Deja Vu……BTK’s in Frontline Mantle Cell Lymphoma

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City of Hope

Disclosures

Tycel J. Phillips, MD serves as a consultant for Abbvie, ADCT, AstraZeneca, Beigene, BMS, Caribou, Genmab, Genentech, Gilead, Ipsen, Janssen, Merck, Pharmacyclics, Regeneron, and Xencor

Serves on the advisory board for Genmab, Genentech, and Merck, and receives institutional research funding from Abbvie and Genentech.

Dr. Phillips plans to discuss the unapproved/investigational use of BTKI.

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Outline

- Historical role of chemotherapy
- BTKi
  - Younger
  - Older

Dichotomy of the Problem

- No Standard front-line therapy exists currently

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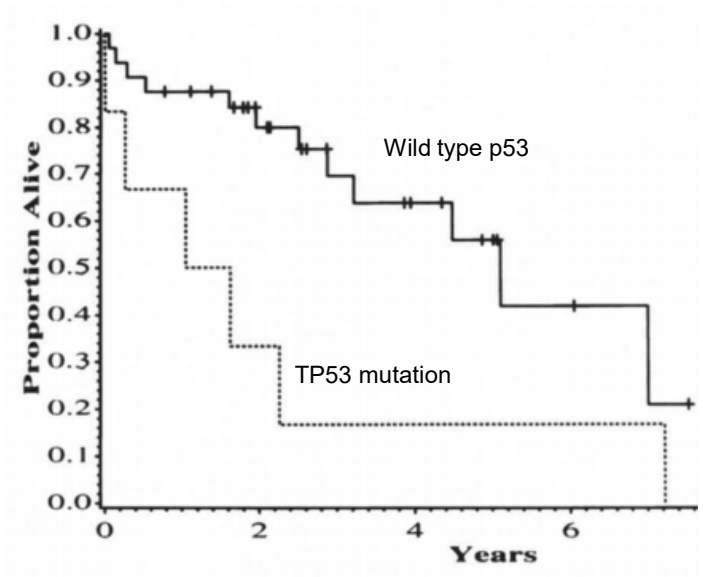
Problems with Chemotherapy

- Major concerns
  1. Ageism
     - HiDAC isn't tolerable beyond a certain age
     - Concern that BR isn't enough
  2. Long term risk
     - Non-Relapse Mortality remains lingering concern
  3. Paper Champ
     - Effectiveness in High-Risk patients is questionable

