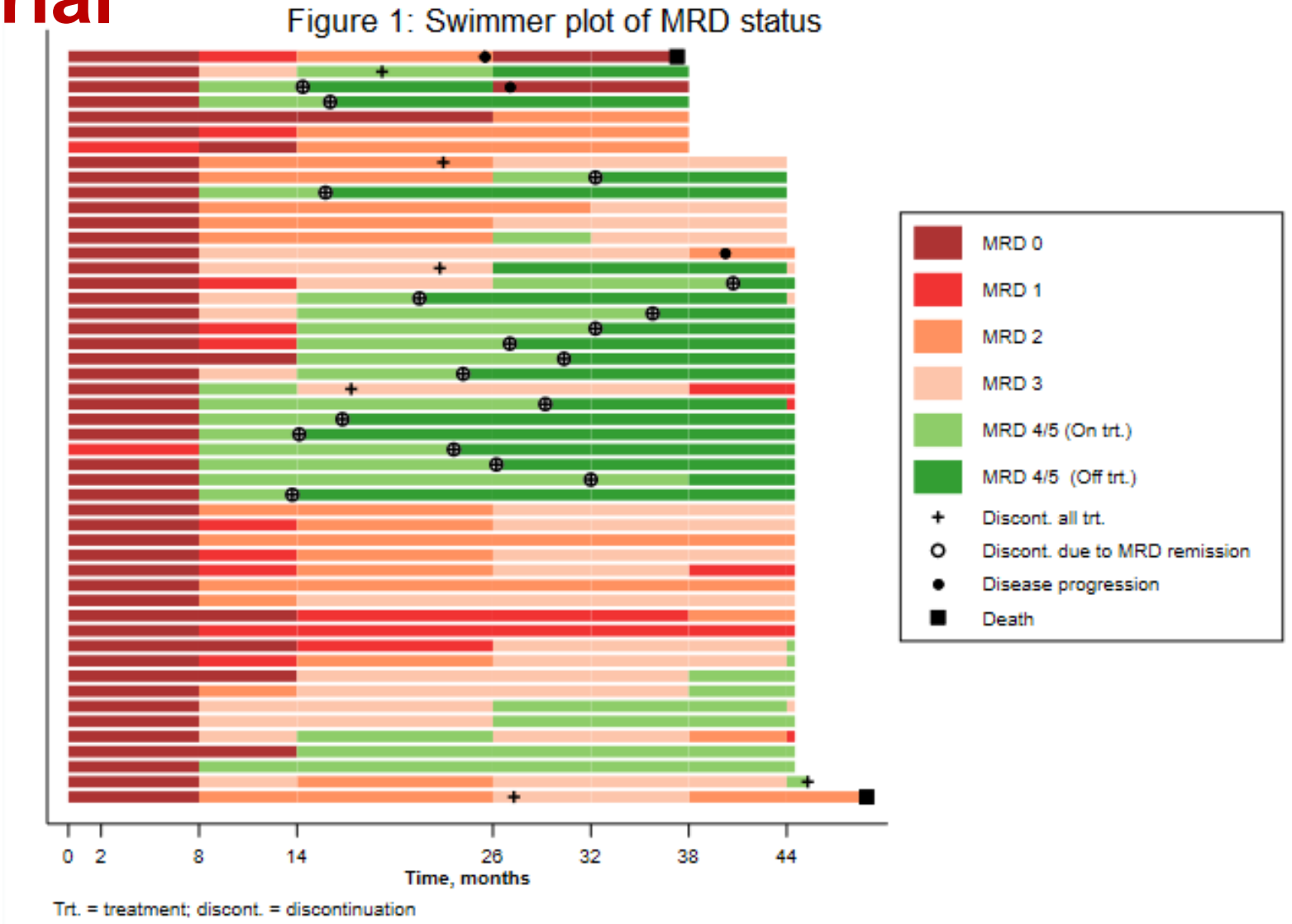


Hillmen et al, J Clin Oncol 2019
Hillmen et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Phase 2 CLARITY Trial

- 4 patients discontinued ibr in first 8 weeks and were replaced
- 23 pts stopped both treatments at or before M38, 17/23 were in uMRD4
- 40% achieved uMRD at month 14 and 48% at M26



