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e Pesquisa

Sifting Through the Smoke.....Making Sense of 1L Treatment Options in MCL

Tycel J. Phillips, MD

Associate Professor of Medicine

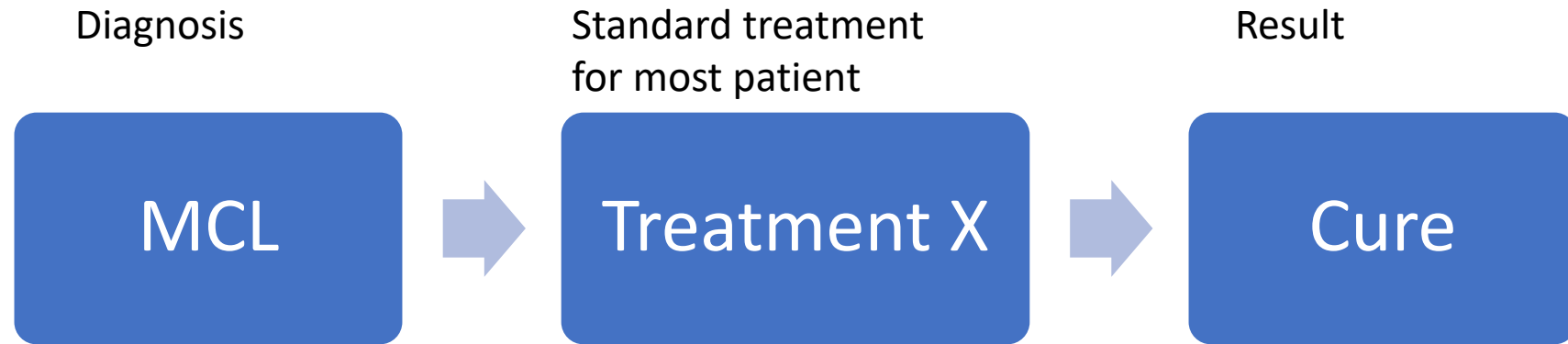
Department of Hematology and Bone Marrow Transplantation

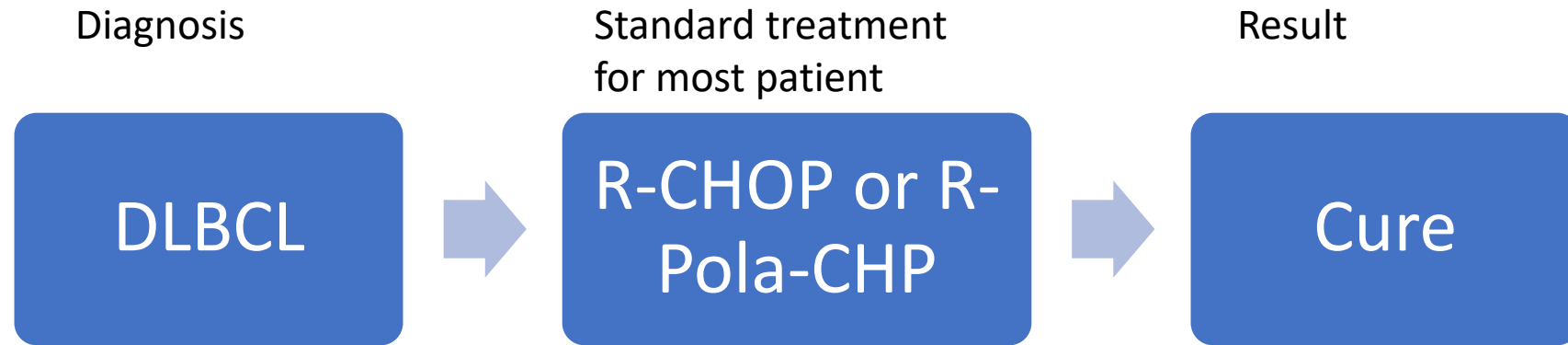
City of Hope National Medical Center

Duarte, CA 91010

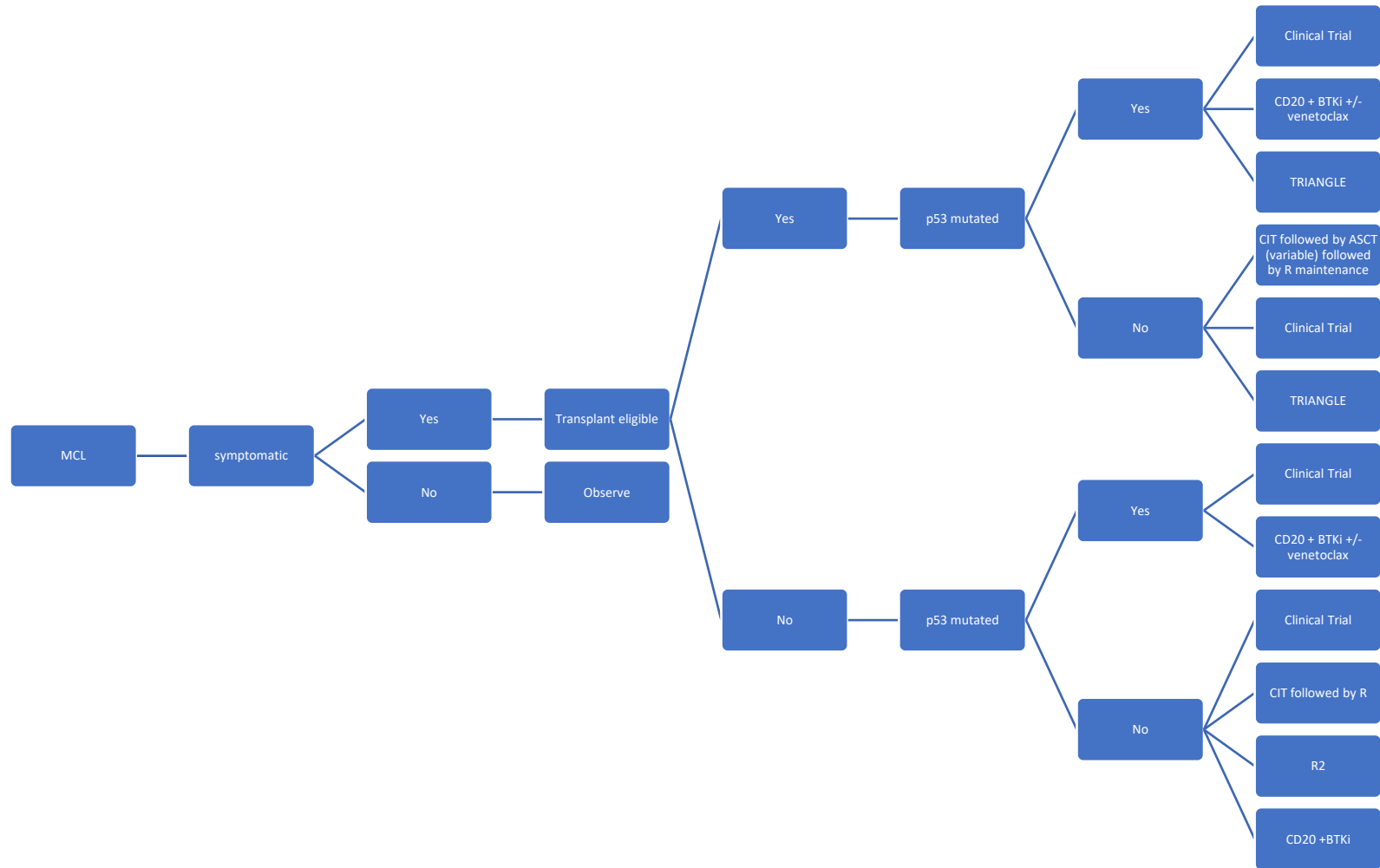


If this was a movie.....

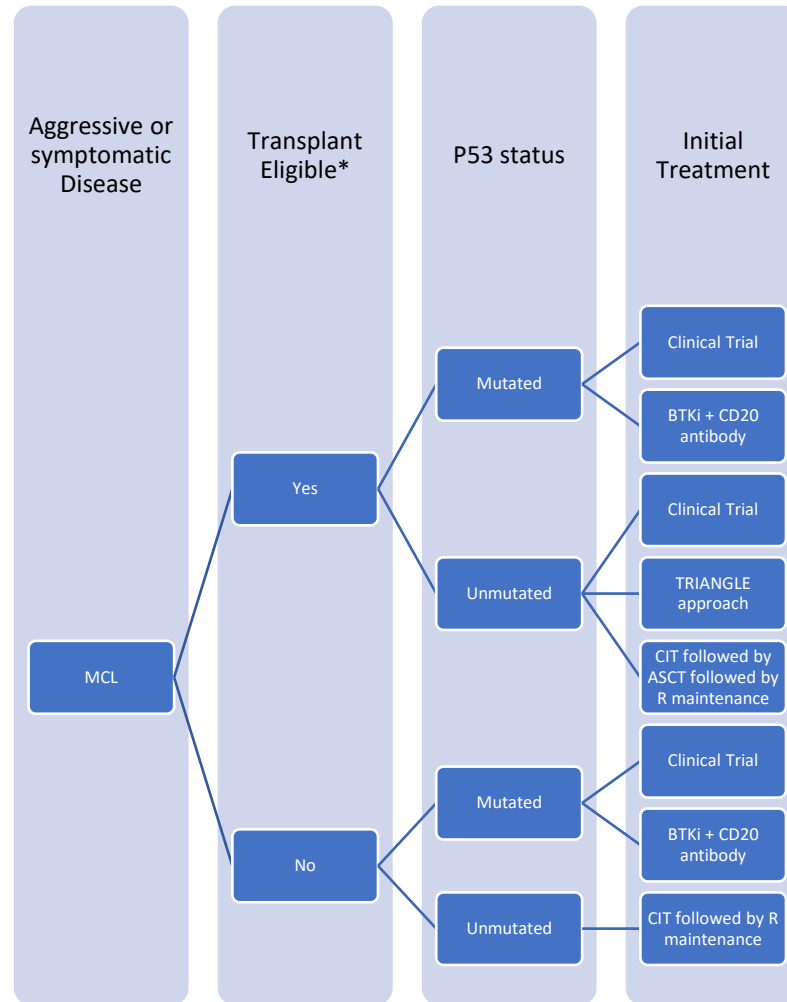




MCL Reality



Reality for 1L MCL (simplified)