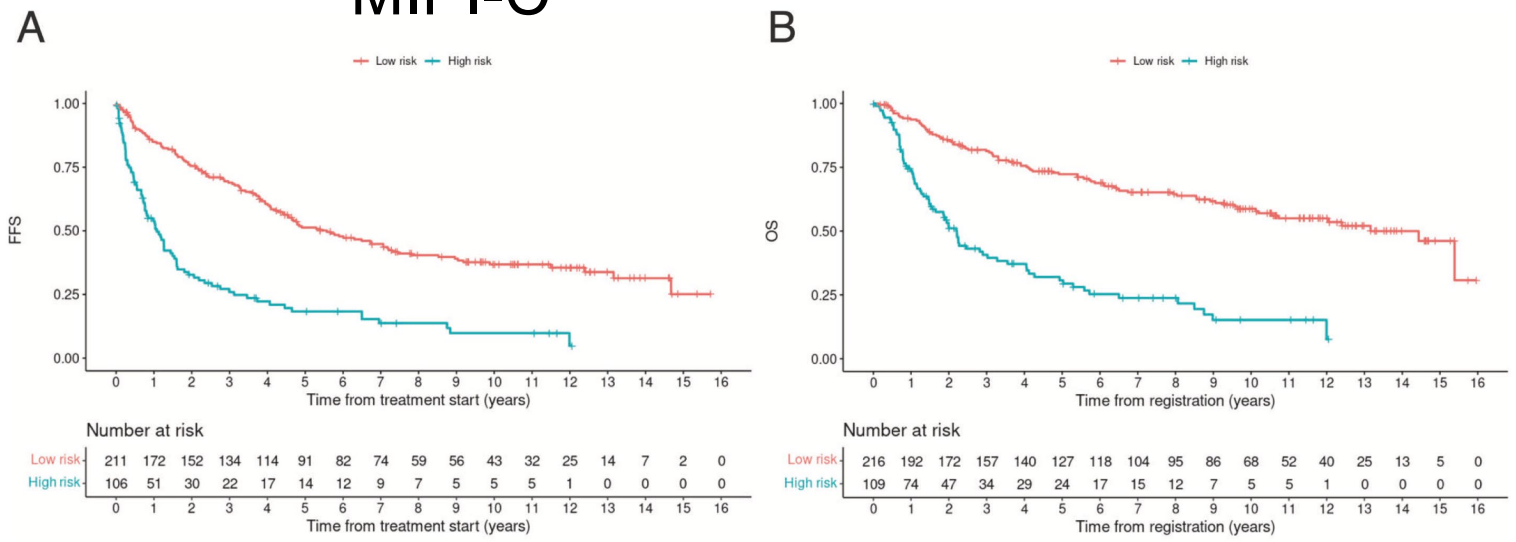
Data for p53 and other risk factors

p53



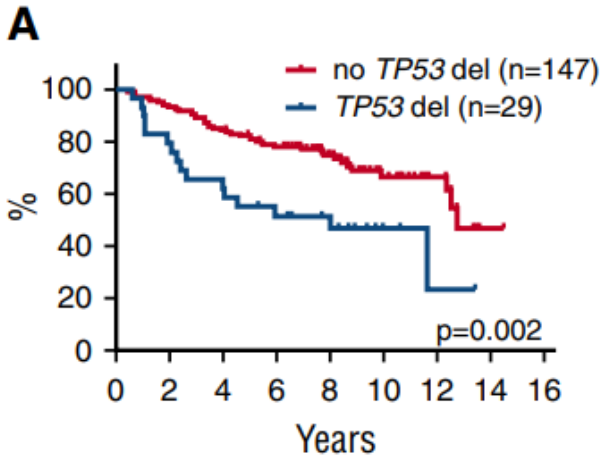
Greiner TC, Blood 1996

MIPI-C



Scheubeck G, Leukemia 2023[14]

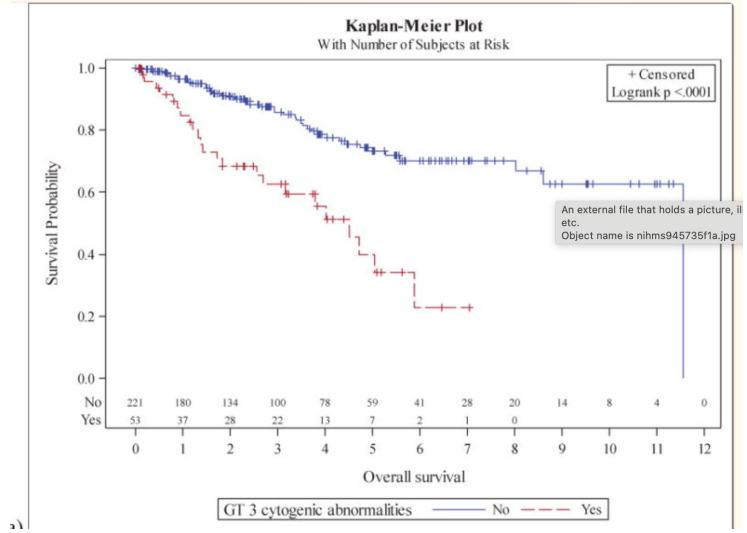
OS



R-CHOP/RHiDAC (ASCT)

