9th POSTGRADUATE
Lymphoma
Conference

Actual and New Strategies for Relapsed/Refractory MCL Patients

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Disclosures

Disclosures of Michael E. Williams, MD, ScM

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Allos	xx						
Janssen	xx					xx	
Pharmacyclics	xx					xx	
Abbvie						xx	
AstraZeneca						xx	
Beigene						xx	
Celgene						xx	
Kite						xx	

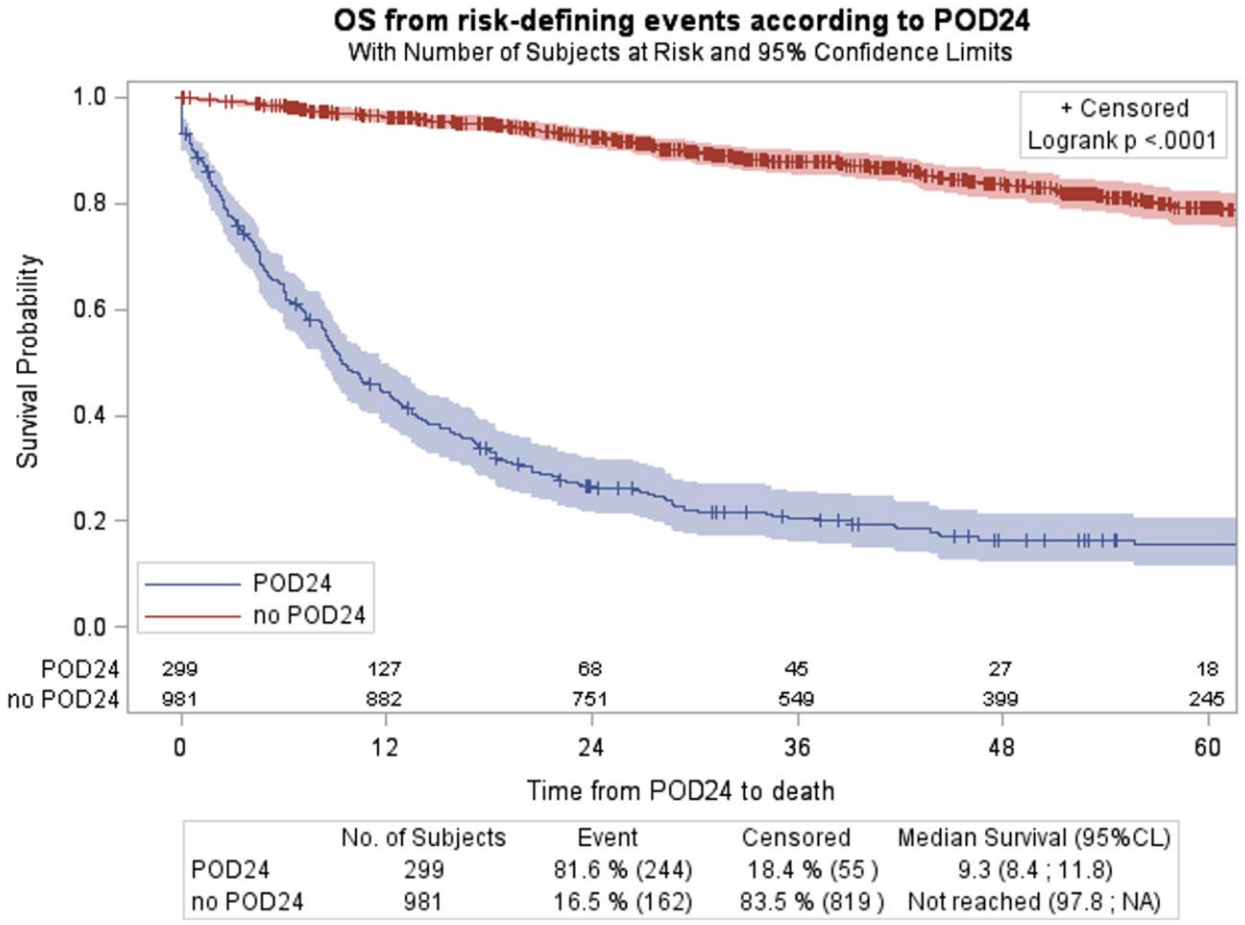
The evolving therapeutic landscape for R/R MCL in 2025….

- New realities of front-line therapy
  - *…. De-escalated induction therapy: No high-dose cytarabine, no ASCT*
  - *…. BTKi incorporation into induction and maintenance regimens*
  - *…. Chemo-free regimens: BOVen, AVO, ALR*
- Younger, medically fit at relapse
  - *…. Re-induction → CAR-T consolidation? Maintenance?*
  - *…. Allo transplant? (remains the only established curative therapy)*
- Older or less fit at relapse
  - *…. CAR-T or Bispecific mAb in selected patients*
  - *…. BTKi +/- anti-CD20 mAb, BCL2i; Lenalidomide/anti-CD20 mAb*
- Important considerations
  - *…. TP53-mutated, Blastoid variant, MRD status, POD24 vs later relapse*

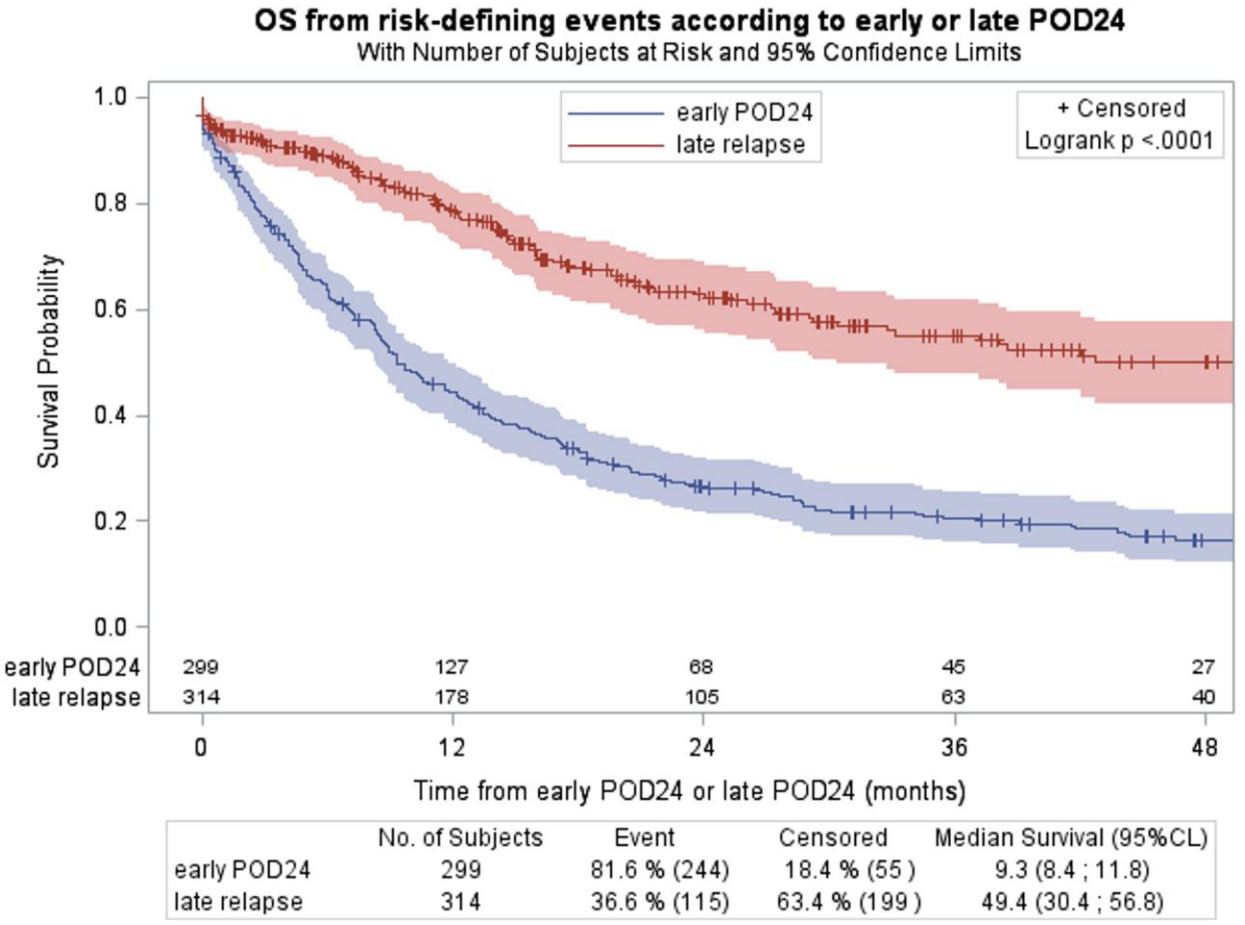
The relevance of POD24 and MCL patient outcomes….

Validation of POD24 As a Robust Early Clinical End Point of Poor Survival in MCL from 1280 Patients on Clinical Trials.

Sarkozy C, et al, *Blood* 2023 (ASH abstract)



	No. of Subjects	Event	Censored	Median Survival (95%CL)
POD24	299	81.6 % (244)	18.4 % (55)	9.3 (8.4 ; 11.8)
no POD24	981	16.5 % (162)	83.5 % (819)	Not reached (97.8 ; NA)



	No. of Subjects	Event	Censored	Median Survival (95%CL)
early POD24	299	81.6 % (244)	18.4 % (55)	9.3 (8.4 ; 11.8)
late relapse	314	36.6 % (115)	63.4 % (199)	49.4 (30.4 ; 56.8)

The relevance of POD24 and MCL patient outcomes….