← This doesn't take into account other features that might steer you away for CIT

So how did we get here



Elderly Unfit patients (Historical)

- Historical data indicated that CHOP was ineffective.
 - Outcomes improved with addition of rituximab
- R-CHOP compared to FR followed by maintenance rituximab vs. interferon
 - Demonstrated improvement in PFS with maintenance rituximab after R-CHOP
- German study (Rummel et al.) and Bright Trial (US)
 - Demonstrated that BR is a superior regimen to R-CHOP in MCL only
- VR-CAP
 - Improved PFS vs. R-CHOP in randomized study (24.7 months vs 14.4 months)
- BRAC (Italian Regimen)
 - ORR > 90%
 - Toxicity??

CHOP – Cytoxan, Adriamycin, Vincristine, Prednisone

B – Bendamustine

R - Rituximab

V – Velcade

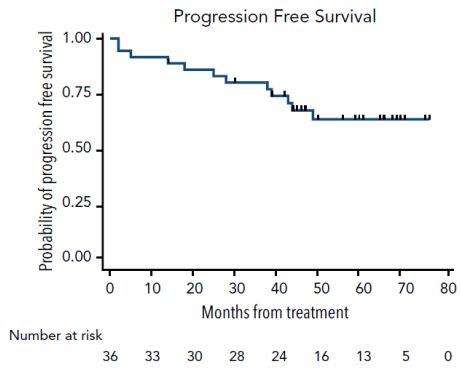
CAP – Cytoxan, Adriamycin, Prednisone

AC - Cytarabine

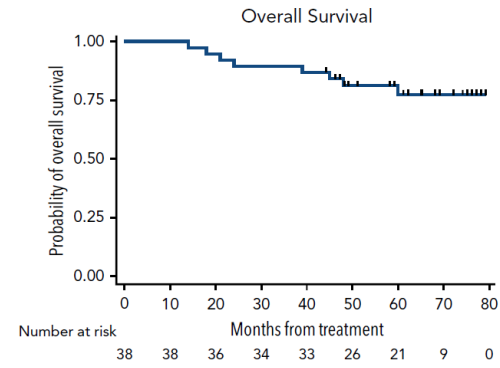
“Non” Chemotherapy

Lenalidomide

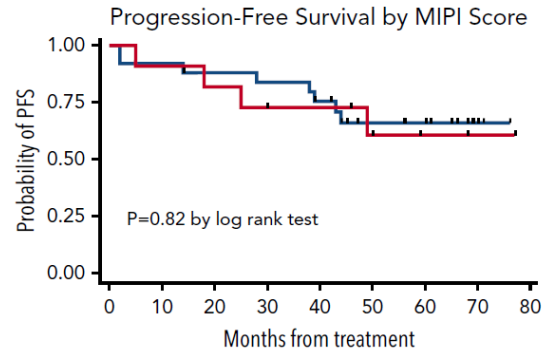
- Rituximab + lenalidomide
- N=38 evenly distributed amongst low, intermediate and high risk MIPI
- ORR: 87%, CR: 64%



5 yr PFS: 64%

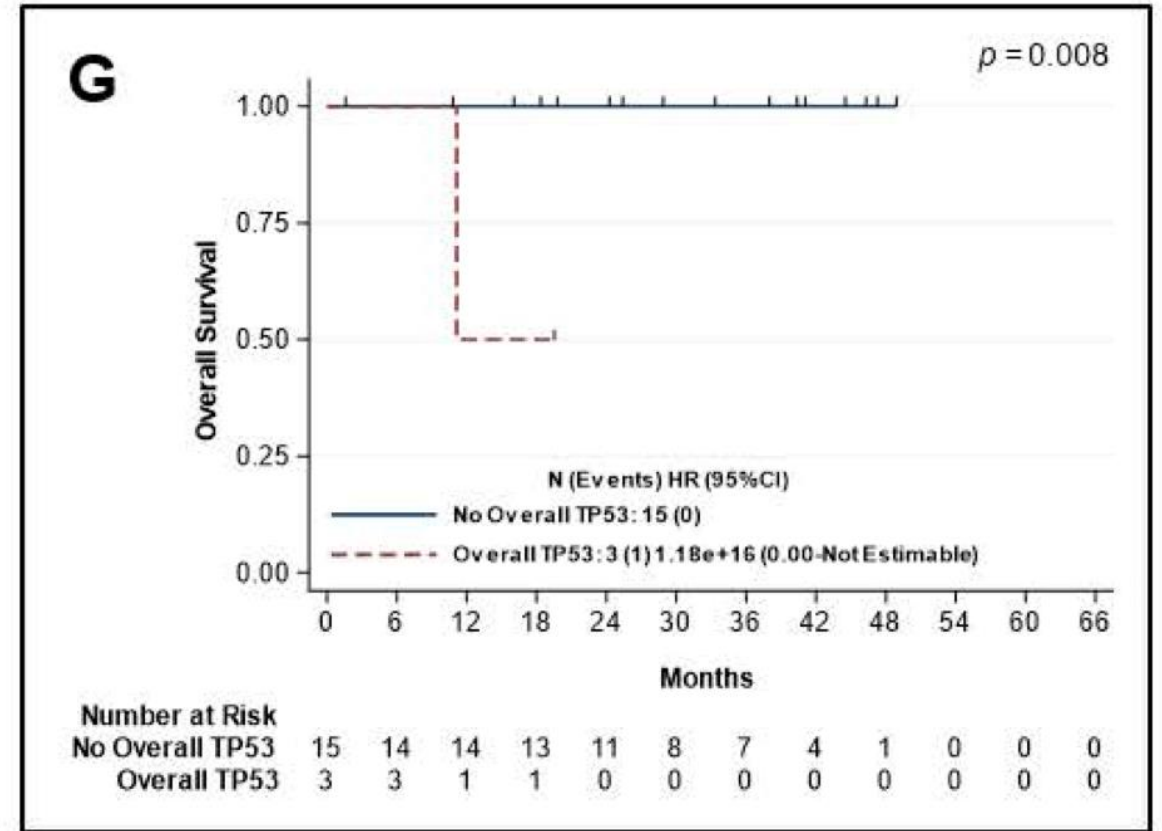
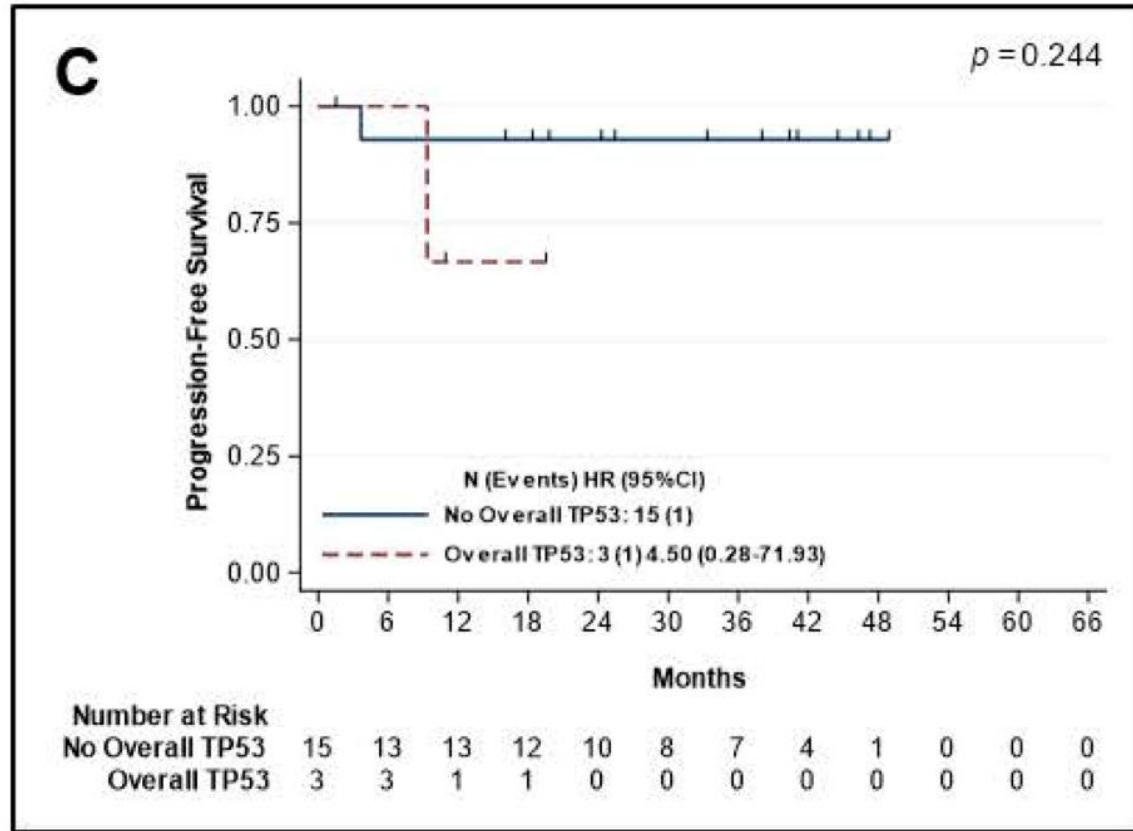