Eskelund CW, Blood 2017

Complex Cytogenetics



Greenwell. Cancer 2018

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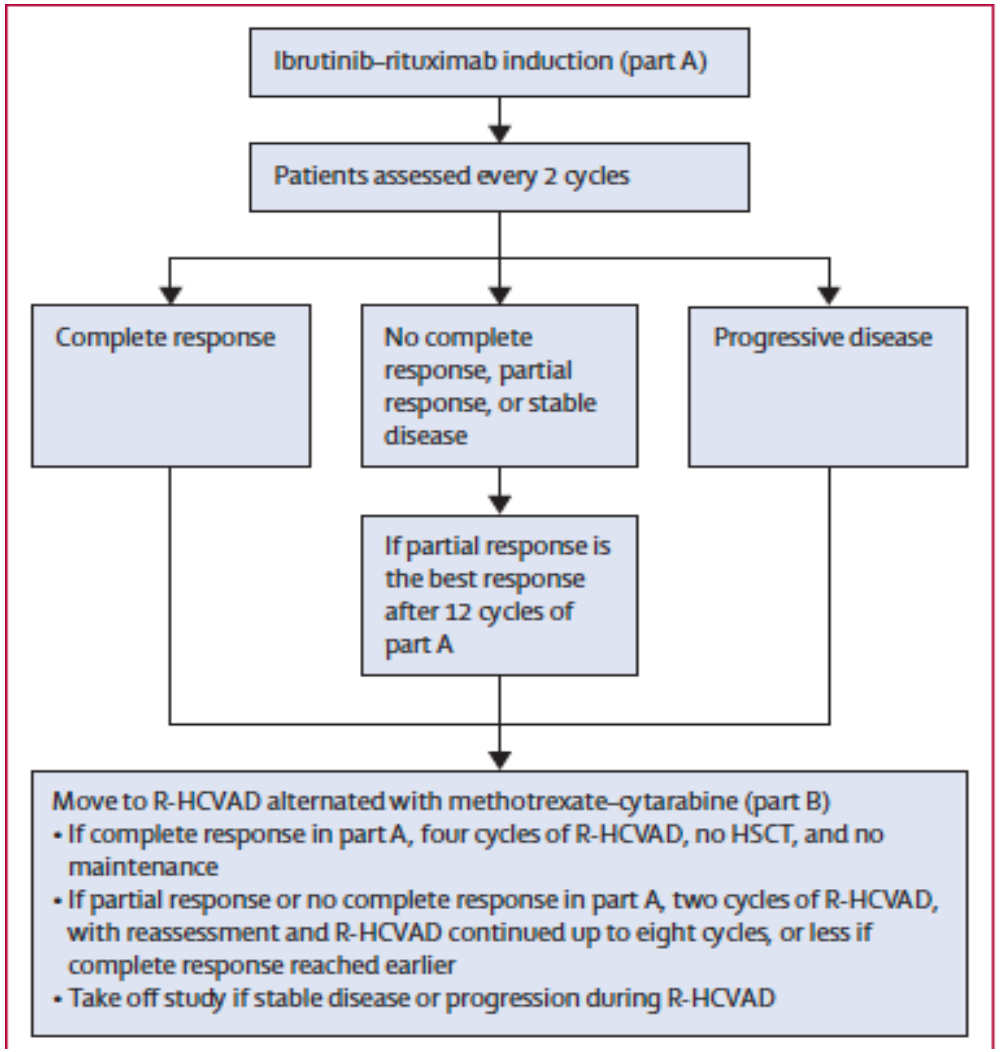
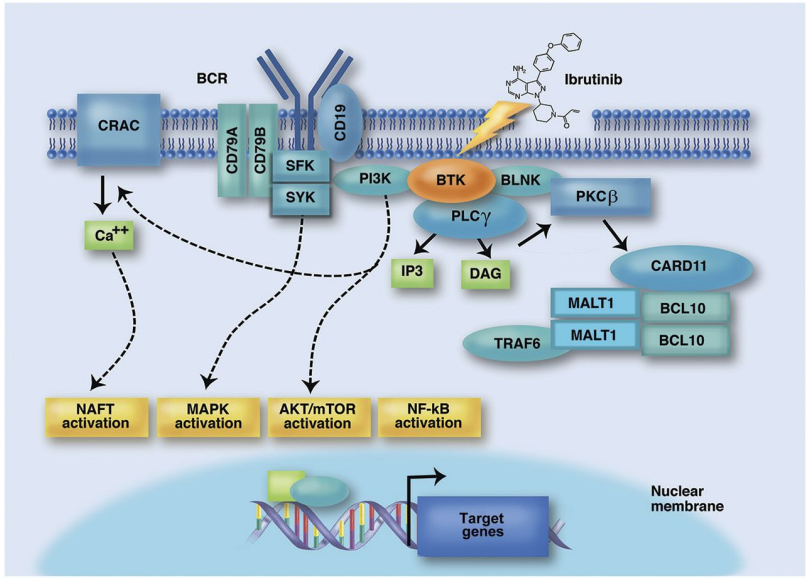
BTKi

- Highly effective oral agents that are well positioned in the 2L setting
  - As with most treatments……if it works well in the 2L space then as a field we always look to move earlier lines of therapy
  - But at what cost??
    - Relapses post BTKi are difficult to treat w/ very few approved durable options
      - CAR-T
        - This treatment while effective has its warts
          - Brexu-cel is toxic
          - Liso-cel has questionable efficacy post BTKi.

But let's dive in…….

WINDOW STUDY





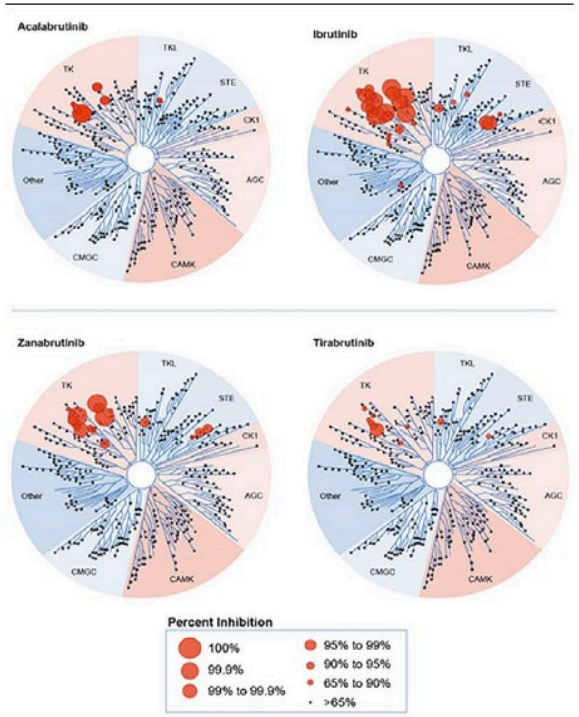


FIGURE 1 Kinome profiling of Bruton tyrosine kinase (BTK) inhibitors at a single dose of 1 μmol/L. Adapted with permission from Figure 1 in Kaptein *et al.*, 2018[24].