Hillmen et al, J Clin Oncol 2019
Hillmen et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Conclusions

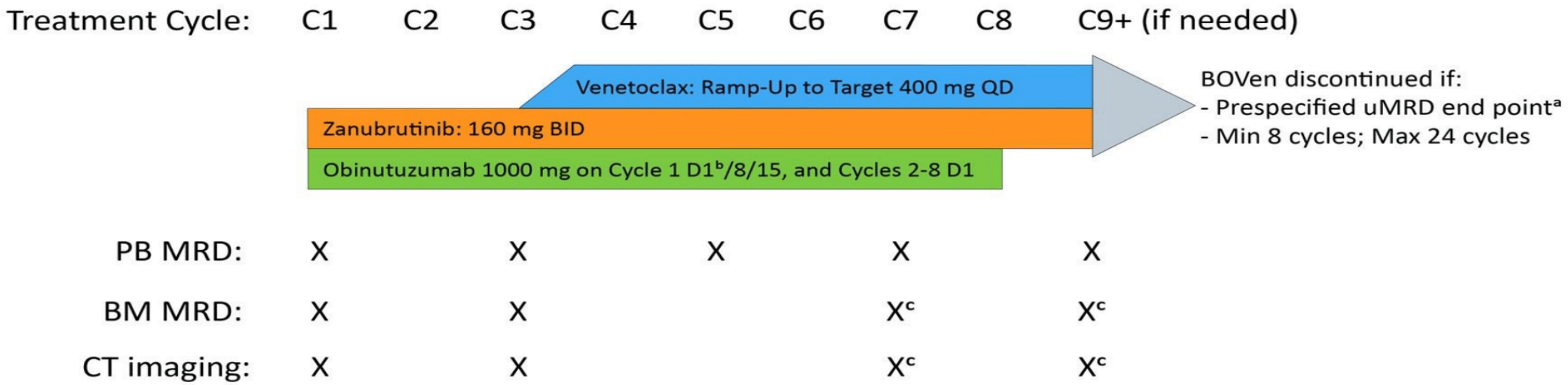
- **Clinical Implications**
  - Ibrutinib/Venetoclax demonstrates deep remissions in relapsed CLL
- **Future Directions**
  - Remission duration is not yet known for any of these combination therapies
  - Fixed duration vs MRD or response driven approaches have not been compared

Hillmen et al, J Clin Oncol 2019
Hillmen et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Phase 2 BOVen in TN CLL

- 39 patients
- 72% high or very-high CLL-IPI



a- Once peripheral blood (PB) uMRD is determined and confirmed in bone marrow (BM), patients complete 2 additional cycles followed by confirmatory MRD peripheral blood testing; if PB uMRD x 2 and BM uMRD x 1, therapy is discontinued.
b- Obinutuzumab split over days 1-2 of cycle 1 if ALC >25,000.
c- BM biopsy obtained at Screening and C3D1; thereafter BM is only obtained if PB-uMRD.
CT imaging obtained at Screening, C3D1, C7D1, EOT, then every 6 months during post-treatment surveillance.

Soumerai et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Phase 2 BOVen in TN CLL

- Median follow-up 14 months
  - 92% have achieved uMRD in peripheral blood and 84% in marrow
  - Median time to BM uMRD is 6 months
  - 77% of patients discontinued therapy at median 10 months
  - No recurrent MRD or progression has been observed

Soumerai et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Conclusions

- **Clinical Implications**
  - Zanubrutinib/Venetoclax/Obinutuzumab shows high rates of uMRD in bone marrow
- **Future Directions**
  - These uMRD rates are higher than demonstrated in ibrutinib and acalabrutinib studies
  - Will be helpful to see longer follow-up with this as other doublet/triplet studies

Courtesy of Jennifer Woyach, MD

Phase 1b AVO or AVR in Treatment Naïve or RR CLL

- Primary endpoint: safety
- Secondary Endpoints: ORR, uMRD, PFS, OS

Cohort 3[a]: RR CLL

Patients with ≥1 prior treatment[b]

n=12

→

Acalabrutinib, venetoclax, rituximab (AVR)[c]