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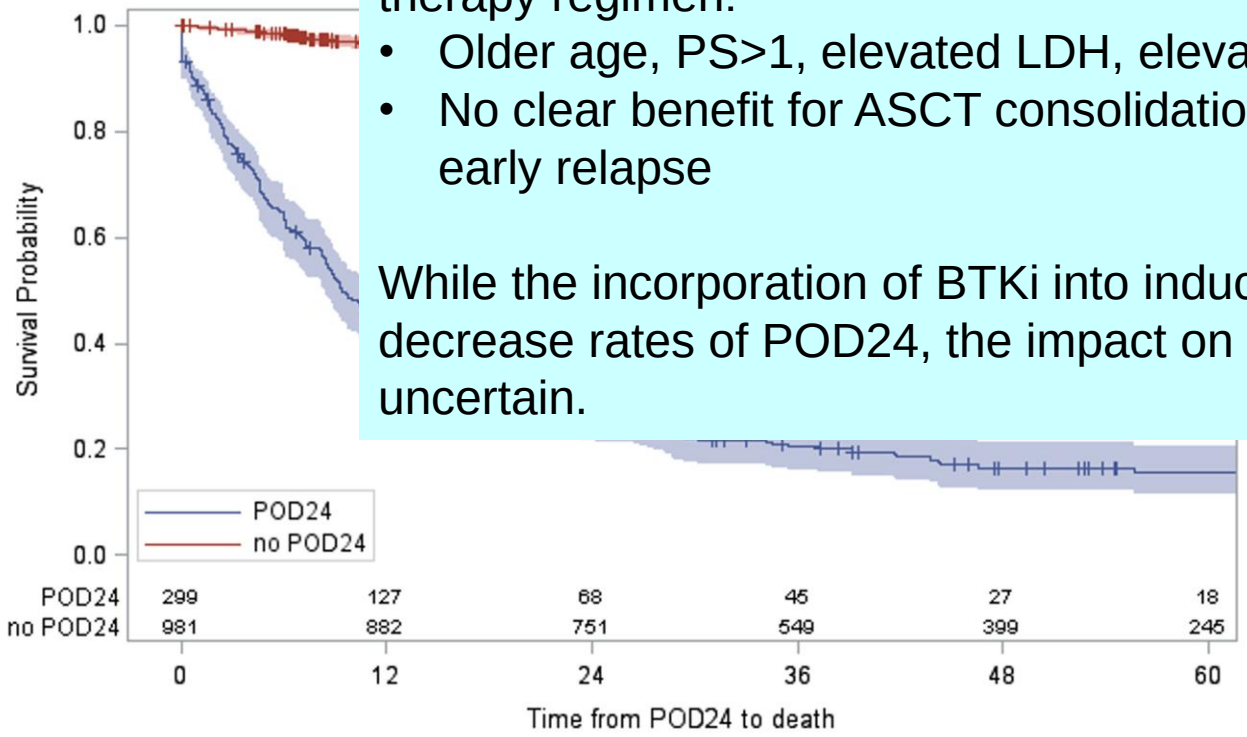
Sarkozy C, et al, *Blood* 2023 (ASH abstract)

POD24 was associated with clinical and biologic factors at diagnosis, *not* front-line therapy regimen:

- Older age, PS>1, elevated LDH, elevated WBC, Ki-67 >30%, blastoid morphology
- No clear benefit for ASCT consolidation or rituximab maintenance in preventing early relapse

While the incorporation of BTKi into induction and maintenance regimens may decrease rates of POD24, the impact on response to subsequent lines of therapy is uncertain.



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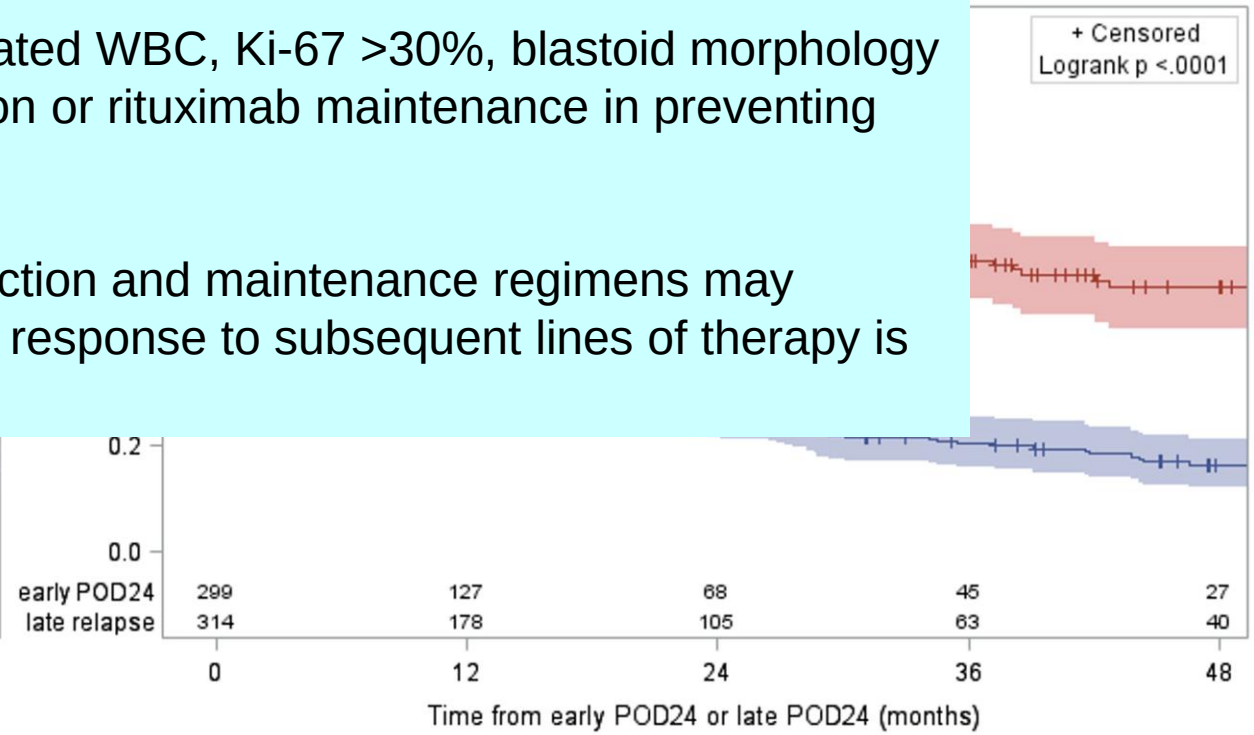

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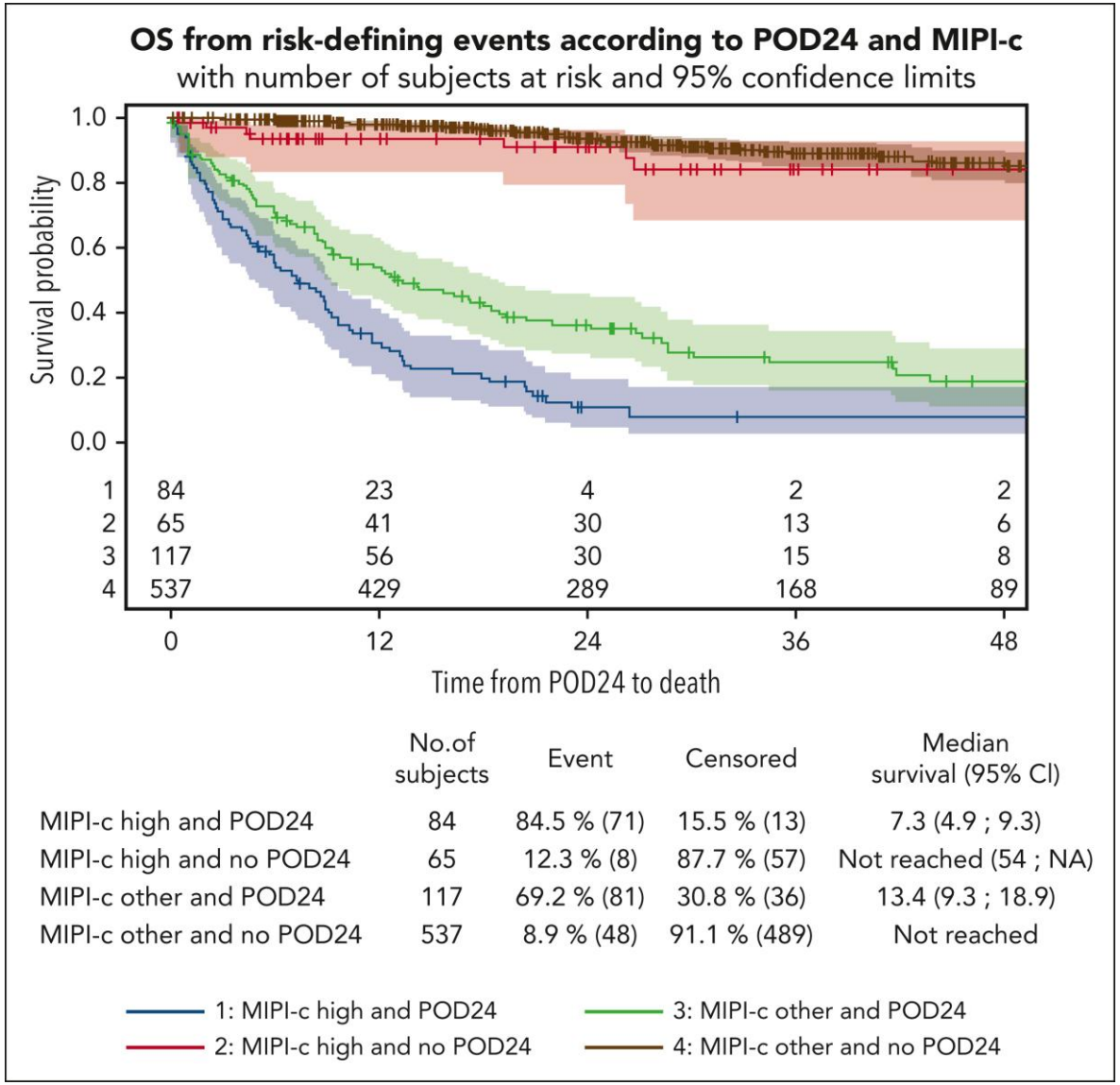
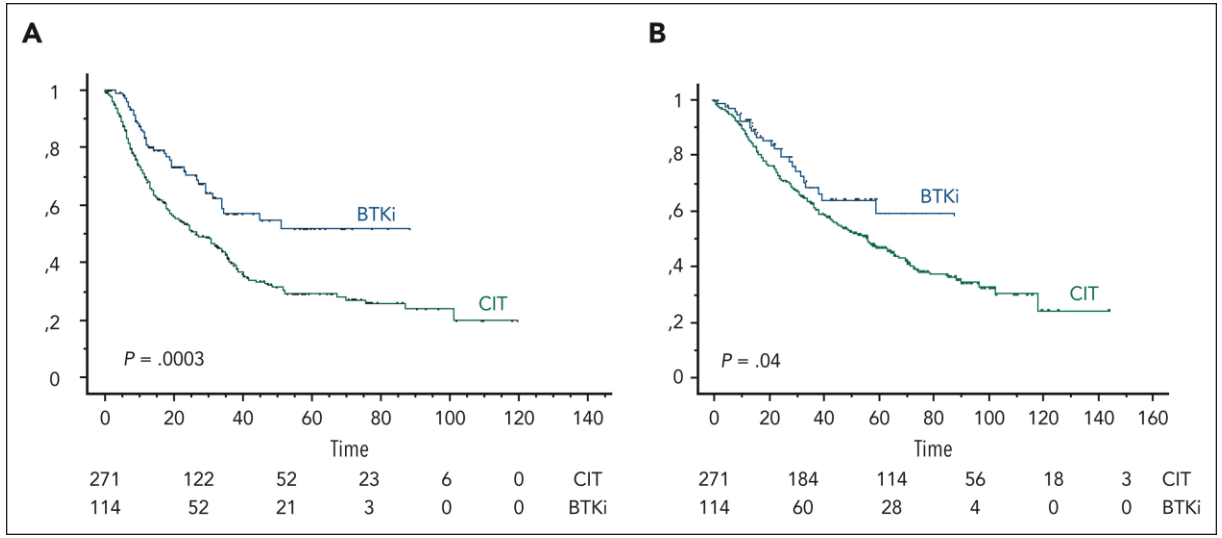
MCL Outcomes: Impact of POD24 and MIPI-c Score on Overall Survival in 800 Patients