Wang et al. Lancet Oncol. 2022 Mar;23(3):406-415.

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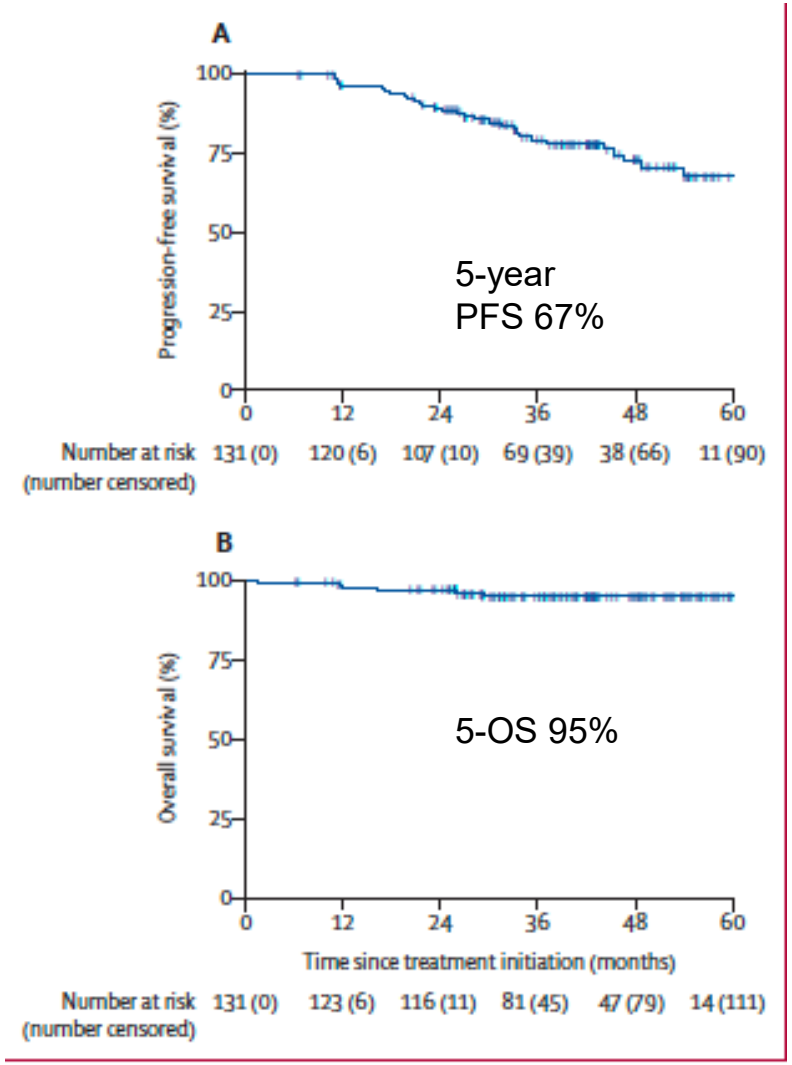
	Patients with positive PET-CT at baseline (n=97)*	All patients (n=131)
Part A best response†		
Evaluable patients	93‡	129
Overall response	93/131 (71%)	129 (98%)
Complete response	91/131 (69%)	114 (87%)
Partial response	2/131 (2%)	15 (11%)
Time to complete response in part A, months	..	5 (4-7)
Overall response after part A	..	129 (98%)
Complete response	..	114 (87%)
Partial response	..	15 (11%)
Part B best response§		
Evaluable patients	108	118
Overall response	108 (82%)	118 (90%)
Complete response	108 (82%)	117 (89%)
Partial response	0	1 (1%)
Overall response after part A and part B	..	117 (89%)
Complete response	..	90 (77%)
Partial response	..	1 (<1%)
Minimal residual disease-negative at best response¶	..	86 (65%)
Duration of response, months	..	28 (18–41)



CR for p53 mut 55% vs. 91% for those w/o.