5 yr OS: 77%



Ruan J, NEJM 2015, Blood 2018

IR Elderly

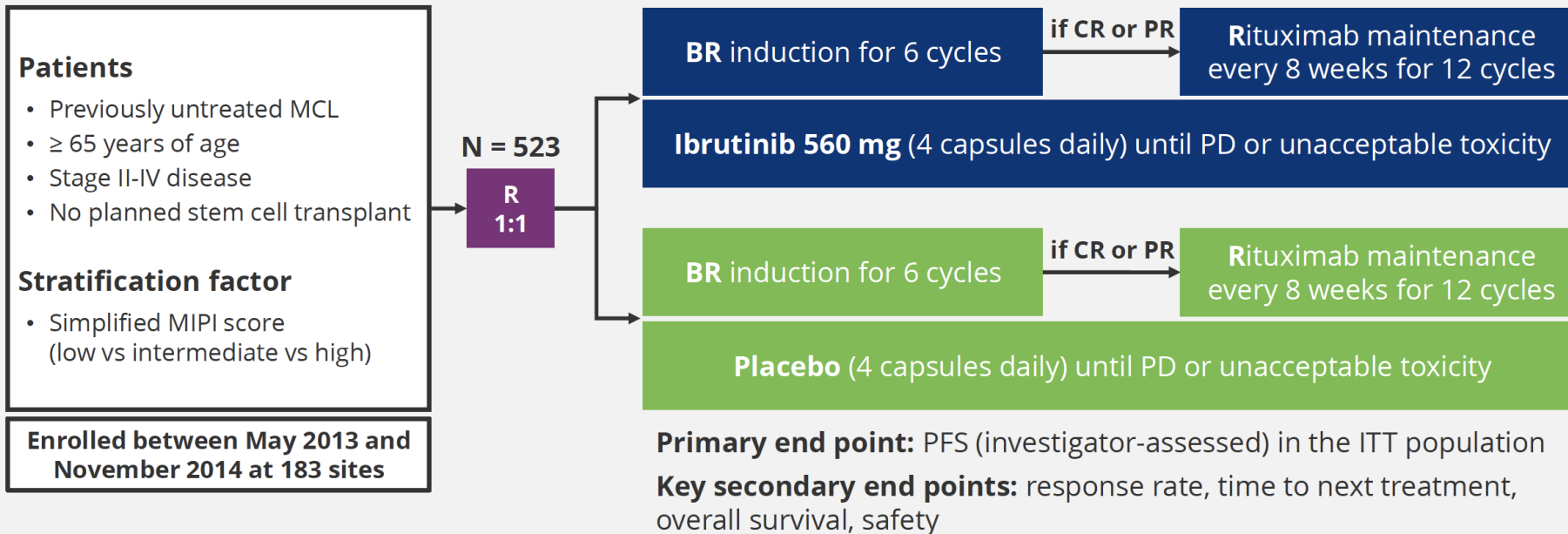


| Patients | Total | ORR | CR | PFS |
|-----------------------|-------|-----|-----|----------------|
| Overall | 48 | 96% | 71% | 87% at 3 years |
| P53 mutation negative | 15 | 94% | 67% | |
| P53 mutation Positive | 3 | 66% | 33% | |

Safety looks better with rituximab-acalabrutinib in this patient population

Paradigm Shift??

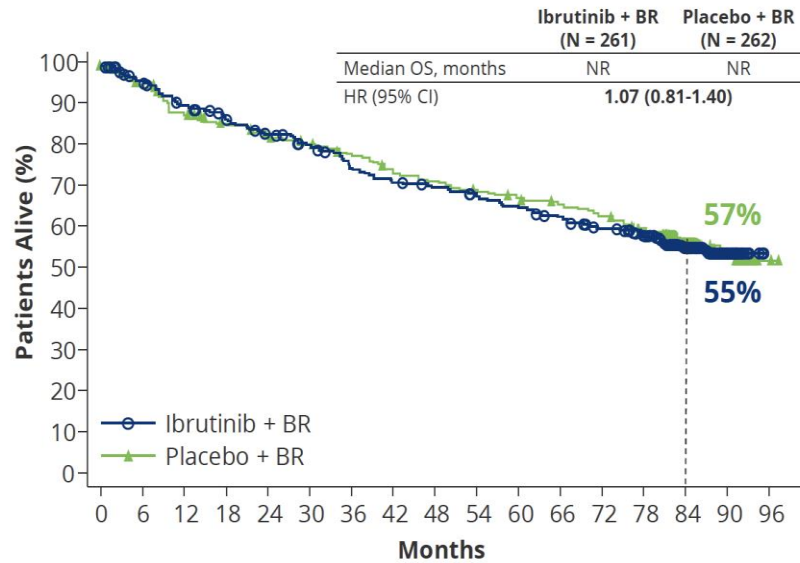
SHINE: A Randomized, Double-Blind, Phase III Study



Induction: Bendamustine 90 mg/m² Days 1 and 2, Rituximab 375 mg/m² Day 1, Q4W. A cycle is defined as 28 days.

CR, complete response; ITT, intent-to-treat; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; PFS, progression-free survival; PR, partial response.





Patients at Risk

| | | | | | | | | | | | | | | | | | |
|----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|---|
| Ibrutinib + BR | 261 | 239 | 221 | 208 | 197 | 187 | 171 | 163 | 158 | 152 | 145 | 138 | 128 | 118 | 70 | 25 | 0 |
| Placebo + BR | 262 | 244 | 223 | 212 | 203 | 197 | 188 | 177 | 171 | 165 | 159 | 154 | 147 | 137 | 90 | 31 | 2 |

*The most common grade 5 TEAE was infections in the ibrutinib and placebo arms: 9 versus 5 patients. Grade 5 TEAE of cardiac disorders occurred in 3 versus 5 patients, respectively. CI, confidence interval; HR, hazard ratio; NR, not reached; PD, progressive disease; TEAE, treatment-emergent adverse event.

*Significance boundary for superiority was $p < 0.023$.

| Cause of death | Ibrutinib + BR (N = 261) | Placebo + BR (N = 262) |
|--|-----------------------------|---------------------------|
| Death due to PD and TEAE | 58 (22.2%) | 70 (26.7%) |
| Death due to PD | 30 (11.5%) | 54 (20.6%) |
| Death due to TEAEs* | 28 (10.7%) | 16 (6.1%) |
| Death during post-treatment follow-up excluding PD and TEAEs | 46 (17.6%) | 37 (14.1%) |
| Total deaths | 104 (39.8%) | 107 (40.8%) |

- Death due to Covid-19: 3 patients in the ibrutinib arm during the TEAE period and 2 patients in the placebo arm after the TEAE period
- Exploratory analysis of cause-specific survival including only deaths due to PD or TEAEs showed an HR of 0.88



Tarnished SHINE

- Toxicity with combination is an issue
 - Experimental arm with unexplained deaths
- Questionable benefit in high risk patients
 - Trend towards benefit in blastoid patients but no clear evidence for benefit in subset analysis for this group or p53 mutated patients
- Data suggests that sequential utilization provides equivalent benefit
- FOMO?
 - Do we risk some patients never getting a BTKI?

So where are we going with elderly patients???