Silkenstedt E, Dreyling M. *Blood,* 2025; 145:673-82

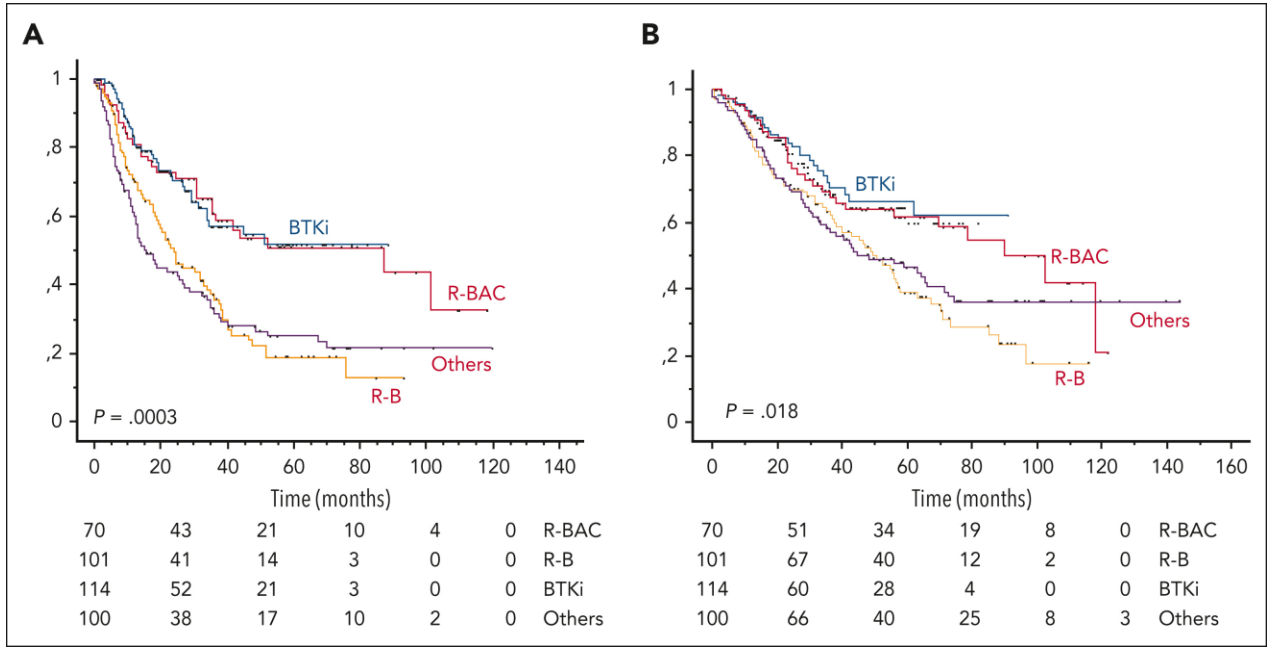
Outcomes of younger patients with MCL experiencing late relapse (>24 months): the LATE-POD study. Malinverni C, et al. *Blood* 2024; 144:1001-9



Survival curves of 385 patients with late POD according to second-line treatment.

(A) **PFS** from time of second-line therapy (PFS-2) of BTKi (median not reached) vs CIT (median, 26 months).

(B) **OS** from time of second-line therapy (OS-2) of BTKi (median, 88 months) vs CIT (median, 56 months).



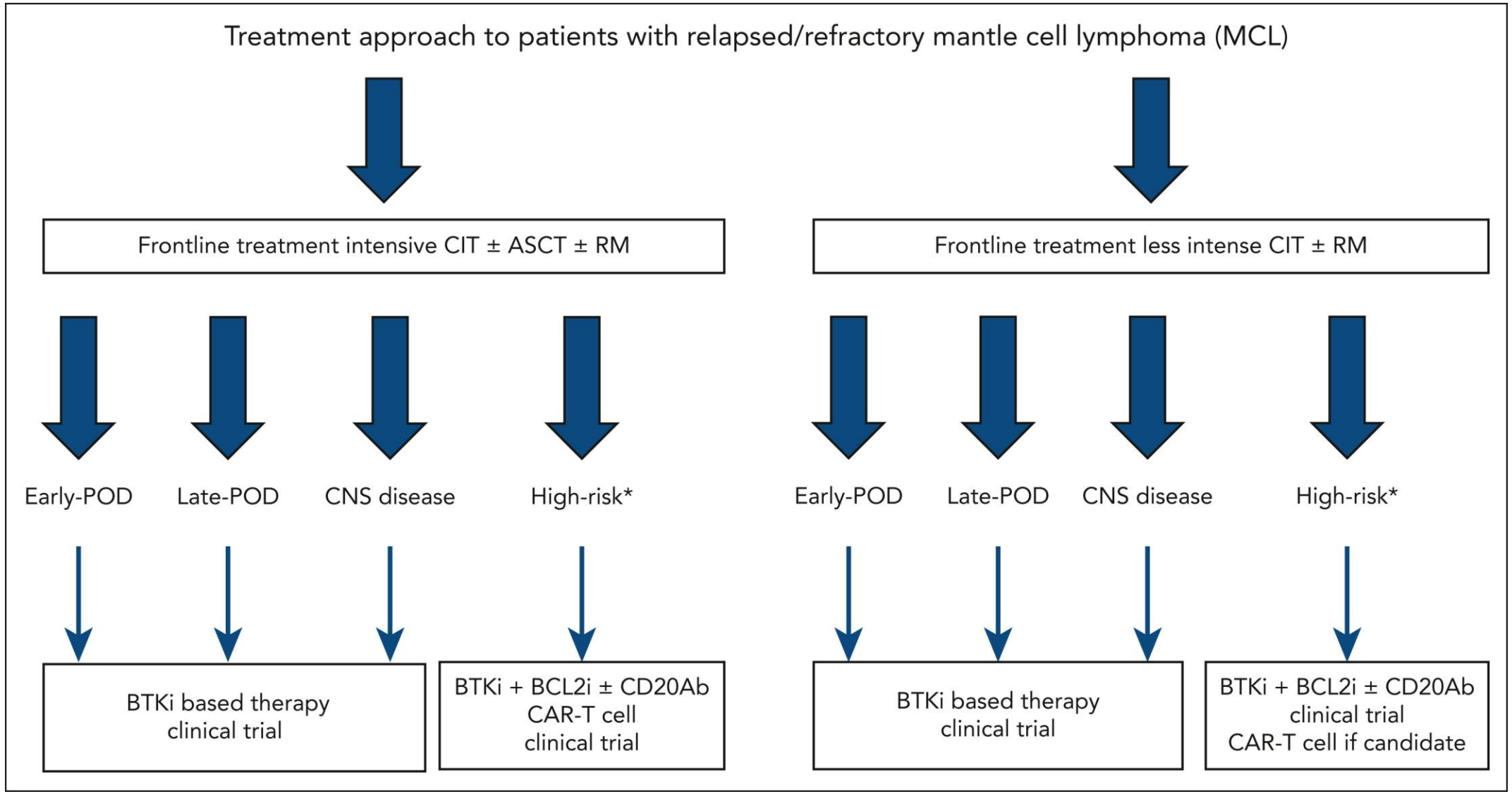
Survival curves of 385 patients with late POD divided according to second-line regimen.

(A) **PFS** from time of second-line therapy (PFS-2) of BTKi vs R-BAC, R-B, or other approaches.

(B) **OS** from time of second-line therapy (OS-2) of BTKi vs R-BAC, R-B, or other approaches.