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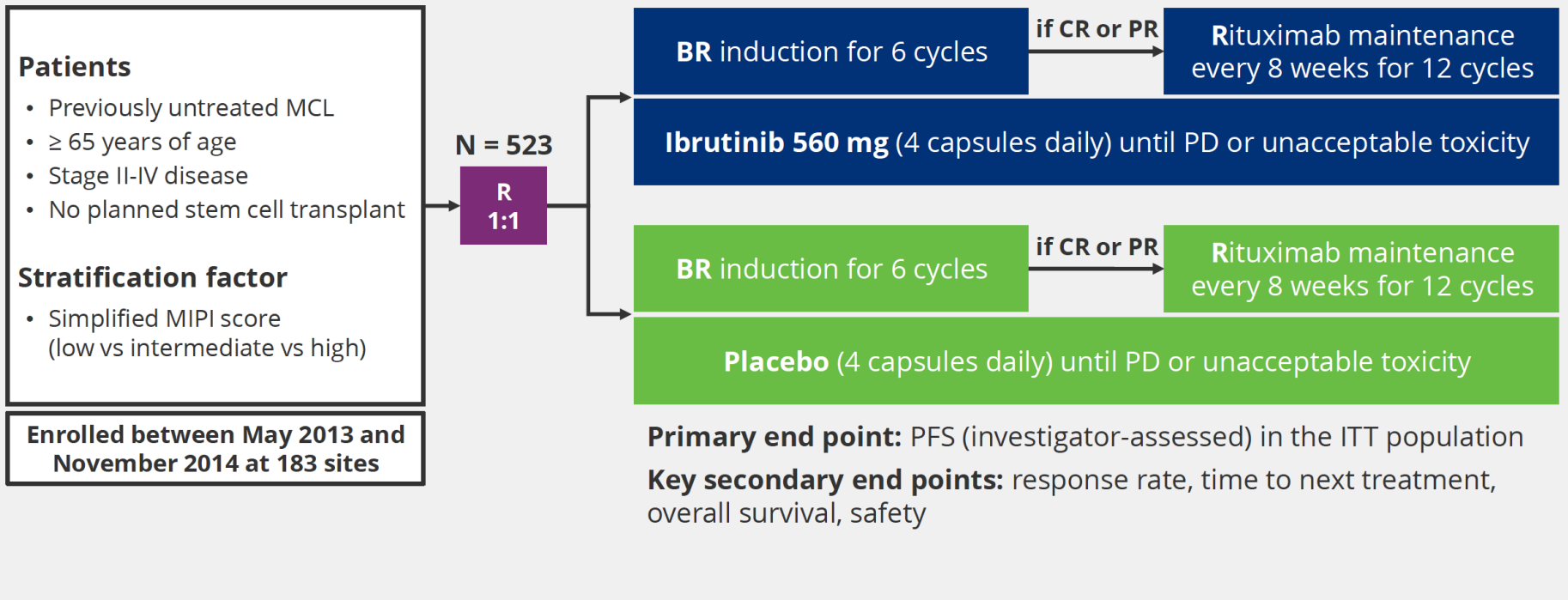
First Attempt at Improvement

- The study was a first step to incorporate BTKi
  - Used in this study as lead into chemotherapy but demonstrated the feasibility and effectiveness of agent in 1L patients.
  - Unfortunately, HyperCVAD not feasible in older patients.
  - No long term follow up reported.
  - Several iterations of this concept since then (Window 2/3)

SHINE

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



Induction: **B**endamustine 90 mg/m2 Days 1 and 2, **R**ituximab 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.