- Echo study was reported as meeting its primary endpoint!!
 - So.....that's a good thing....
 - Maybe...SHINE met its endpoint yet still led to the withdrawal of ibrutinib in the US
 - So, the details on toxicity will matter as very unlikely the study has an OS benefit.
- Mangrove
 - Study evaluating zanubrutinib + R vs. BR
 - Would suspect of the 3 studies looking at BTKi in patients aged 65+ this one will clearly demonstrate benefit
 - Control arm handicapped
- Can we do better....
 - Maybe....bispecific combination or Liso-cel in 1L

What about in transplant eligible patients



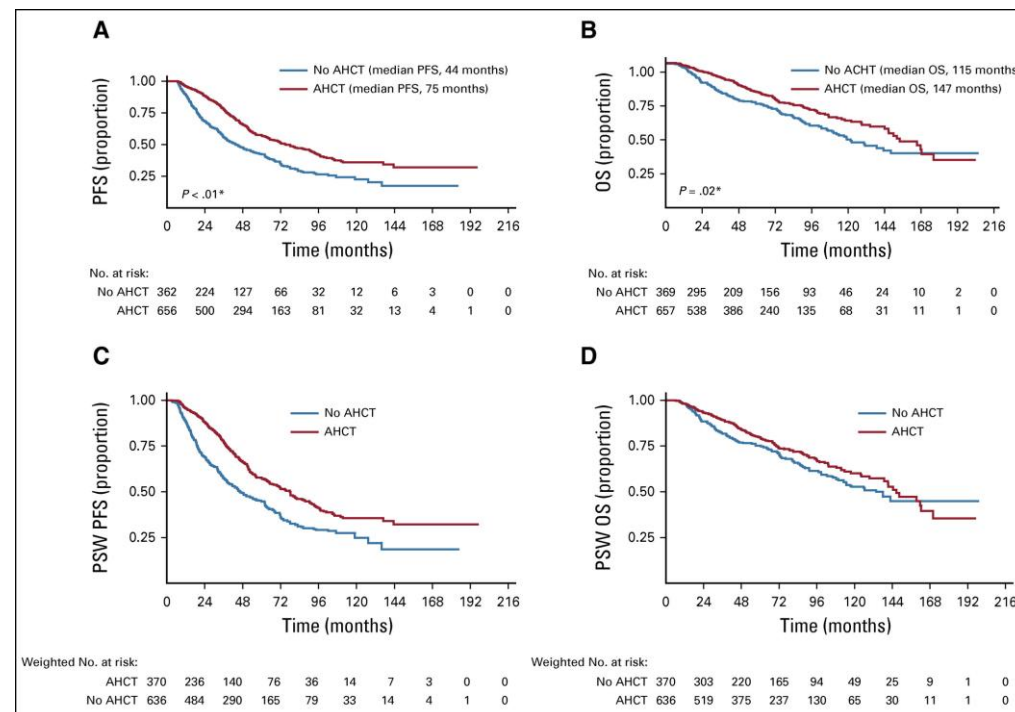
Treatment Options (Outcomes with intensive induction for MCL)

| REGIMEN | EFFICACY | TOXICITY |
|--|--|----------------------------|
| Nordic (R-maxiCHOP/R-araC) followed by auto-HCT ¹ | Median PFS: 8.5 years Median OS: 12.5 years | NRM: 7.5% MDS/AML: 3.1% |
| RCHOP/RDHAP followed by auto-HCT ² | Median PFS: 9.1 years Median OS: 9.8 years | NRM: 3.4% MDS/AML: 2.4% |
| Any induction followed by auto-HCT (CIBMTR real world data) ³ | 5 yr PFS: 52% 5 yr OS: 61% | NRM: 3% |
| R-HyperCVAD (without auto-HCT) ⁴ | Median PFS: 4.6 years 10 yr OS: 64% | NRM: 8% MDS/AML: 5% |

1. Eskelund CV, BJH 2016, 2. Hermaine O, Lancet 2016, 3. Fenske T, JCO 2014, 4. Romaguera JE, BJH 2010

Does (ASCT) improve outcomes

- Retrospective study in 1029 patients
 - 25 centers; restricted to patients who would have been transplant eligible
 - 2/3 got auto up front; 1/3 did not
 - On initial analysis, PFS and OS benefit in favor of ASCT
 - After propensity weight analysis, clear PFS benefit but OS benefit not significant



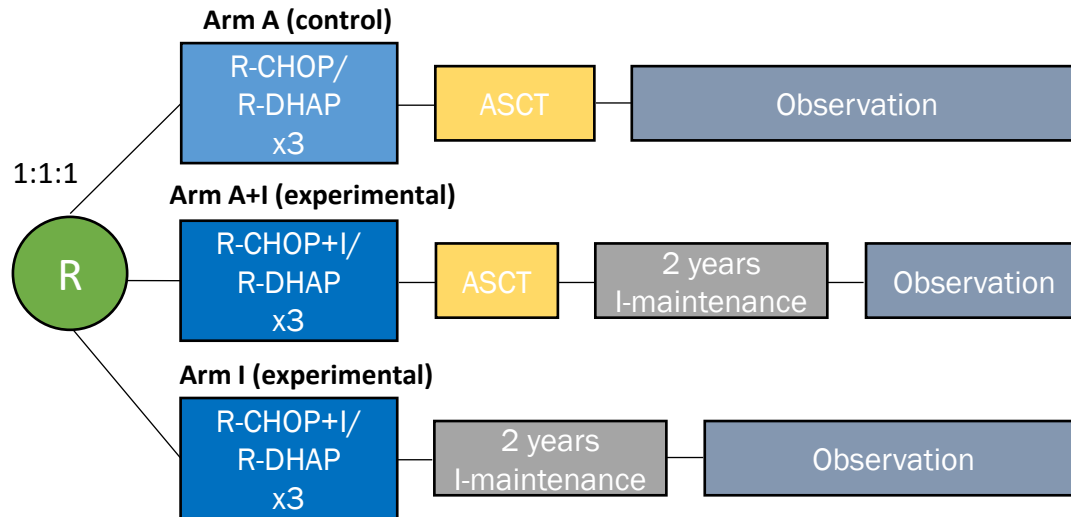
| Survival | HR | 95% CI | P |
|-----------------|------|--------------|-------|
| PFS (n = 1,003) | 0.70 | 0.59 to 0.84 | < .01 |
| OS (n = 1,003) | 0.87 | 0.69 to 1.10 | .24 |

TRIANGLE Phase 3 Study of Ibrutinib + SOC as a Substitute for ASCT in Younger Patients With MCL: Study Design and Patients

Key Eligibility Criteria

- Previously untreated stage II-IV MCL
- Age <66 years
- Suitable for HA and ASCT
- ECOG PS 0-2

- R maintenance (\pm I) was added in all 3 trial arms, following national guidelines. It was initiated in 168 (58%) patients in Arm A; 165 (57%) patients in Arm A+I; and 158 (54%) patients in Arm I



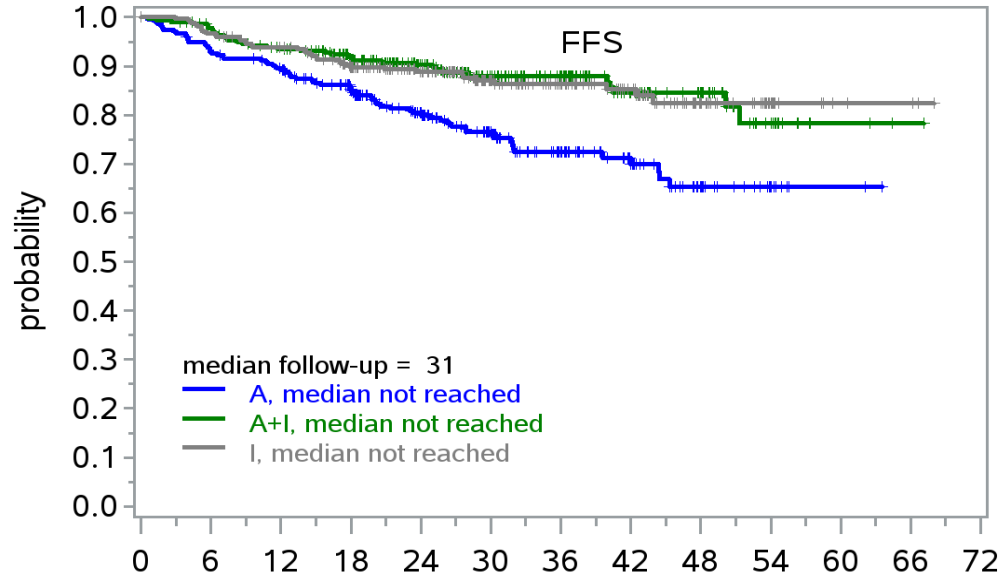
Primary endpoint: FFS

Secondary endpoints: Response rates, PFS, RD, OS, safety

^a2 patients aged 66 & 68 years were randomized. ^b1 CLL, 1 FL. ^c1 NHL NOS, 1 HD, 2 MZL. ^d1 HCL, 1 DLBCL. Dreyling M, et al. ASH 2022. Abstract 1.

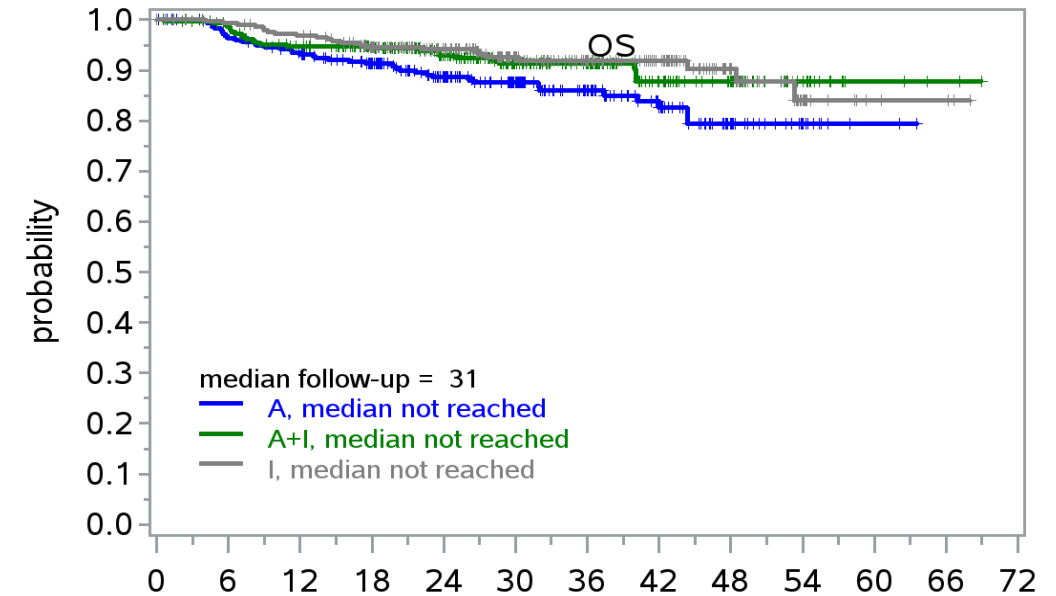
TRIANGLE Phase 3 Study of Ibrutinib + SOC as a Substitute for ASCT in Younger Patients With MCL: Efficacy (cont'd)