Approach to MCL patients with POD24

"BTKi is better: a lesson learned?" Maddocks K, *Blood* 2024; 144:926-7



BTKi-based combinations in R/R MCL

“Actual Strategies”

(focused on ibrutinib-based regimens)

Covalent BTKi in R/R MCL

- Most commonly used 2nd-line therapy following 1st-line R-chemo
  - Efficacy is similar across the agents, but toxicities differ
  - BTKi outperform most CIT in 2nd line, with fewer toxicities
  - In U.S., ibrutinib withdrawn for the MCL indication in 2023
  - Acalabrutinib or zanubrutinib now utilized, alone or in combination

- Outcomes after progression on BTKi are historically poor

- A 2nd–line BTKi MIPI predicts PFS2 and OS2 (*Blood Adv* 2023; 7:4576-85)
  - **Factors:** 1) Time to POD, 2) Ki-67 at diagnosis, 3) MIPI score at diagnosis

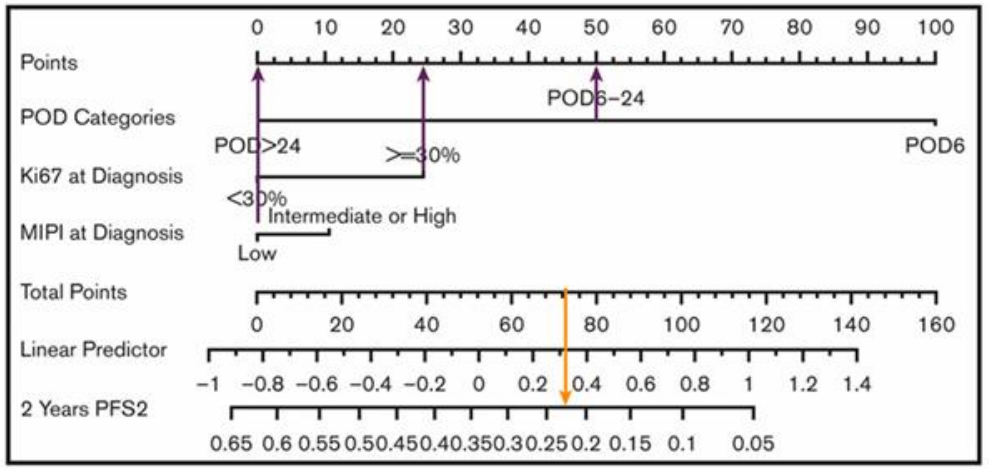
Time to progression of disease and outcomes with second-line BTK inhibitors in R/R MCL

Villa D, et al. *Blood Adv* 2023; 7:4576-85

A calculator predictive of PFS2 and OS2 – the **2L BTKi MIPI**

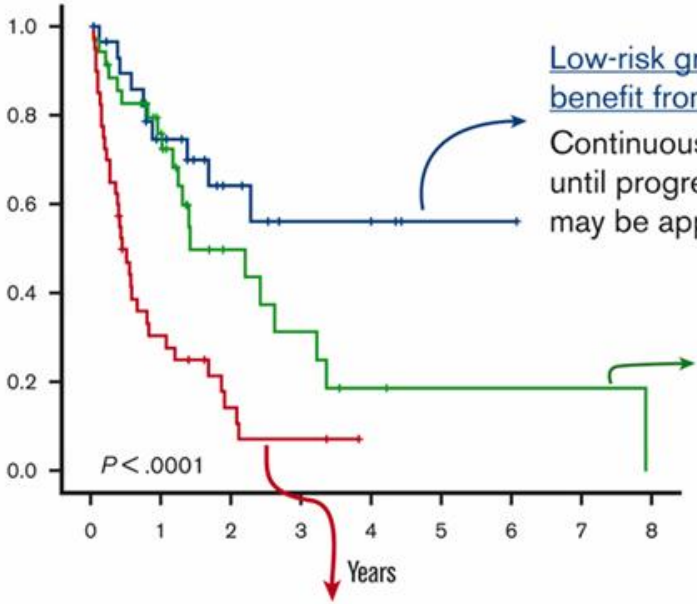
Estimating duration of benefit from second line BTK inhibitors in patients with relapsed/refractory mantle cell lymphoma

Time to progression of disease after 1L rituximab-based therapy, Ki67, and MIPI collectively contribute to PFS from the point of 2L BTKi initiation (PFS2), summarized in the nomogram below and the online calculator in QxMD.



Example: Patient with relapsed MCL 12 months after 1L rituximab-based therapy (POD6-24 = 50 points), high Ki67 (24 points), and low-risk MIPI (0 points) is assigned 72 points (purple arrows show individual point contribution). This translates to a 2-year PFS2 20-25% (orange arrow, bottom line).

The MCL BTKi MIPI categorizes these results into three clinically relevant PFS2 subgroups (also in QxMD).



Low-risk group: sustained benefit from 2L BTKi

Continuous BTKi monotherapy until progression or toxicity may be appropriate

Intermediate-risk group:

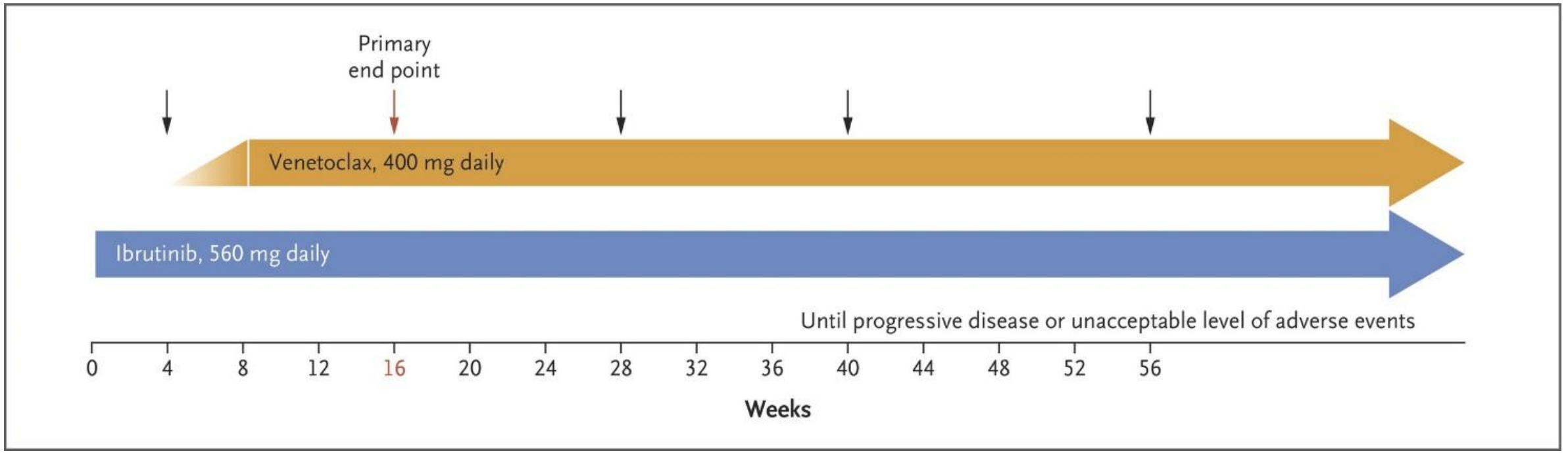
Either approach is reasonable

High-risk group: limited benefit from 2L BTKi

Would benefit from alternatives to continuous BTKi monotherapy

- Early CAR T-cell therapy
- Early Allogeneic SCT
- Novel agents as standalone therapy or together with BTKi

Ibrutinib plus venetoclax in Relapsed MCL: The AIM Study



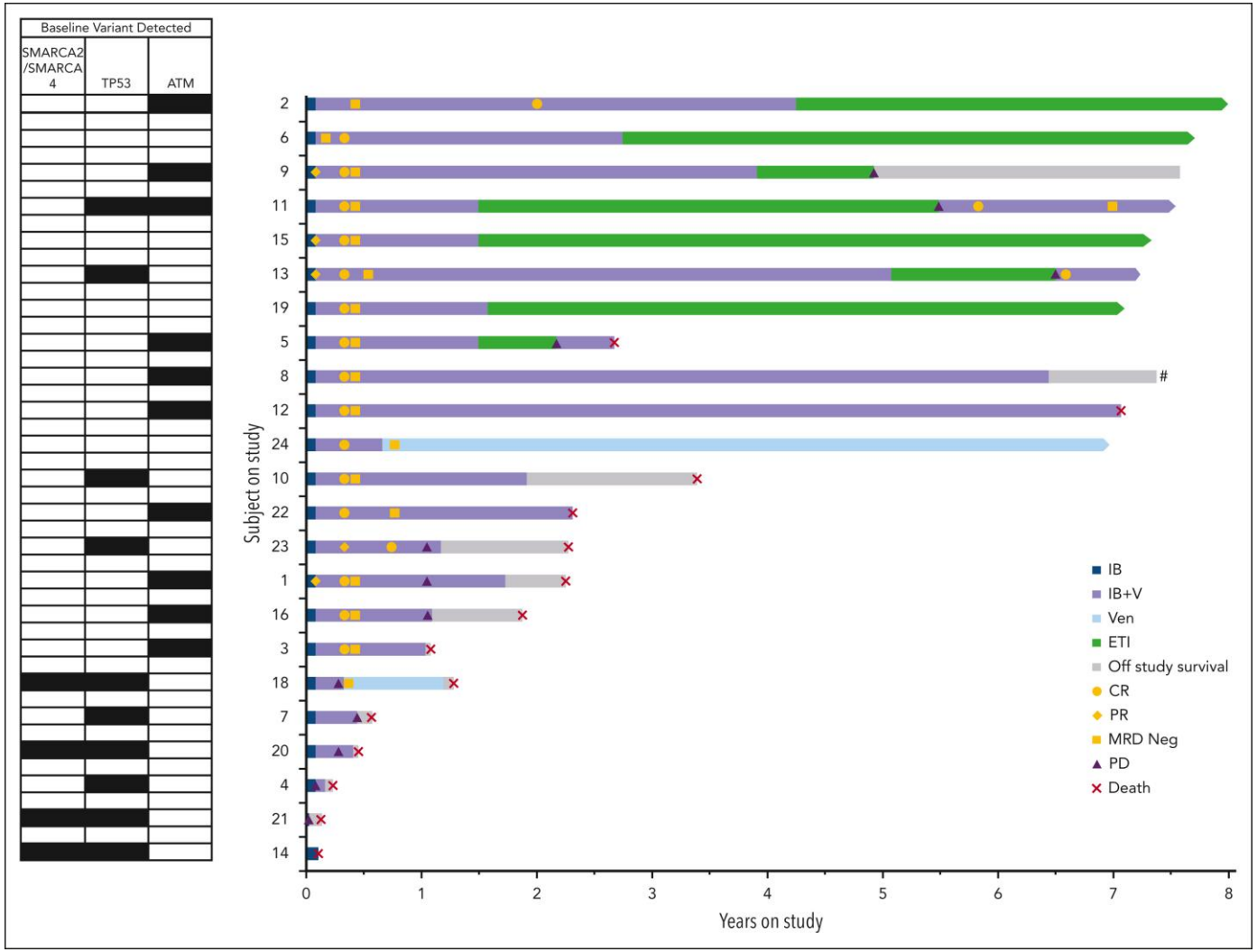
- 24 MCL patients; 23 relapsed or refractory, most with prior ASCT
- Most had poor-risk features, including TP53 del or mutation
- →67% achieved CR and MRD-negative remission (bone marrow)