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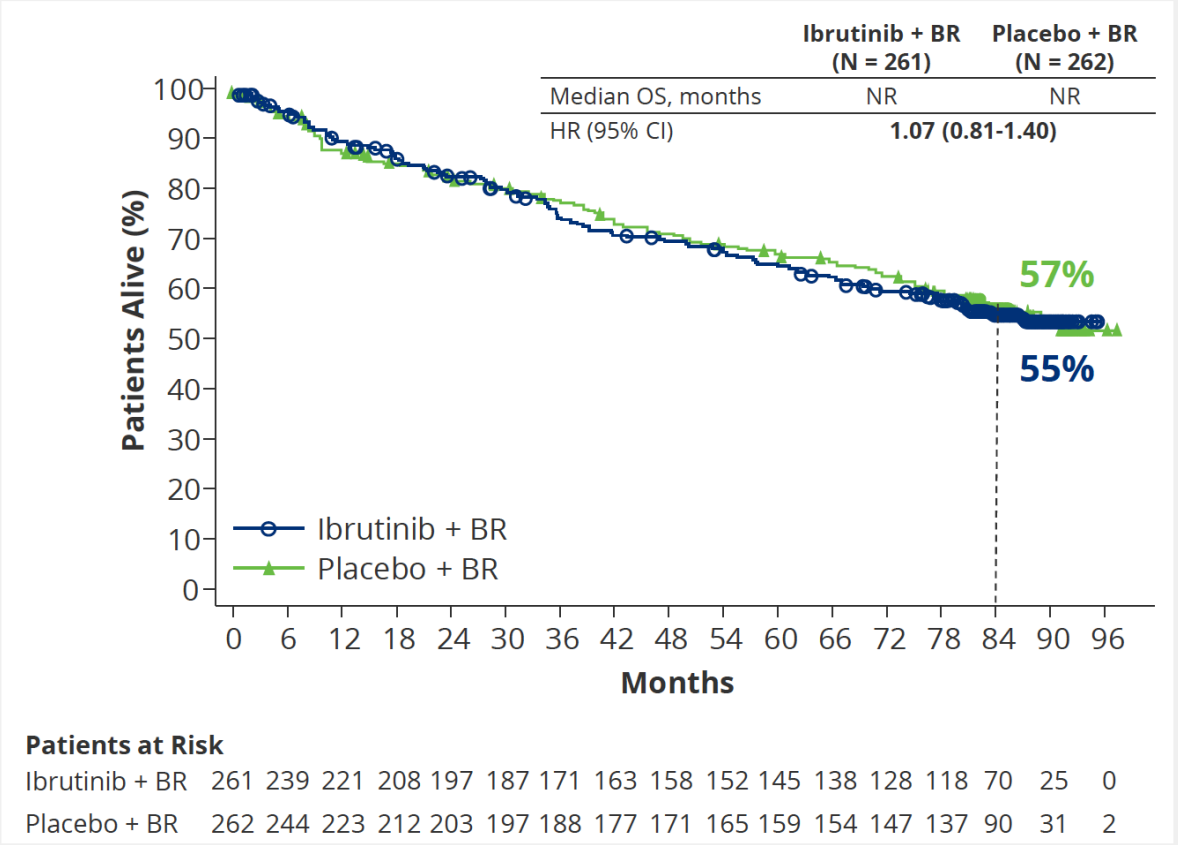
Wang et al. ASCO 2022

SHINE



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

*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.