FFS of A vs A+I vs I



| | months from randomisation | | | | | | | | | | | | |
|-----------------|---------------------------|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|
| Numbers At Risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66 | 72 |
| A | 288 | 252 | 237 | 206 | 162 | 126 | 85 | 54 | 27 | 12 | 2 | 0 | |
| A+I | 292 | 270 | 253 | 226 | 184 | 137 | 109 | 65 | 40 | 17 | 3 | 1 | |
| I | 290 | 269 | 257 | 229 | 180 | 133 | 100 | 68 | 34 | 16 | 4 | 3 | |

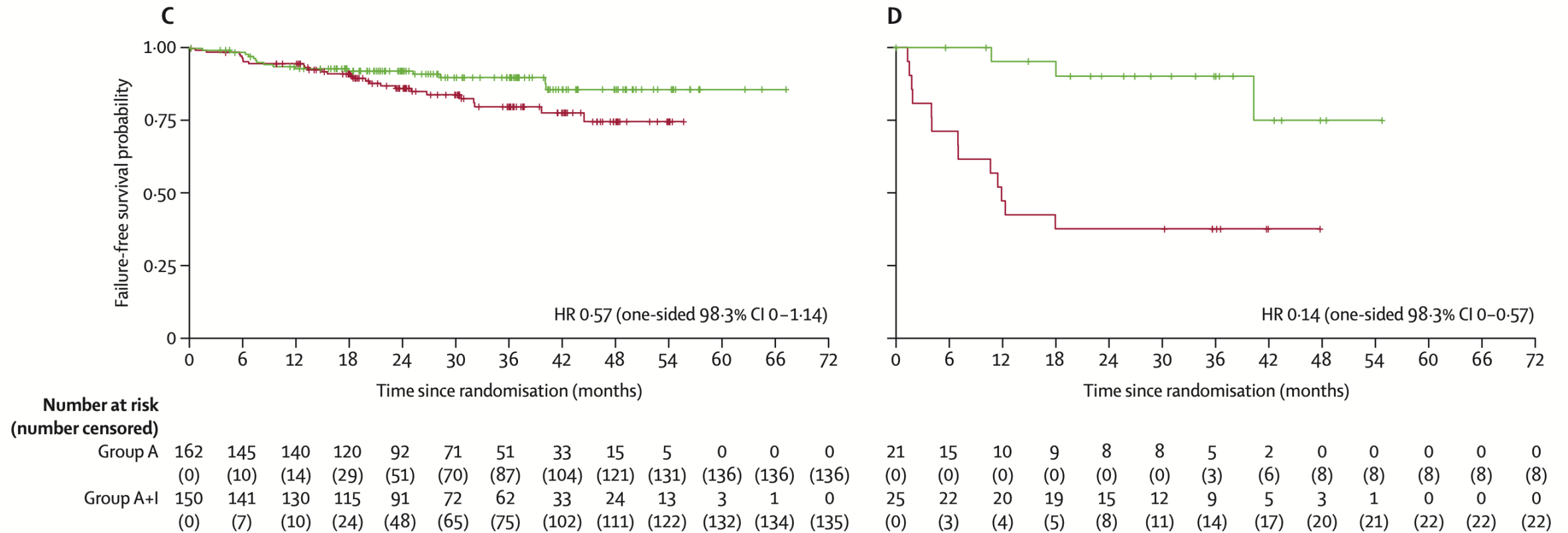
| Next Lymphoma Treatment After 1st Treatment Failure, n (%) | A (n=68) | A+I (n=35) | I (n=37) |
|--|----------|------------|----------|
| With ibrutinib | 34 (79) | 4 (24) | 3 (11) |
| Without ibrutinib | 9 (21) | 13 (76) | 24 (89) |
| No treatment | 25 | 18 | 10 |



| | Months from randomization | | | | | | | | | | | | |
|-----------------|---------------------------|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|
| Numbers At Risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66 | 72 |
| A | 288 | 270 | 256 | 230 | 181 | 145 | 97 | 63 | 32 | 15 | 2 | 0 | |
| A+I | 292 | 280 | 262 | 238 | 195 | 142 | 113 | 67 | 42 | 19 | 4 | 2 | |
| I | 290 | 281 | 272 | 248 | 197 | 145 | 109 | 77 | 38 | 16 | 4 | 3 | |

- 3-year OS: A 86%; A+I 91%; I 92%
- Too early to determine statistical significance
- Test for A+I vs I FFS is ongoing

TRIANGLE (P53 status) and beyond



- How much of FFS benefit is driven by p53 mutated patients
- Did lack of R maintenance in half of the patients impact the p53 low cohorts
- Does either question matter....If I maintenance is equivalent to ASCT does anything else matter????

So now what???

- Honestly..... 🙋♂
 - Study supports that in younger (median age 57) European patients that ibrutinib and likely any BTKi can be combined with intensive CIT in the 1L setting
 - What it doesn't answer is whether we can safely stop taking these patients to transplant
 - Follow up remains extremely short for all arms less than 3 years.
 - Can we be sure that the ibrutinib w/o transplant arm will maintain its benefit over standard arm
 - Or that I arm will maintain equivalence with A +I
 - Can we truly compare those arms, since study wasn't originally designed to compare them??

TRIANGLE Continued....

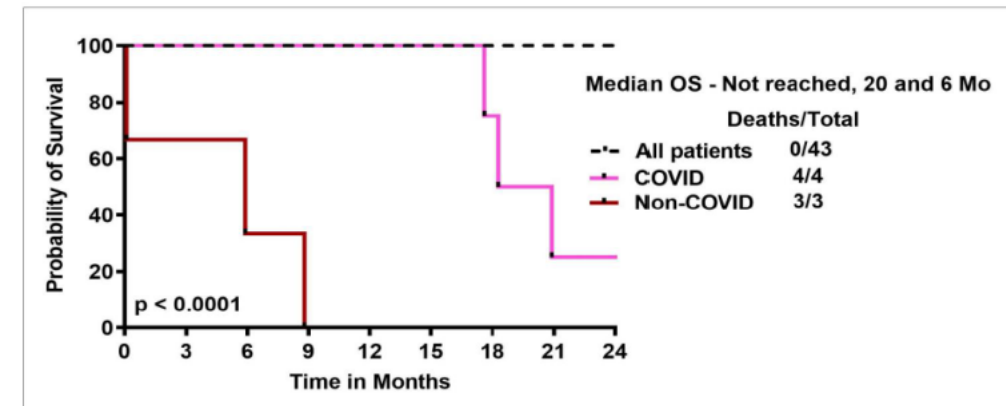
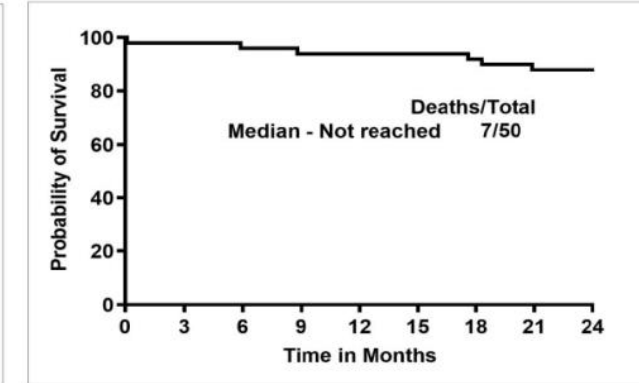
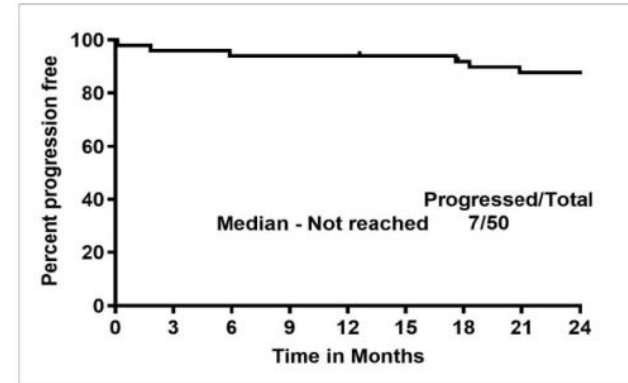
- So is it practice changing.
 - Depends on who you ask
 - Some centers in the US adopted TRIANGLE after the abstract
 - Some utilized it for patients when transplant wasn't available
 - Others continue with prior standards
 - Doesn't address the difficulty in treating some high risk groups
 - See blastoid patients
 - How long is response in ibrutinib only arm?
 - Will those patients respond to re-challenge of a BTKi
- Is BR a better partner for HiDAC and BTKi?
- Is a MRD driven approach better
 - US cooperative group trials (E4151 and E4181)

Can we avoid chemotherapy....