Tam CS et al. N Engl J Med 2018;378:1211-1223

The NEW ENGLAND JOURNAL of MEDICINE

Seven-year outcomes of venetoclax-ibrutinib therapy in MCL: The AIM Study
Durable responses and treatment-free remissions

Sasanka M, et al. *Blood* 2024; 144:867-72



Key findings:

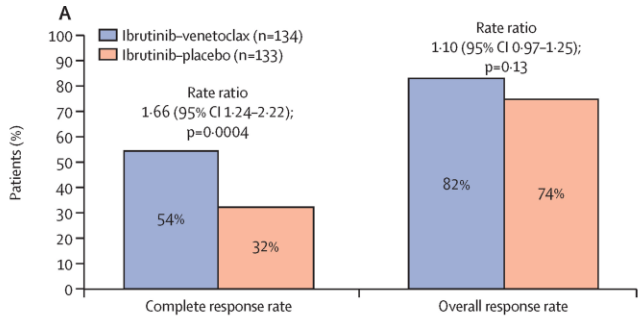
- A subset of patients (n=8) had ongoing response after elective treatment interruption [**Green arrows**]
- 4 relapsed while off Rx; 2 had second remissions with Ibr/Ven
- Of 7/10 pts with TP53 mutation, only 2 had durable responses
- 4 pts with TP53 plus SMARCA2/4 mutations had minimal/no response and very short survival

Ibrutinib Combined With Venetoclax in Relapsed Mantle Cell Lymphoma (SYMPATICO)

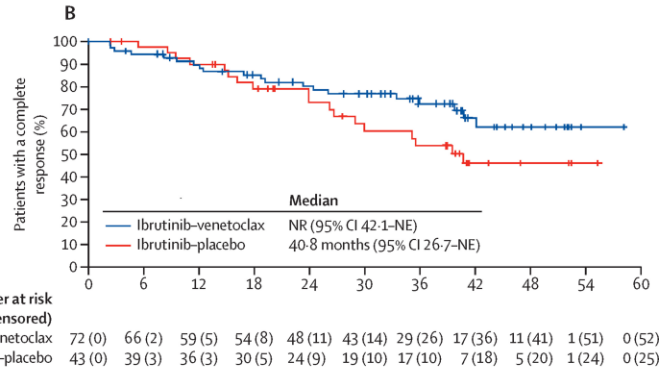
Wang ML et al, Lancet Oncol 2025;

Phase 3 double-blind study: **Ibrutinib/Venetoclax vs. Ibrutinib/Placebo** in R/R MCL, 1-5 prior lines of Rx

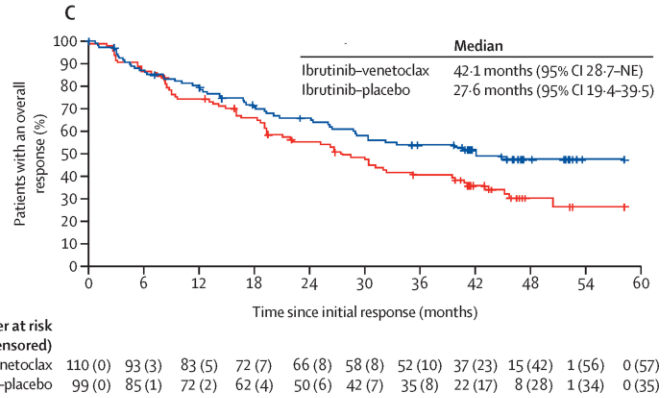
CR and ORR

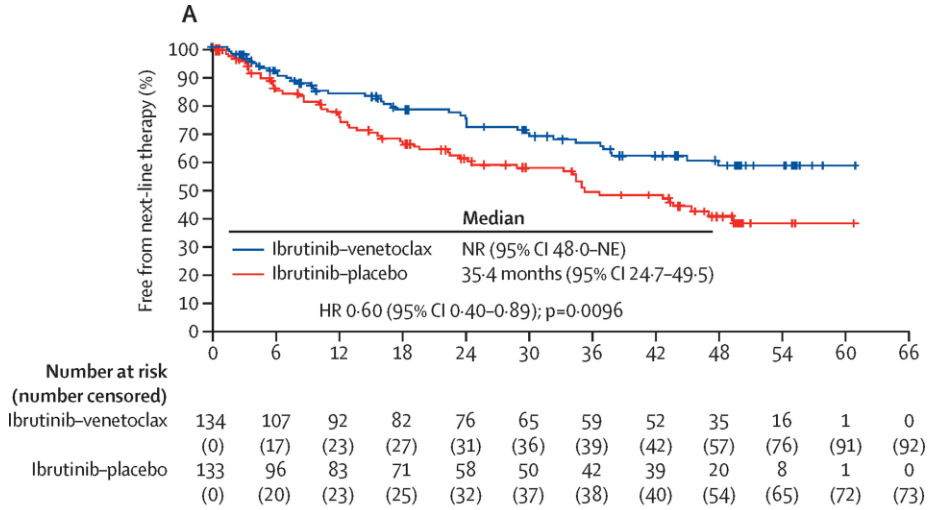


PFS: pts with CR

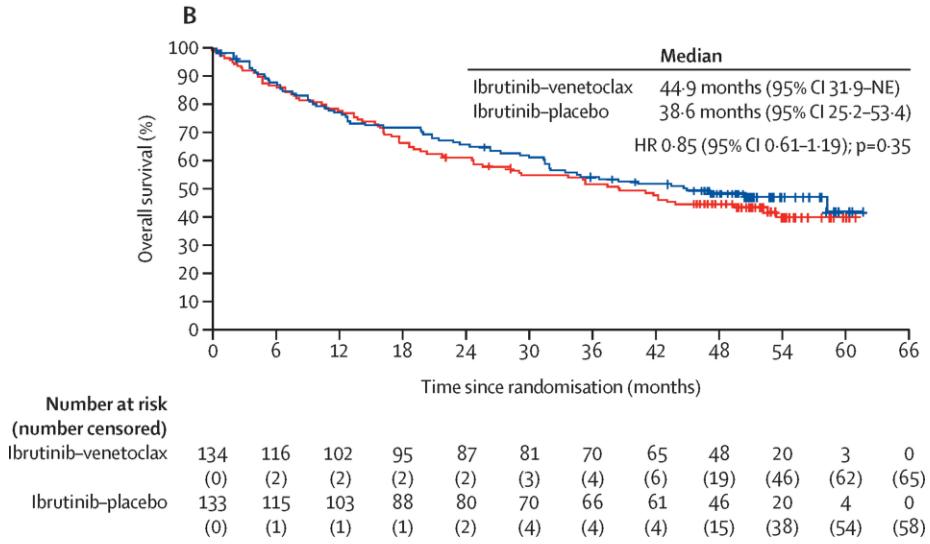


PFS: pts with response





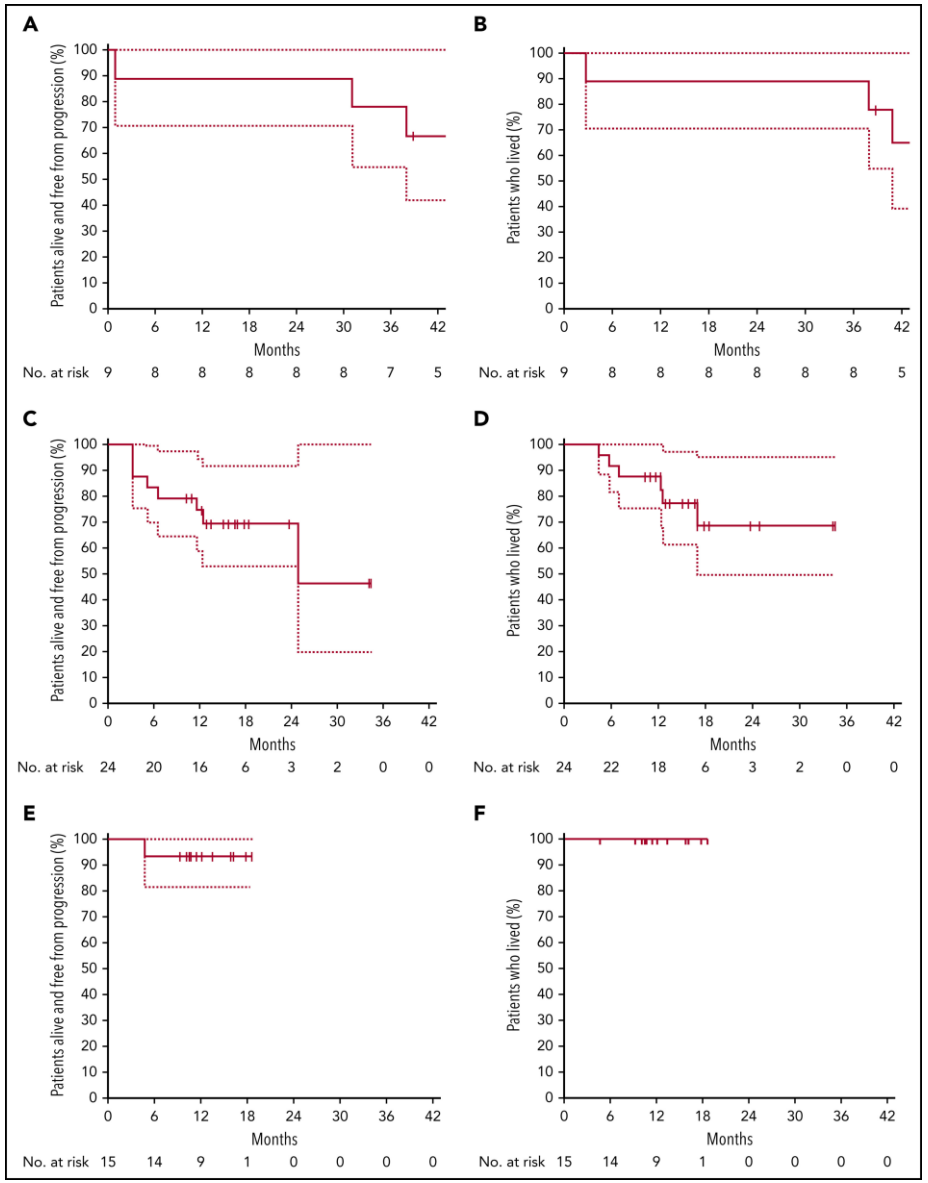
Free from next Rx



OS

Ibrutinib, obinutuzumab, and venetoclax in relapsed and untreated patients with MCL: a phase 1/2 trial (OAsIs Trial).