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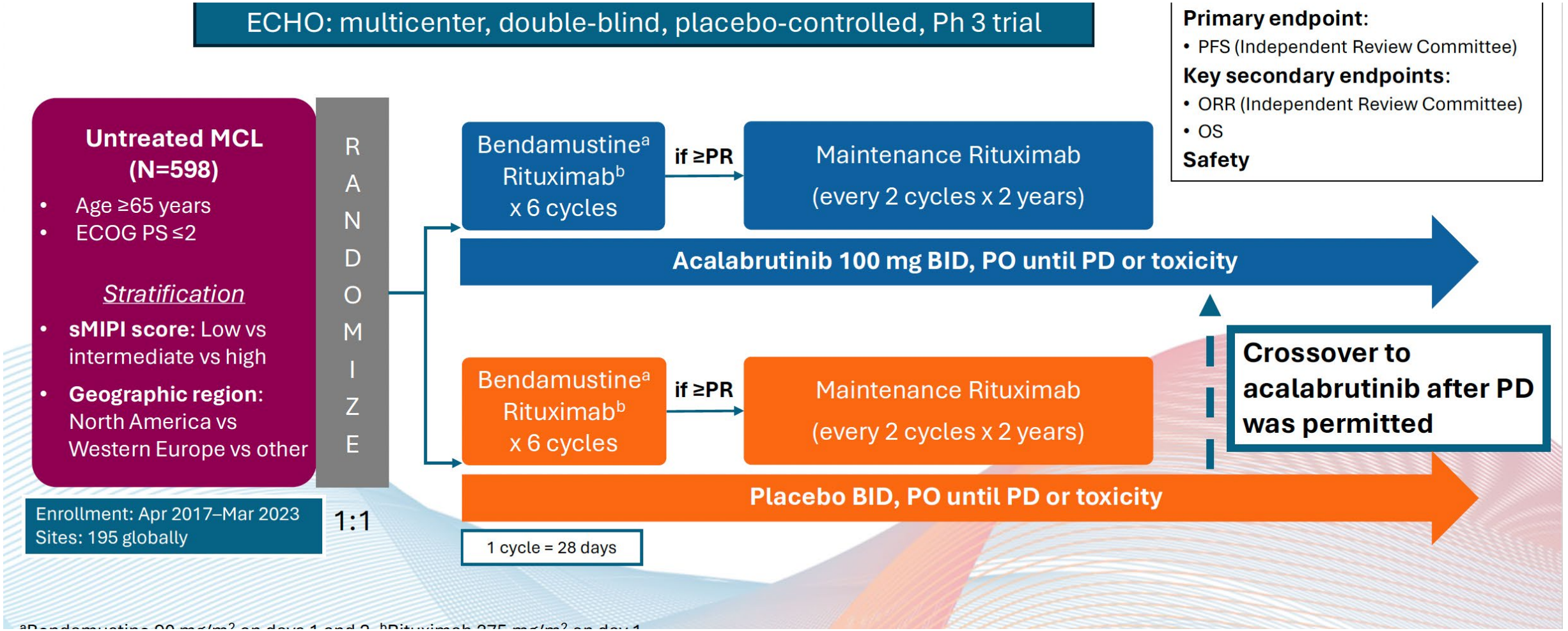
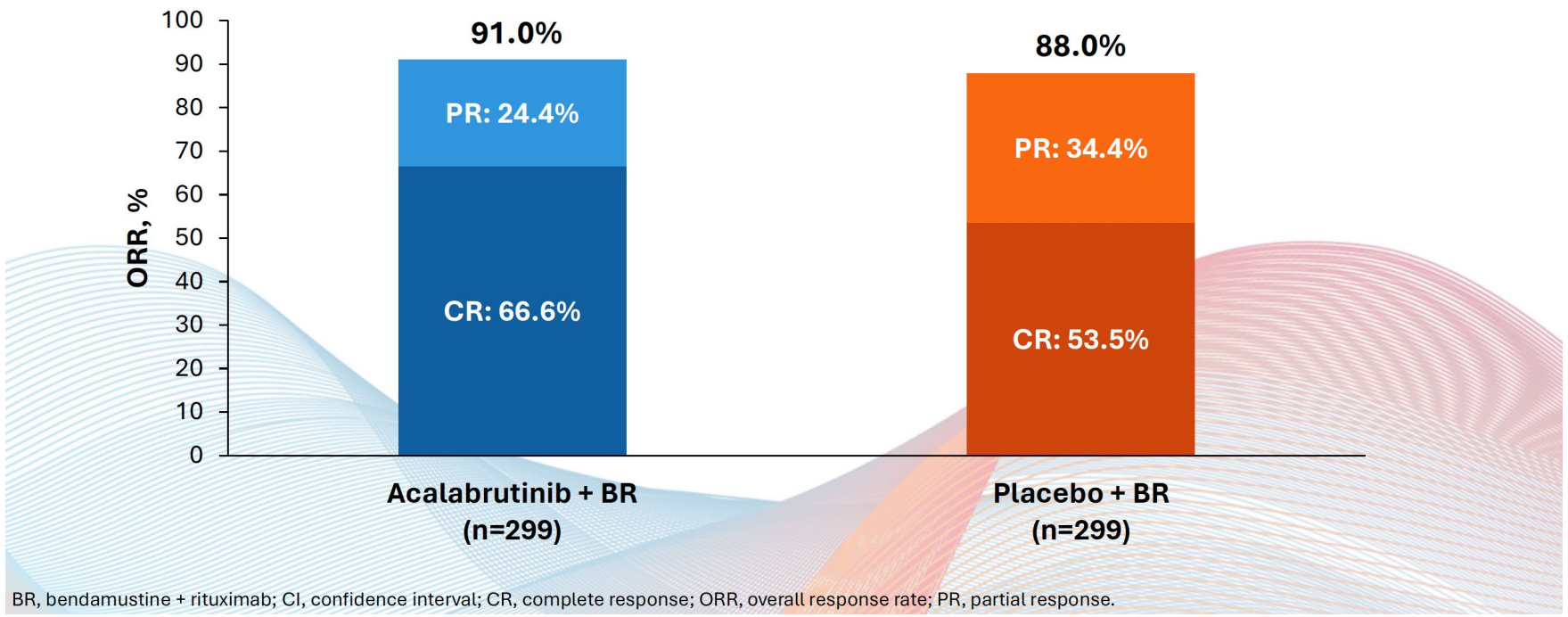
Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma (MCL): Results from the phase 3, double-blind, placebo-controlled ECHO trial