- Several studies of novel combination have looked to address place of targeted agents in 1L
- Hope is to improve tolerance and/or improve outcomes in high risk patients
 - WINDOW 2
 - ALR
 - BOVEN (designed p53 mutated patients)

Phase II Window – 2 Trial (presented by M. Wang MD)

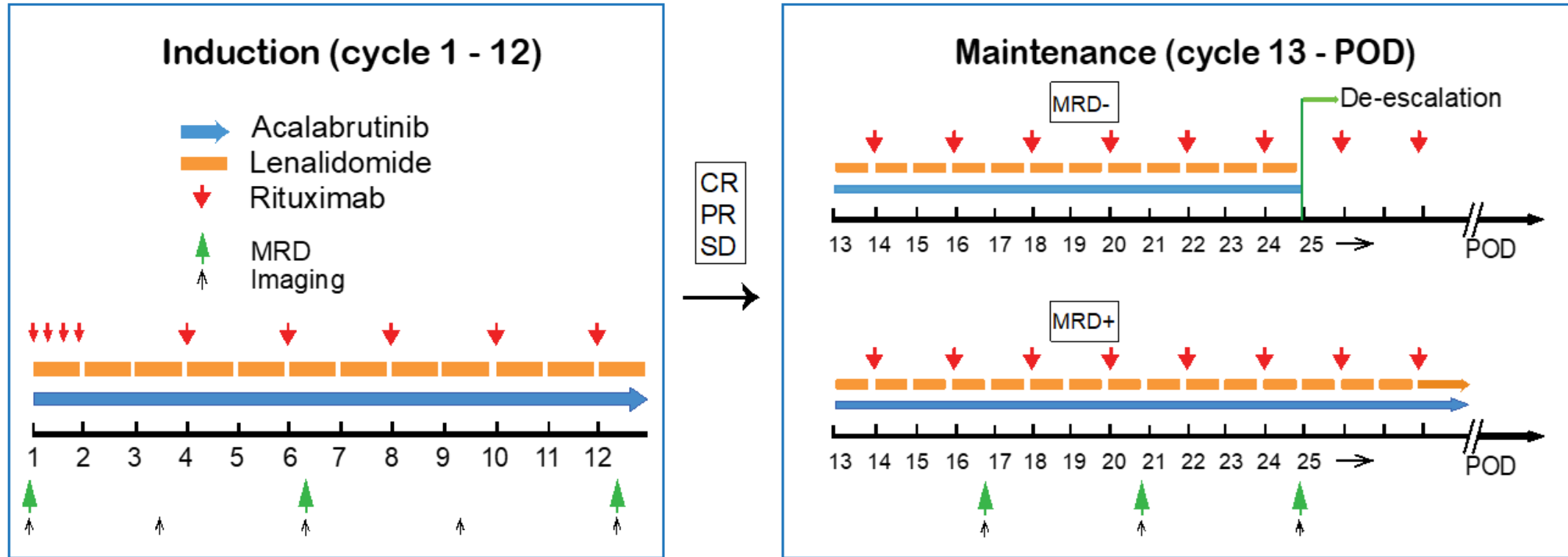
- 50 patients with untreated MCL enrolled to receive IR x 12 cycles with venetoclax added at cycle 5 with consolidation with R-HyperCVAD based on risk at diagnosis
 - None with low risk
 - 2 cycles with intermediate risk
 - 4 cycles with high risk
- ORR/CR – 100%
 - 54% of patients off study for AEs (9 related to COVID)



- Window – 3 is ongoing
 - RISE OF THE CAR-T

Study Design

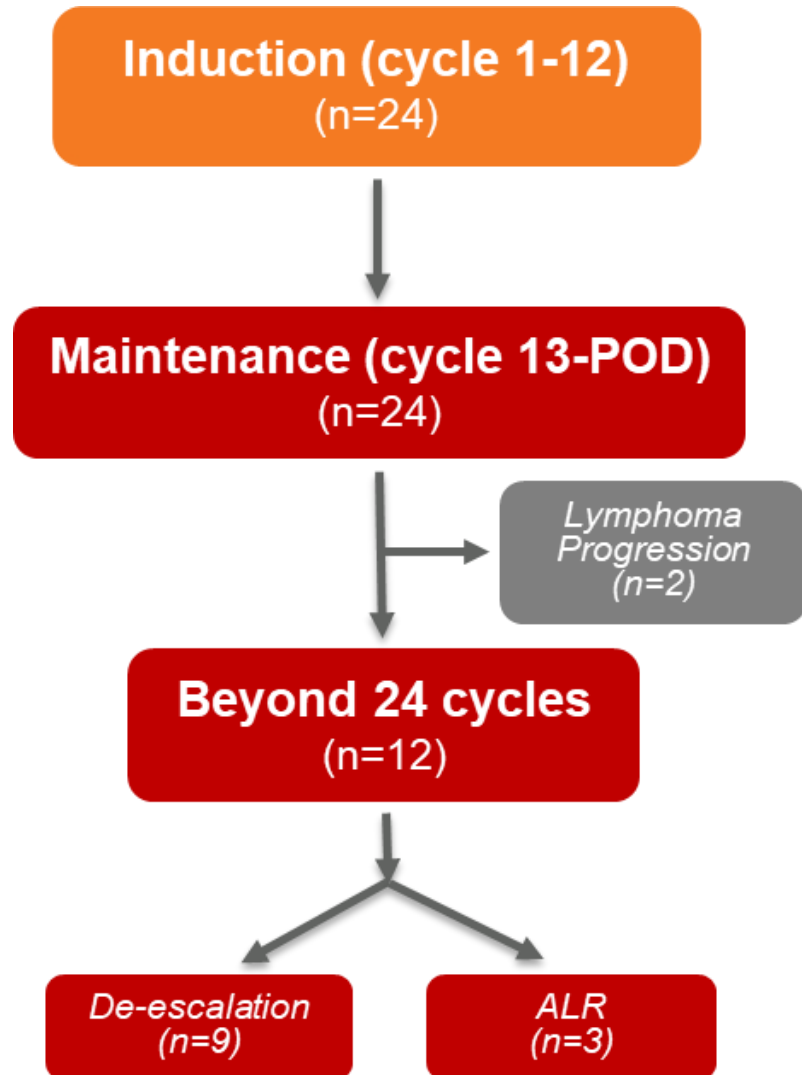
Sample size N=24



1st – CR rate after induction
2nd – ORR, safety and survival
Exploratory: MRD, NGS

- Acalabrutinib and lenalidomide can be discontinued after 24 cycles of treatment for subjects achieving MRD-negative CR during maintenance.
- Imaging studies: PET/CT is required at baseline and time to confirm CR.