LeGouill, et al. *Blood* 2021; 137:877-87



PFS and OS according to cohort:

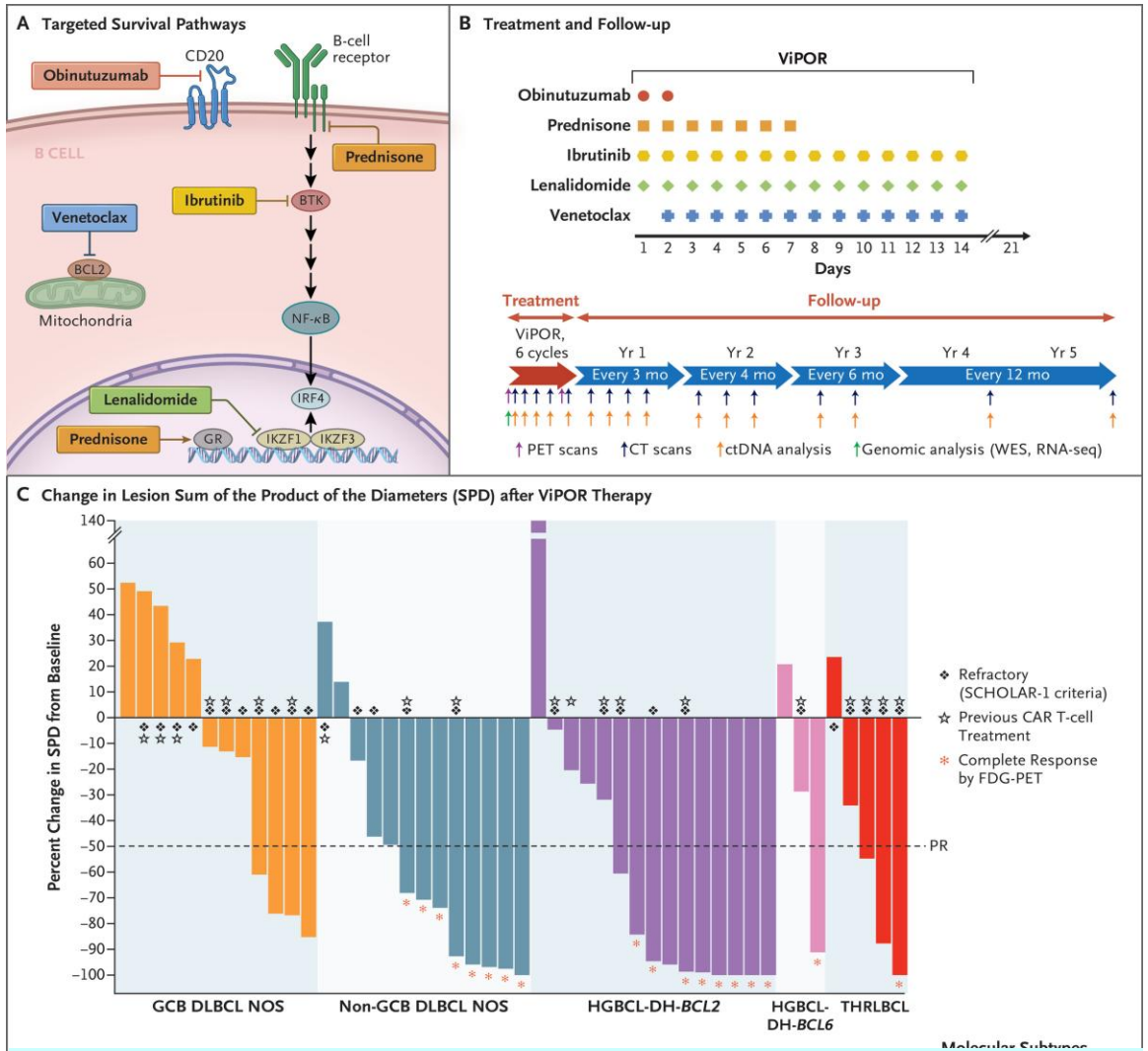
PFS (A) and OS (B) in cohort A (ibrutinib plus obinutuzumab), **relapsed** patients; 7/9 achieved CR

PFS (C) and OS (D) in cohort B (ibrutinib, obinutuzumab, and venetoclax), **relapsed** patients; 16/24 achieved CR

PFS (E) and OS (F) in cohort C (ibrutinib, obinutuzumab plus venetoclax), **untreated** patients; 14/15 achieved CR

Toxicities: grade 3-4 neutropenia and thrombocytopenia; Afib (1 pt), TLS (2 pts); no DLT

Phase 1b/2 Study of Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Lenalidomide (ViPOR) in R/R and Treatment-Naïve MCL: Preliminary Analysis of Safety, Efficacy, and Minimal Residual Disease. Melani C, et al. *Blood* 2024 (ASH abstract #750)



Combination Targeted Therapy in Relapsed Diffuse Large B-Cell Lymphoma. Melani et al, *NEJM* 2024; 390:2143-55

36 MCL patients enrolled: R/R= 16; TN= 20

- Half had prior BTKi; none had Ven or Len
- No maintenance therapy; 1 R/R pt → allo SCT
- No DLT in Ph 1b → Ven 400 mg as RP2D

Biomarkers: Blastoid in 25%, Ki-67>30% in 37%, TP53 mutation or deletion in 32%

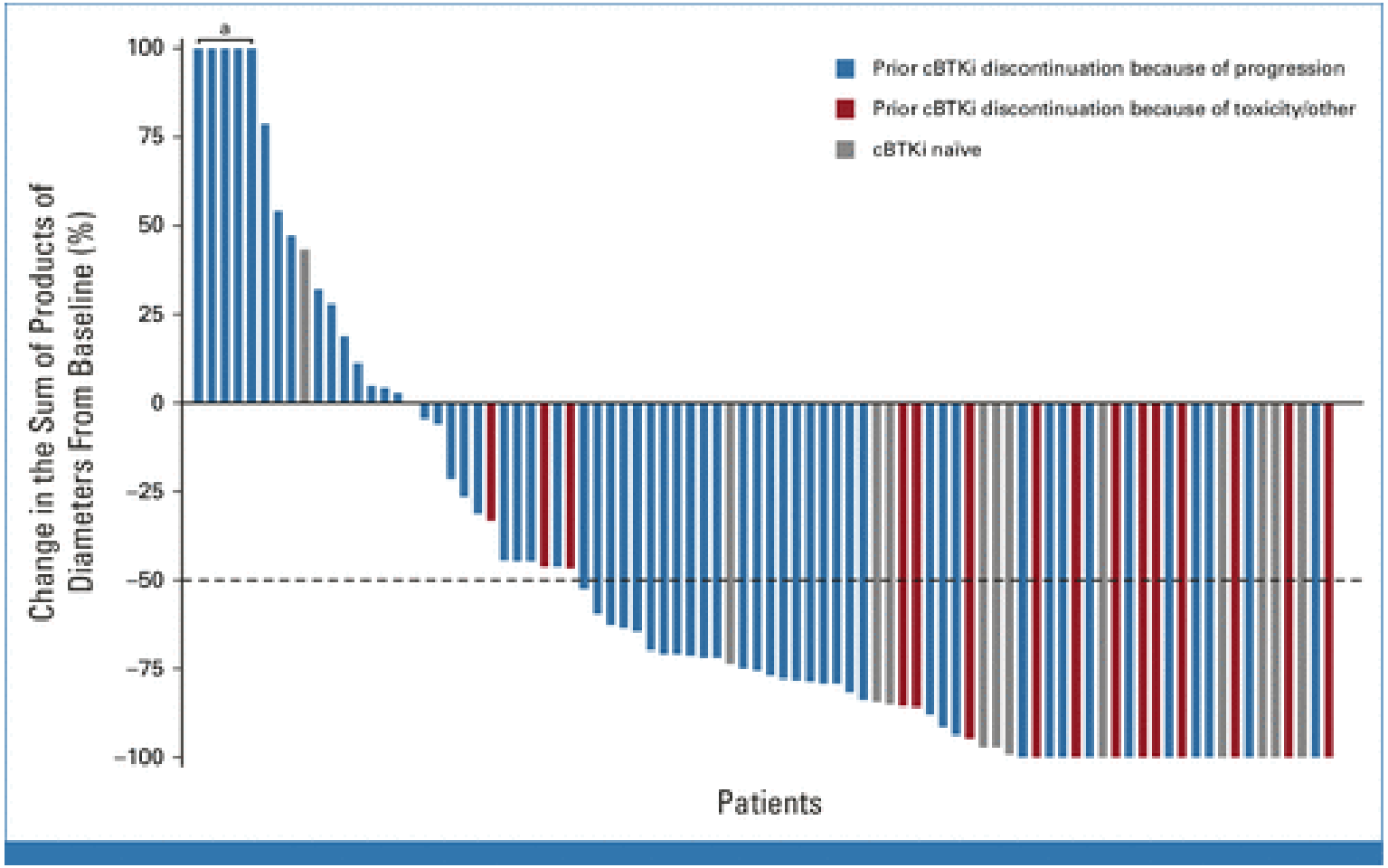
Toxicity: grade 3-4 cytopenias in 10-15%; no febrile neutropenia; hypokalemia 89%, rash 58%