A: 100 mg PO BID until progression or end of Cycle 24[d]

V: Cycle 3 ramp-up dose weekly; Cycle 4, Day 1, 400 mg/day until end of Cycle 15

R: 375 mg/m^2 IV for 9 infusions; Cycle 2, Days 1, 8, 15, 22; Cycles 3–7, Day 1)

Cohort 4: TN CLL

Previously untreated patients[b]

n=12

→

Acalabrutinib, venetoclax, obinutuzumab (AVO)[c]

A: 100 mg PO BID until progression or end of Cycle 24[d]

V: Cycle 3 ramp-up dose weekly; Cycle 4, Day 1, 400 mg/day until end of Cycle 15

O: Standard dosing IV; Cycle 2, Days 1, 2, 8, 15; Cycles 3–7, Day 1

Woyach et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Phase 1b AVO or AVR in Treatment-Naïve or RR CLL

- Median follow-up 23 mo for RR, 22 mo for TN
  - 3 pts off treatment (AE and pt choice)
  - ORR 92% in RR and 100% in TN
  - 50% achieved CR or CRi with uMRD
  - 18 mo PFS 100% in both cohorts

Woyach et al, ASH 2020

Courtesy of Jennifer Woyach, MD

Conclusions

- **Clinical Implications**
  - Acalabrutinib/Venetoclax/Obinutuzumab induces deep remissions
- **Future Directions**
  - Will be helpful to eventually differentiate among BTKi in these doublets/triplets
  - Optimal treatment course not determined