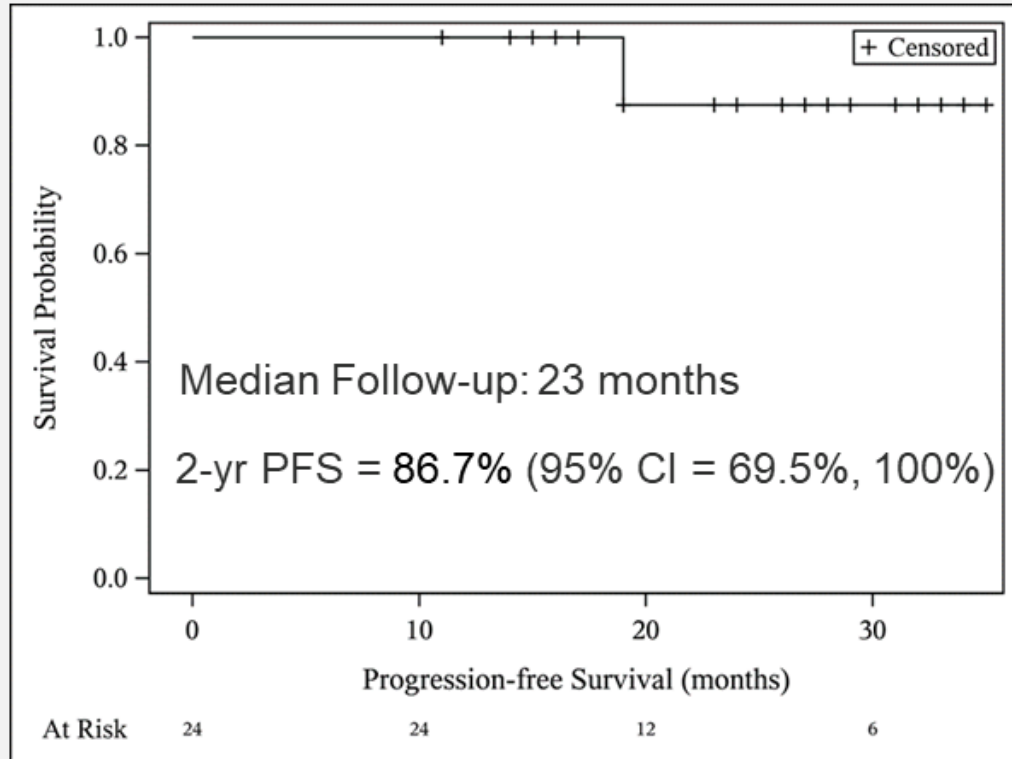
Efficacy: Objective Responses



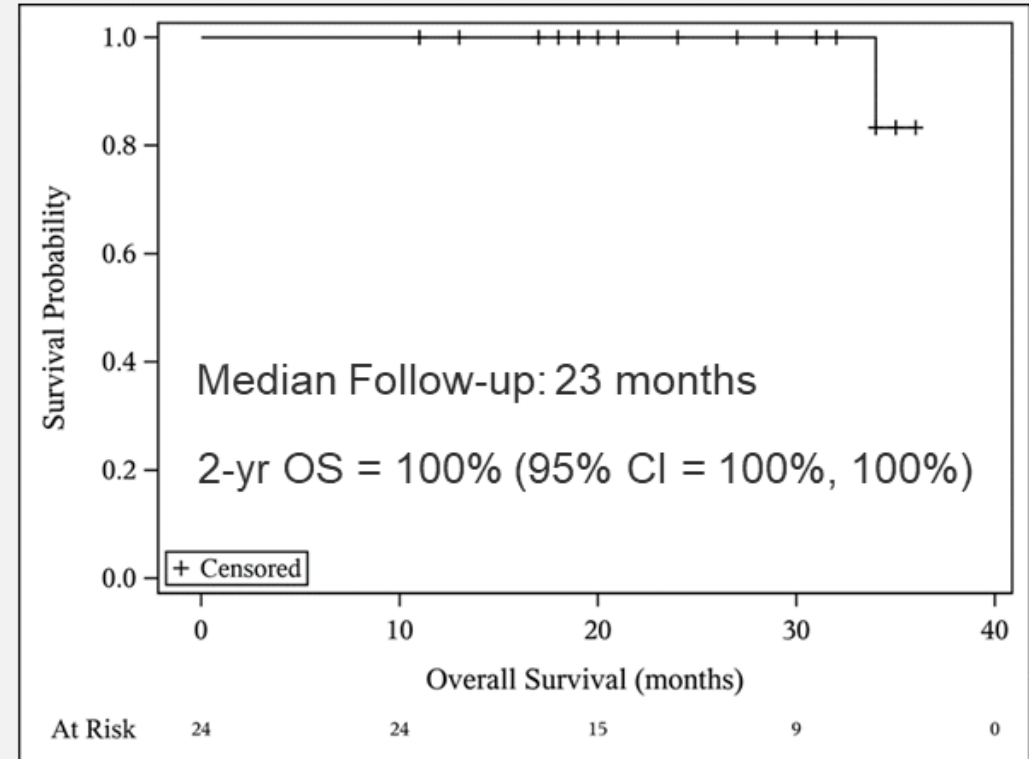
| Response | End of Induction* (12 cycles) | |
|---|----------------------------------|------------|
| | No. Pt | ITT |
| ORR | 24 | 100% |
| CR | 20 | 83% |
| PR | 4 | 17% |
| SD | 0 | 0 |
| PD | 0 | 0 |
| Median Follow-up | 23 months (range 12-36) | |
| * *: EOI following 12 cycles of treatment; response per Lugano criteria | | |

Efficacy: Survival

Progression-free Survival



Overall Survival



Moving Forward

- Do we have a standard of care in MCL



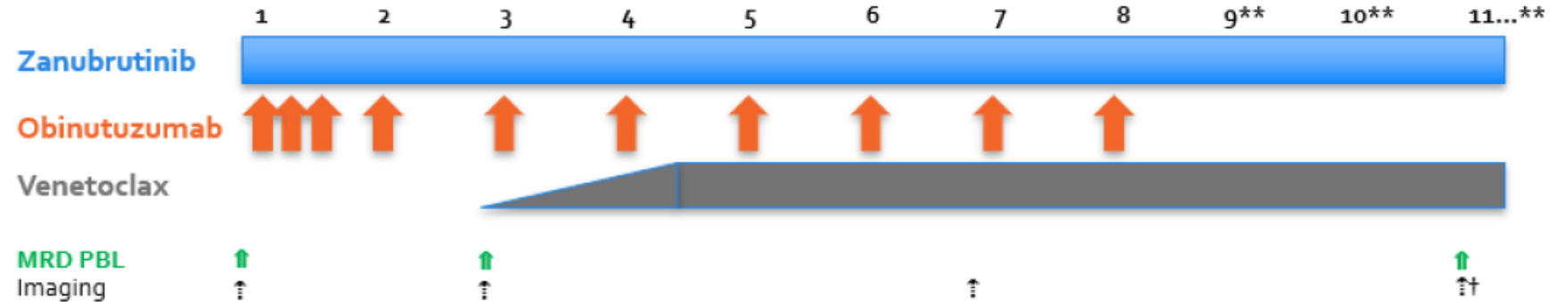
Moving Forward continued.....

- MCL issue...thus far no standard comparator arm suitable for all patients
 - Majority of patients older which limits the agents that can be used
 - TRIANGLE vs. SHINE
 - Can we create, enroll and get results from a study quick enough to keep up with introduction of new agents and ever changing field (opinions)
- So, in the end....the search for our R-CHOP continues.....
- Other questions...
 - R vs. O (does recent MAIC change preferred antibody partner?)
 - p53 mutated patients.....

Phase II Multicenter Study of BOVen

Key Eligibility Criteria:

- Previously untreated MCL (except localized RT prior)
- *TP53* mutation (any variant allele frequency allowed)
- ECOG PS ≤ 2
- ANC >1 , PLT >75 , HGB ≥ 9 (unless if due to MCL)



Dosing:

Zanutrutinib 160 mg oral twice daily
Until EOT or intolerance**

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
Until EOT or intolerance**

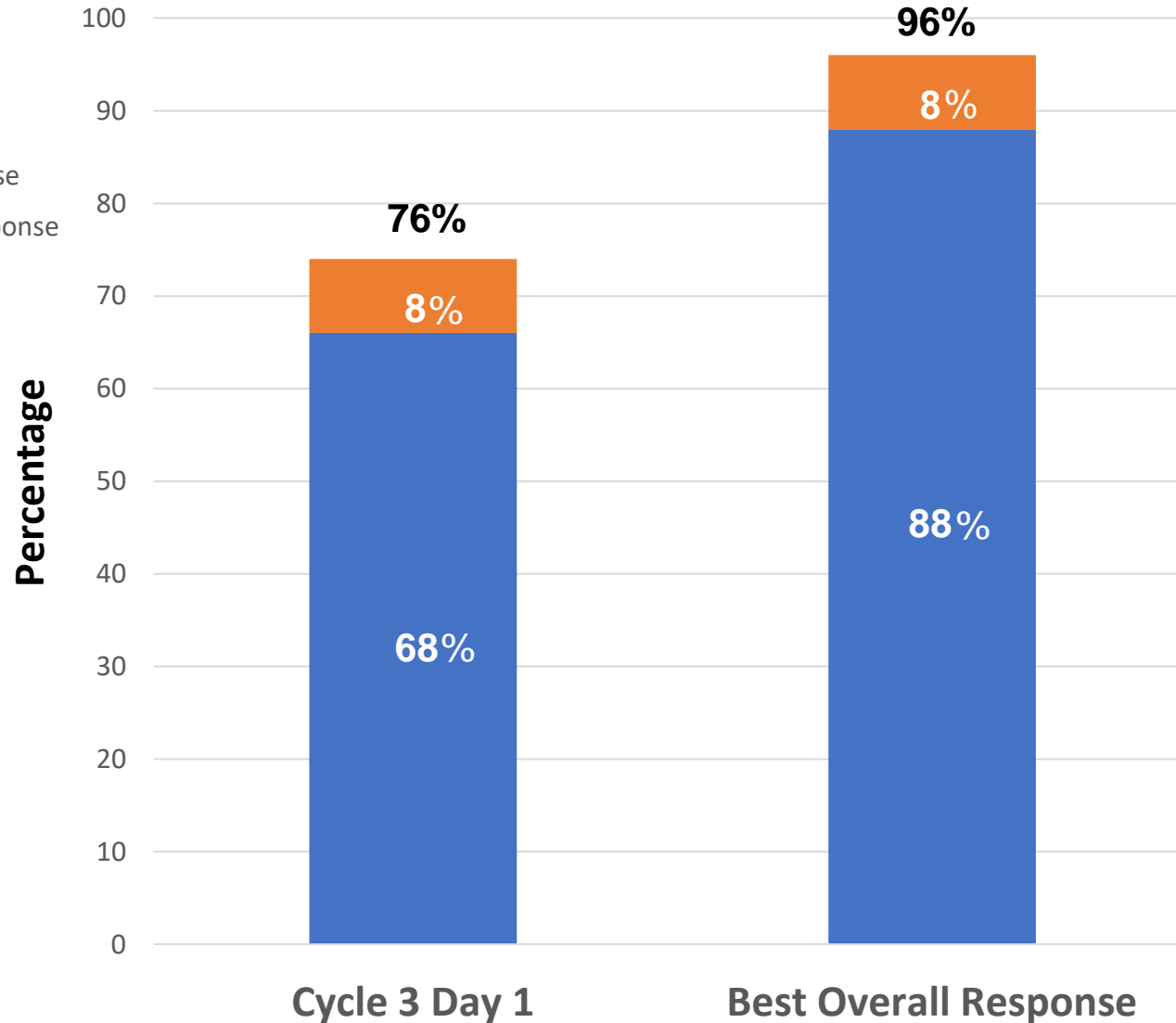
Total # of cycles: 24 (2 years)

After 24 cycles, if CR and MRD undetectable (uMRD), then no further tx. If $<$ CR and/or MRD positive, then continue zanutrutinib and venetoclax.