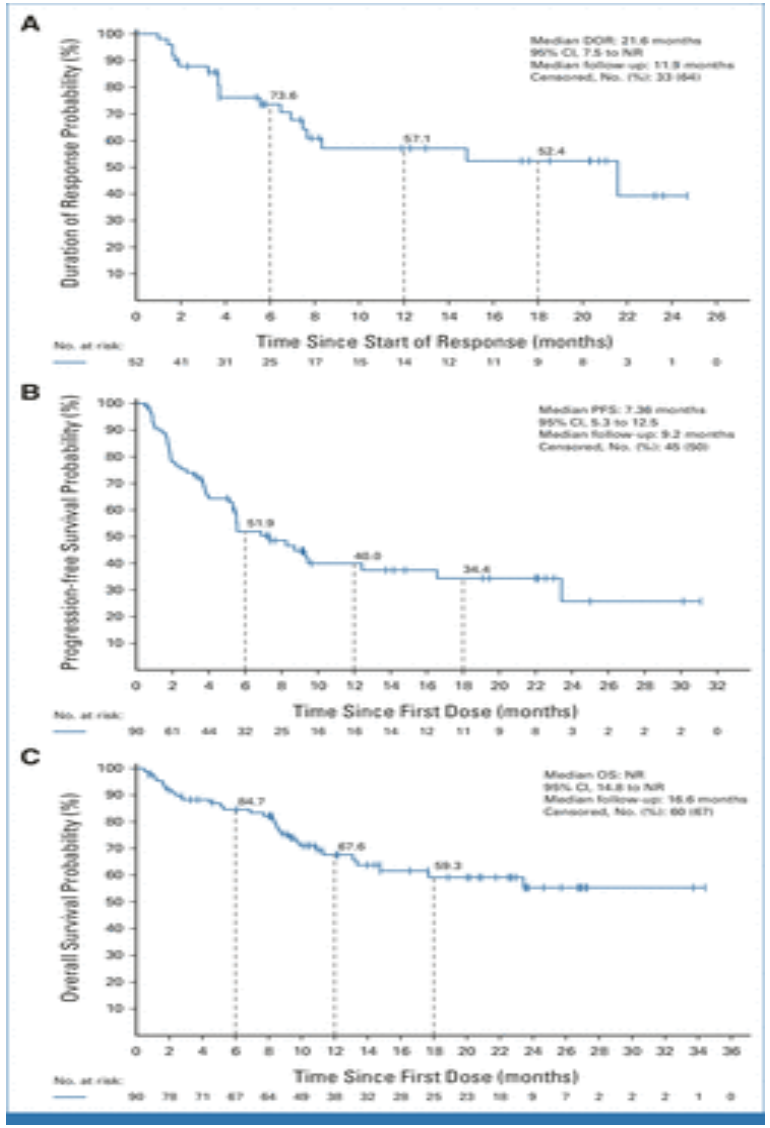
Response after 6 cycles (n=35): CR = 100%

- @ median f/u 24 mo: 19/20 TN and 11/15 R/R responses are ongoing
- End-of-therapy uMRD in 27/28

Pirtobrutinib in R/R and covalent BTKi-pretreated MCL

Wang ML, et al. *J Clin Oncol* 2023; 41:3988





DOR

PFS

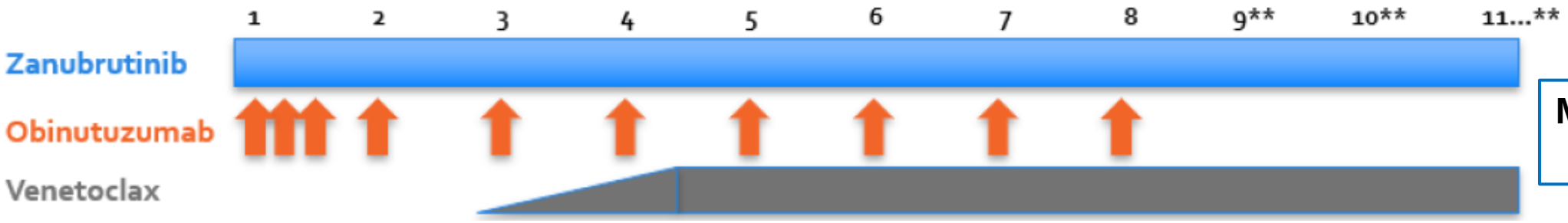
OS

Recent front-line chemo-free combinations for MCL

"New Strategies"

(Not including CAR-T and bispecifics)

Study Design for BOVen *Kumar A, et al, MSKCC*



Minimum of 24 cycles

Dosing:

Zanubrutinib 160 mg oral twice daily

Obinutuzumab 1000 mg IVPB
Cycle 1: day 1, 8, 15
Cycle 2-8: day 1

Venetoclax 400mg oral daily
5-week ramp-up: 1 week each of 20mg; 50mg; 100mg; 200mg; 400 mg oral daily

After 24 cycles, MRD-driven approach to limit treatment duration in selected patients:

CR and uMRD	→	Stop treatment
<CR and/or dMRD	→	Continue ZANU and VEN

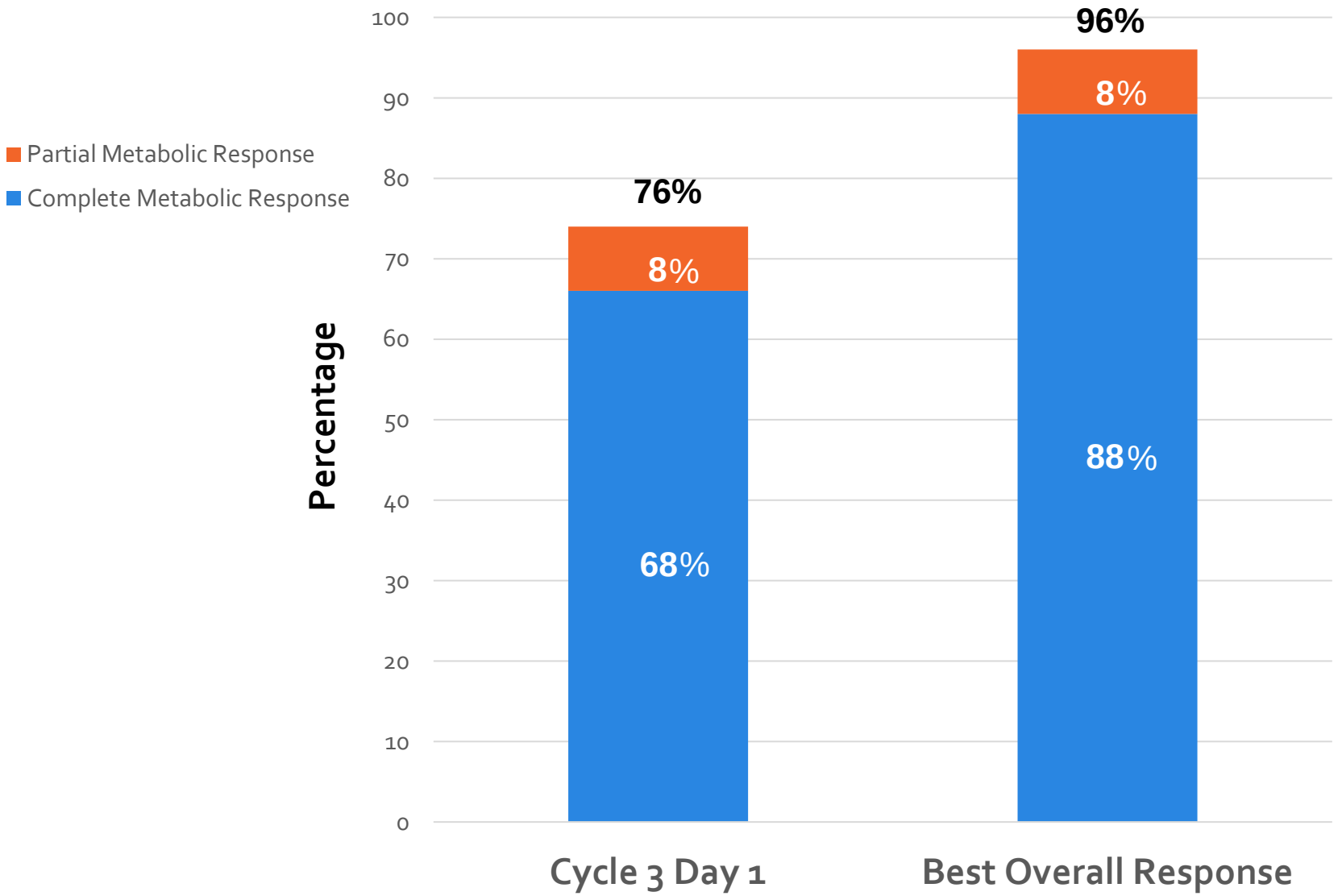
Key Eligibility Criteria:

- Previously untreated MCL (except localized RT prior)
- *TP53* mutation (of any variant allele frequency)
- ECOG ≤2, adequate organ and hematologic function (ANC >1, PLT >75, HGB ≥9 (unless due to MCL))

Primary Endpoint:

- 2-year progression-free survival.
- A promising 2-yr PFS rate ≥55% and an unacceptable rate ≤30%
- If ≥11 patients were progression-free at 2 years, the treatment regimen would be declared effective