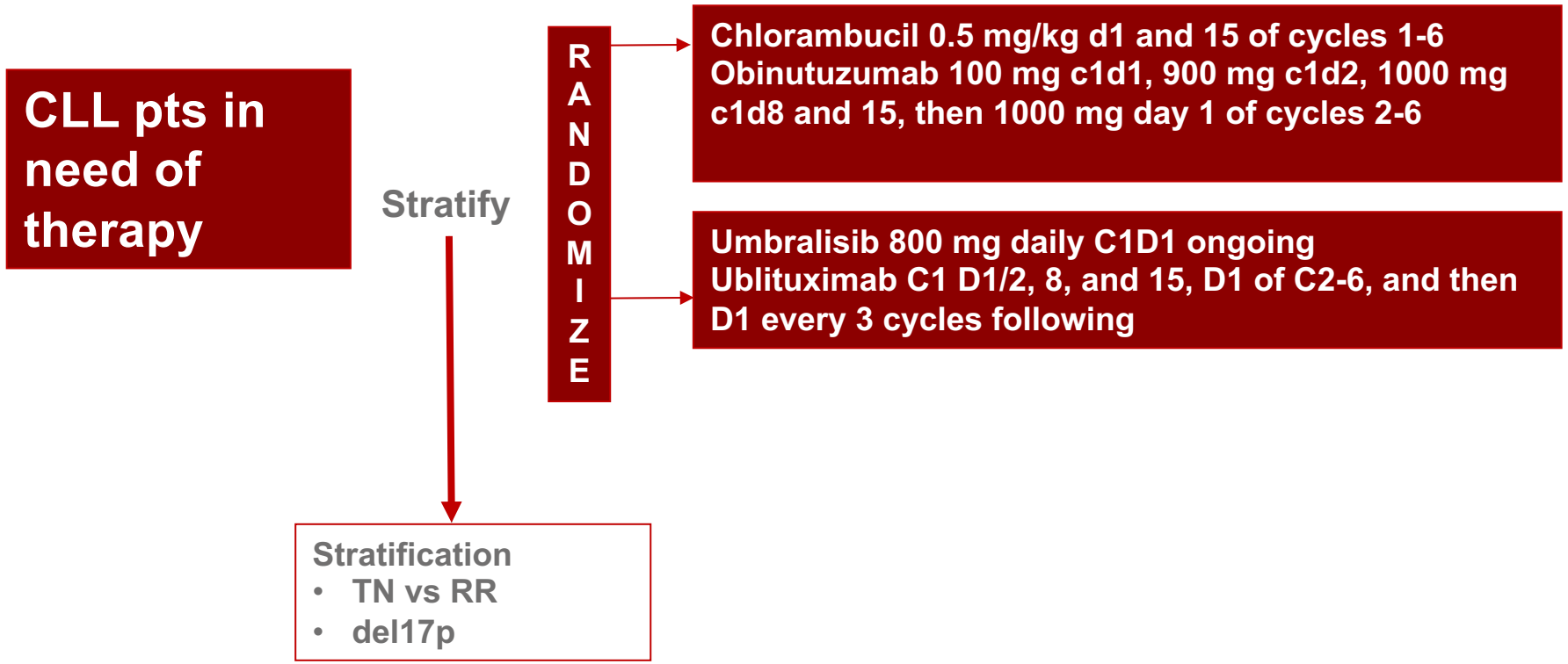
Courtesy of Jennifer Woyach, MD

PI3K Inhibitors

Courtesy of Jennifer Woyach, MD

Phase 3 UNITY-CLL Study

- 421 total patients
- 57% TN
- 56% IGHV unmutated
- 10% del17p



Gribben et al, ASH 2020 Abstract 543

Courtesy of Jennifer Woyach, MD

Phase 3 UNITY-CLL Study

- Median follow-up 36 months
- Median PFS U2 31.9 mo vs 17.9 mo overall
- In TN, U2 PFS 38.5 mo vs 26.1 mo
- In RR, U2 PFS 19.5 mo vs 12.9 mo
- G3+ Colitis in 3.4%, Transaminitis G3+ in 8.3%, G3+ pneumonitis in 2.9%

Courtesy of Jennifer Woyach, MD

Conclusions

- **Clinical Implications**
  - Umbralisib + Ublituximab is superior to Chlorambucil/obinutuzumab (note ongoing ublituximab)
  - PFS with this regimen is shorter than reported with venetoclax or BTKi based regimens, so likely this will be reserved for those with contraindications to other therapies
- **Future Directions**
  - Triplet studies with venetoclax may improve response depth and duration

Courtesy of Jennifer Woyach, MD

CAR-T Cells

Courtesy of Jennifer Woyach, MD

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Phase 1 TRANSCEND CLL 004 Study: Liso-Cel Plus Ibrutinib

- Liso-Cel is 4-1BB CAR-T product with equal CD4/CD8
- In this cohort patients had to have previously received ibrutinib, reinitiated or continued at study start and continued at least 90 days post CAR-T
- Lymphodepletion with Flu/Cy

Wierda et al, ASH 2020 Abstract 544

Courtesy of Jennifer Woyach, MD

Phase 1 TRANSCEND CLL 004 Study: Liso-Cel Plus Ibrutinib

- 19 patients included
- Median 4 prior therapies
- 74% had BTKi as last therapy and 53% had also received venetoclax
- 74% CRS, 1 grade 3; 16% G3+ neurologic events
- ORR 95%, 47% CR/CRi
- 83% maintained response at 3 months
- 79% had uMRD in marrow

Wierda et al, ASH 2020 Abstract 544

Courtesy of Jennifer Woyach, MD

Conclusions

- **Clinical Implications**
  - Liso-Cel with ibrutinib has shown deep remissions and low rate of G3+ CRS and neurologic events
- **Future Directions**
  - Long-term follow-up will be critical to compare to those without ibrutinib and evaluate long-term efficacy

Courtesy of Jennifer Woyach, MD

Phase 1 TRANSCEND CLL 004 Study: Liso-cel monotherapy

- Study schema same as previous, but without ibrutinib
- 23 pts evaluable for safety, 22 for efficacy
- Median 6 prior therapies, all with prior ibr and 48% with ven too
- ORR 82%, CR/CRi 45%
- Median PFS 18 months, 5/8 progressions were RT
- G3+ CRS 9%, G3+ neuro events 22%

Siddiqi et al, ASH 2020 Abstract 546

Courtesy of Jennifer Woyach, MD

Conclusions

- **Clinical Implications**
  - Liso-cel shows impressive responses and durability in very heavily pretreated patients, including those post-ibrutinib and venetoclax
- **Future Directions**
  - Investigations as to best sequencing of CAR-T relative to other therapies will be very important

Courtesy of Jennifer Woyach, MD