Pts with CR/uMRD will be monitored for MRD positivity or recurrence and can restart zanutrutinib and venetoclax.

Aim to enroll 25 pts, if 11 or more alive and progression free at the end of the 2nd year, BOVen will be declared effective in this high-risk population.

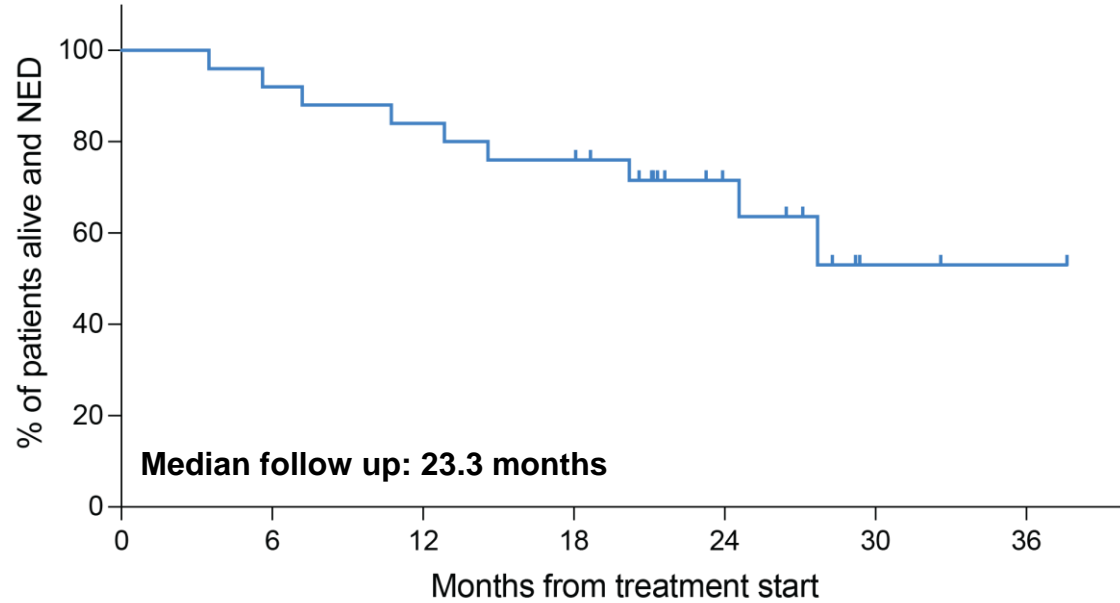
Response Rates By Timepoint



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

- Median follow up:
 - 23.3 months
- There were 9 events:
 - 5 progressions
 - 4 deaths
 - 2 COVID-related
 - 1 unknown
 - 1 PNA / respiratory failure
- The 4 deaths occurred in patients in ongoing response at time of death

Progression-Free Survival

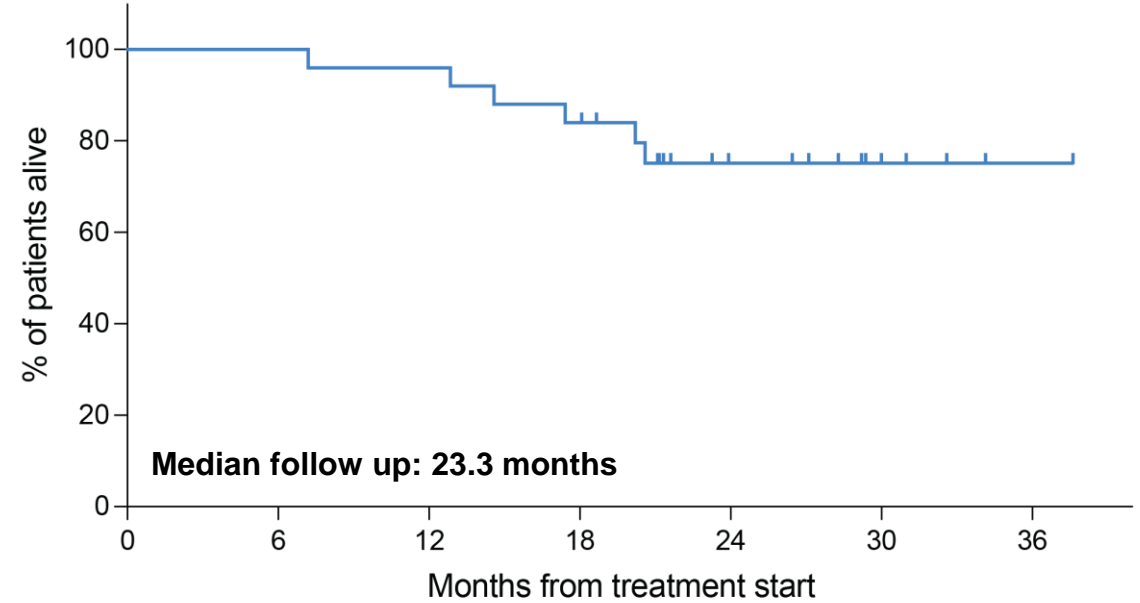


No. at risk 25 23 21 19 9 2 1

2-year PFS: 72% [95% CI: 56, 92]

Median PFS: not reached

Overall Survival



No. at risk 25 25 24 21 10 4 1

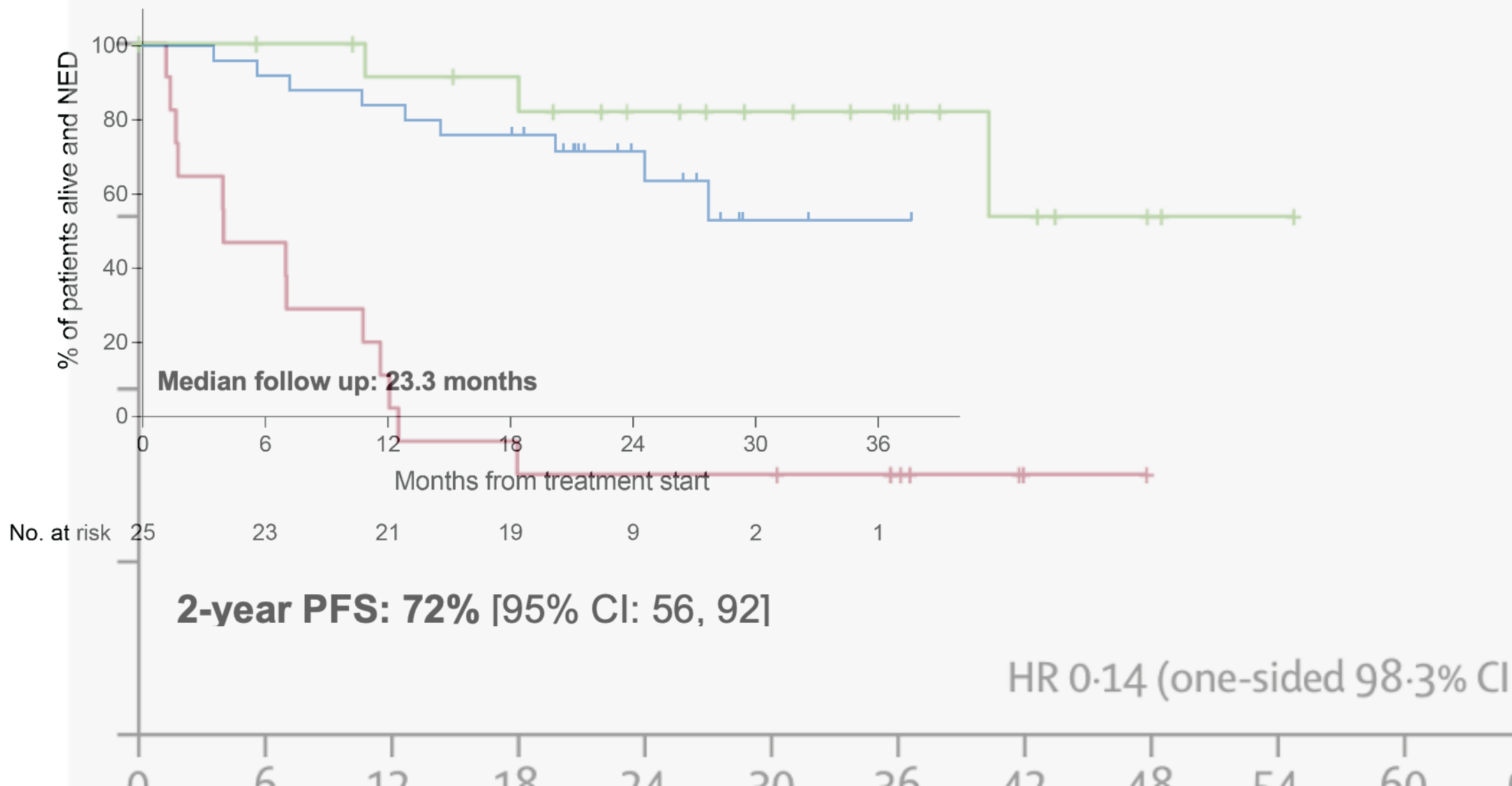
2-year OS: 75% [95% CI: 58, 93]

Median OS: not reached

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

D

Progression-Free Survival





Thank you!

Enter your name

Enter your position, contacts (e-mail) and other related information