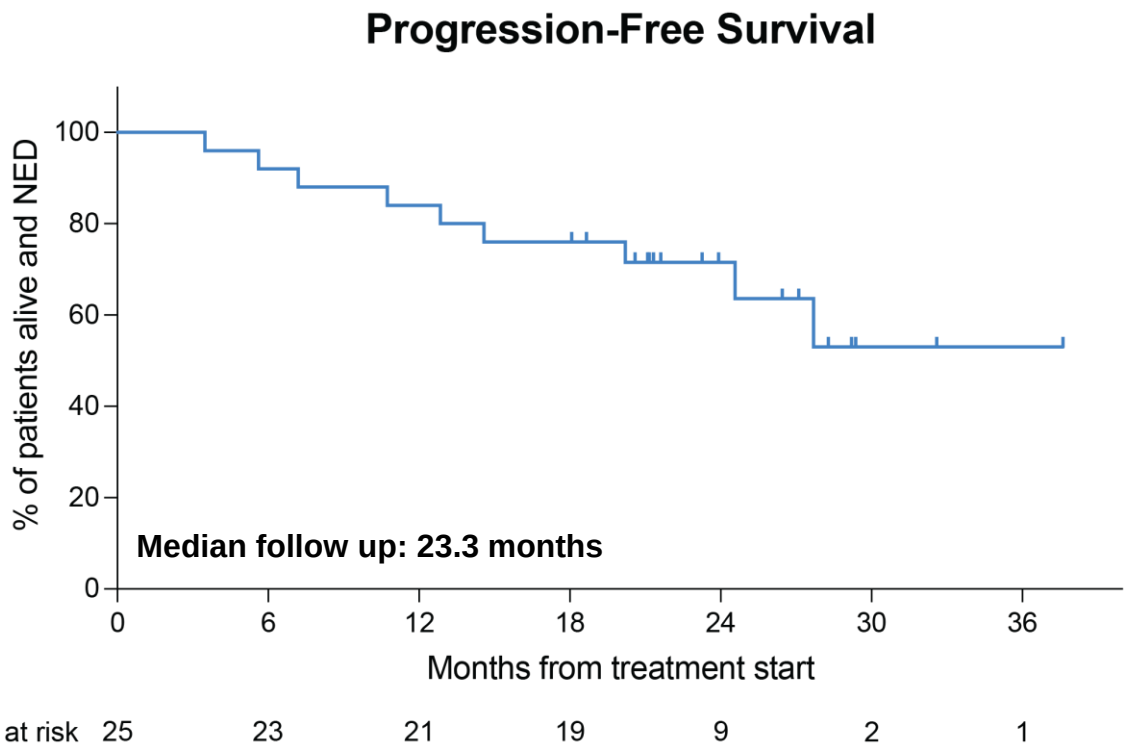
Response Rates By Timepoint

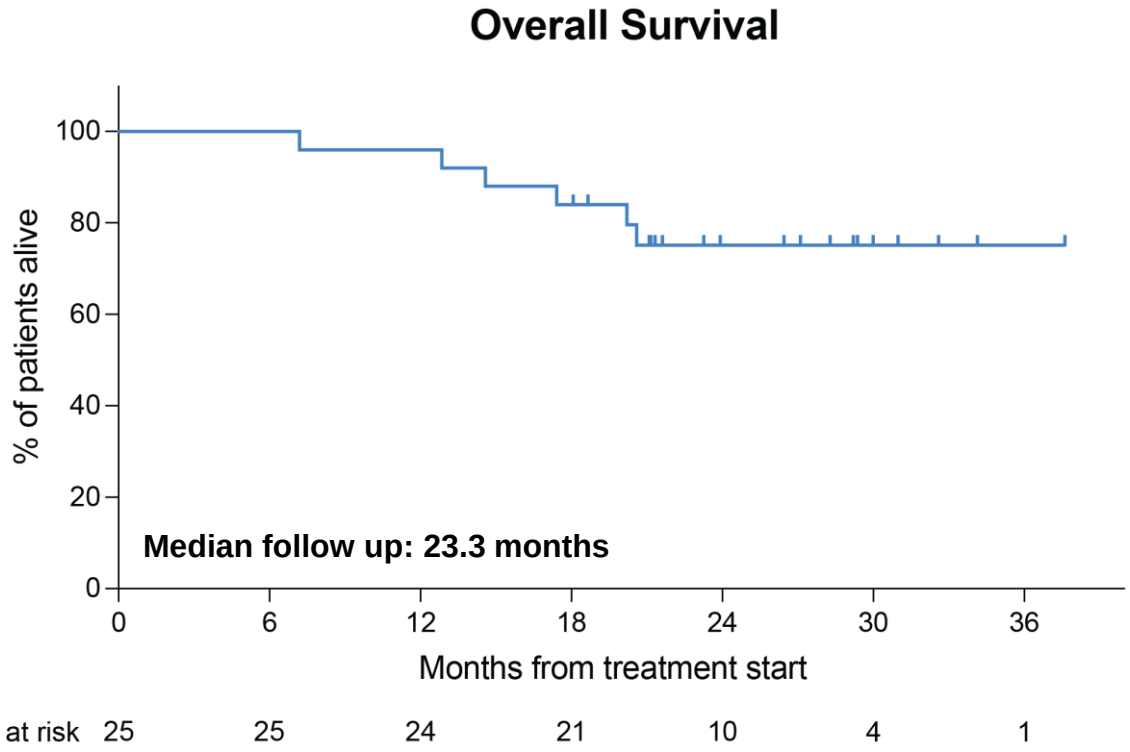


- **High Metabolic Response Rates after 2 cycles of Zanu+Obin**
- **High Overall Metabolic Response Rate with Zanu+Obin+Ven**

Memorial Sloan Kettering Cancer Center

Progression-Free and Overall Survival Outcomes (*see update:* Kumar et al, *Blood* 2025; 145:497-508)





2-year PFS: 72% [95% CI: 56, 92]
Median PFS: not reached

2-year OS: 75% [95% CI: 58, 93]
Median OS: not reached

Primary PFS Endpoint is Met:
11 patients progression-free at 2 years

Memorial Sloan Kettering Cancer Center

MRD-Driven Time-Limited Therapy of Acalabrutinib and Lenalidomide Plus Rituximab (**ALR**) or Obinutuzumab (**ALO**) in Patients with Treatment-Naive MCL: Phase 2 Trial Outcomes with MRD and cfDNA Analyses

- Len/Ritux is highly active as frontline therapy (Ruan et al, *Blood* 2018)
- Regimens:
  - **Acala 100 mg bid continuously**
  - **Len 15-20 mg d 1-21 x 12 (induction), then 15 mg during maintenance**
  - **ALR: Rituximab weekly x 4 in cycle 1, then q 2 mo including maintenance**
  - **ALO: Obinutuzumab weekly x3 cycle 1, monthly cycles 2-6, then q 2 mo**
- Primary endpoint: MRD negative @ 10^{-6} post-induction (PB, by ClonoSeq)
- ALR = 24 pts: Ki67 >30% in 35%; TP53 mutation in 29%
  - Toxicity: Gr 3-4 neutropenia 38%, rash 42%; 4 SPN (1 renal cell, 3 skin ca)
  - Most patients developed COVID infection (Omicron variant, no deaths)
  - No d/c acala or len due to toxicity

Ruan J, et al. ASH 2024, abstract #746

MRD-driven, Time-limited ALR and ALO in Front-line MCL: Responses

- **ALR:** end of induction ORR 100%, CR 83%
  - MRD negative = 67% after 12 cycles, 83% after 24 cycles
  - 3-year PFS 88%, OS 95%
  - MIPI score, Ki67 >30% and TP53 mutation had no impact on Rx response
- **ALO:** n = 10
  - 1-year OS and PFS = 100%

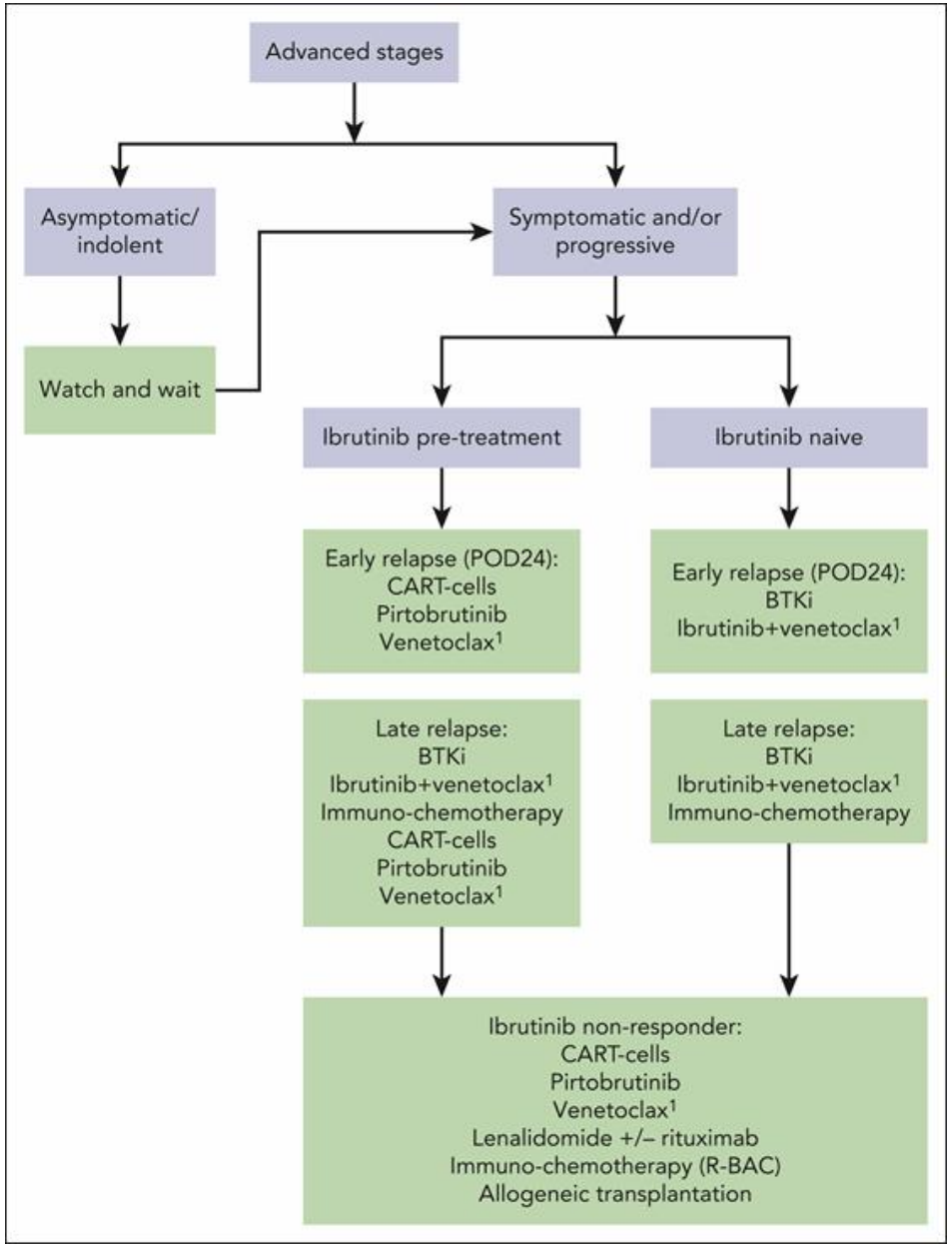
Conclusions:

- High rates of CR and MRD-negative, including high-risk pts
- Well-tolerated
- Allows treatment de-escalation and time-limited therapy
- MRD and cfDNA of PB provide real-time response data and mutational evolution analysis

Ruan et al, ASH 2024, abstract #746

Treatment approaches in R/R MCL: 2025

Silkenstedt E, Dreyling M. *Blood 2025; 145:673-82*



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9th Postgraduate Lymphoma Conference
Florence 21 March 2025

Thanks for your attention! Questions??

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