RESPONSE

Best Overall Response and Complete Response Rates

- An additional 13% of patients achieved CR with acalabrutinib + BR

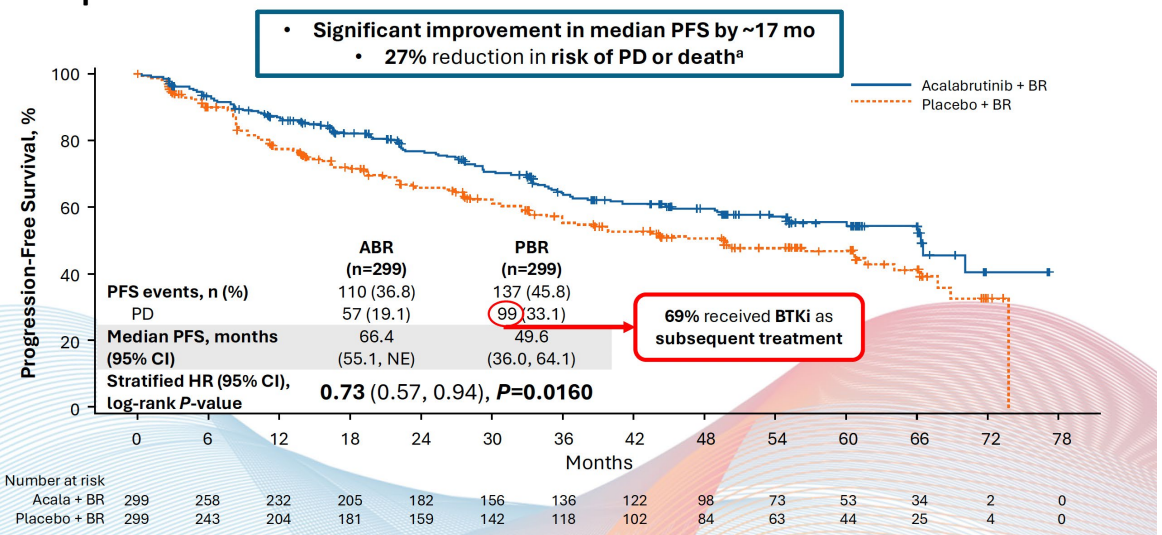


BR, bendamustine + rituximab; CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response.

Response

PFS (primary endpoint) Was Significantly Improved With Acalabrutinib + BR

- **Significant improvement in median PFS by ~17 mo**
- **27%** reduction in **risk of PD or death**[a]



	ABR (n=299)	PBR (n=299)
PFS events, n (%)	110 (36.8)	137 (45.8)
PD	57 (19.1)	99 (33.1)
Median PFS, months (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
Stratified HR (95% CI), log-rank *P*-value	**0.73** (0.57, 0.94), ***P*=0.0160**	

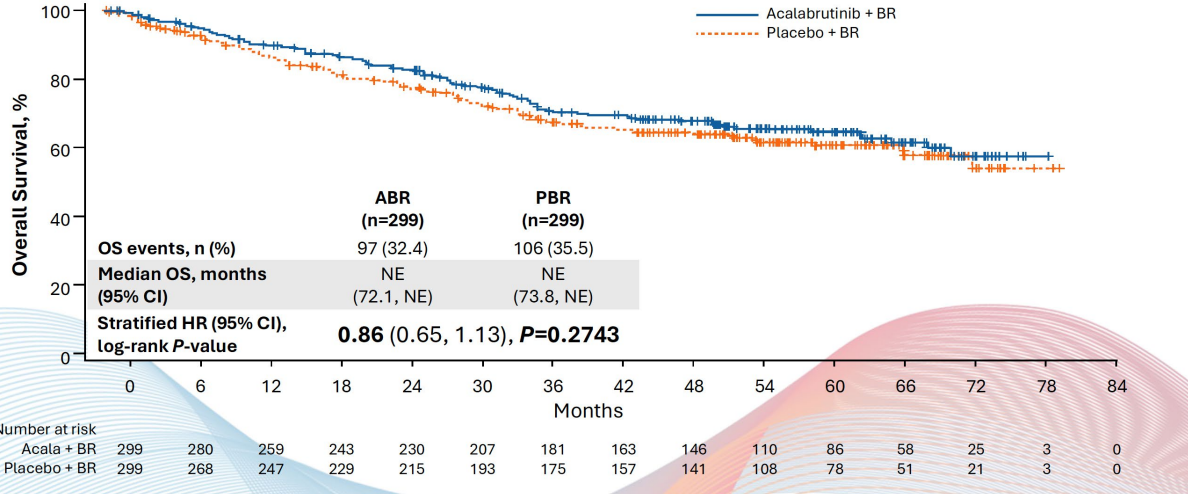
69% received **BTKi** as **subsequent treatment**

Number at risk

Acala + BR	299	258	232	205	182	156	136	122	98	73	53	34	2	0
Placebo + BR	299	243	204	181	159	142	118	102	84	63	44	25	4	0

[a]At a median follow-up of 45 months.
ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; NE, not estimable; PBR, placebo + bendamustine + rituximab; PD, progressive disease; PFS, progression-free survival.

Overall Survival Including Crossover



	ABR (n=299)	PBR (n=299)
OS events, n (%)	97 (32.4)	106 (35.5)
Median OS, months (95% CI)	NE (72.1, NE)	NE (73.8, NE)
Stratified HR (95% CI), log-rank *P*-value	**0.86** (0.65, 1.13), ***P*=0.2743**	

Number at risk

Acala + BR	299	280	259	243	230	207	181	163	146	110	86	58	25	3	0
Placebo + BR	299	268	247	229	215	193	175	157	141	108	78	51	21	3	0

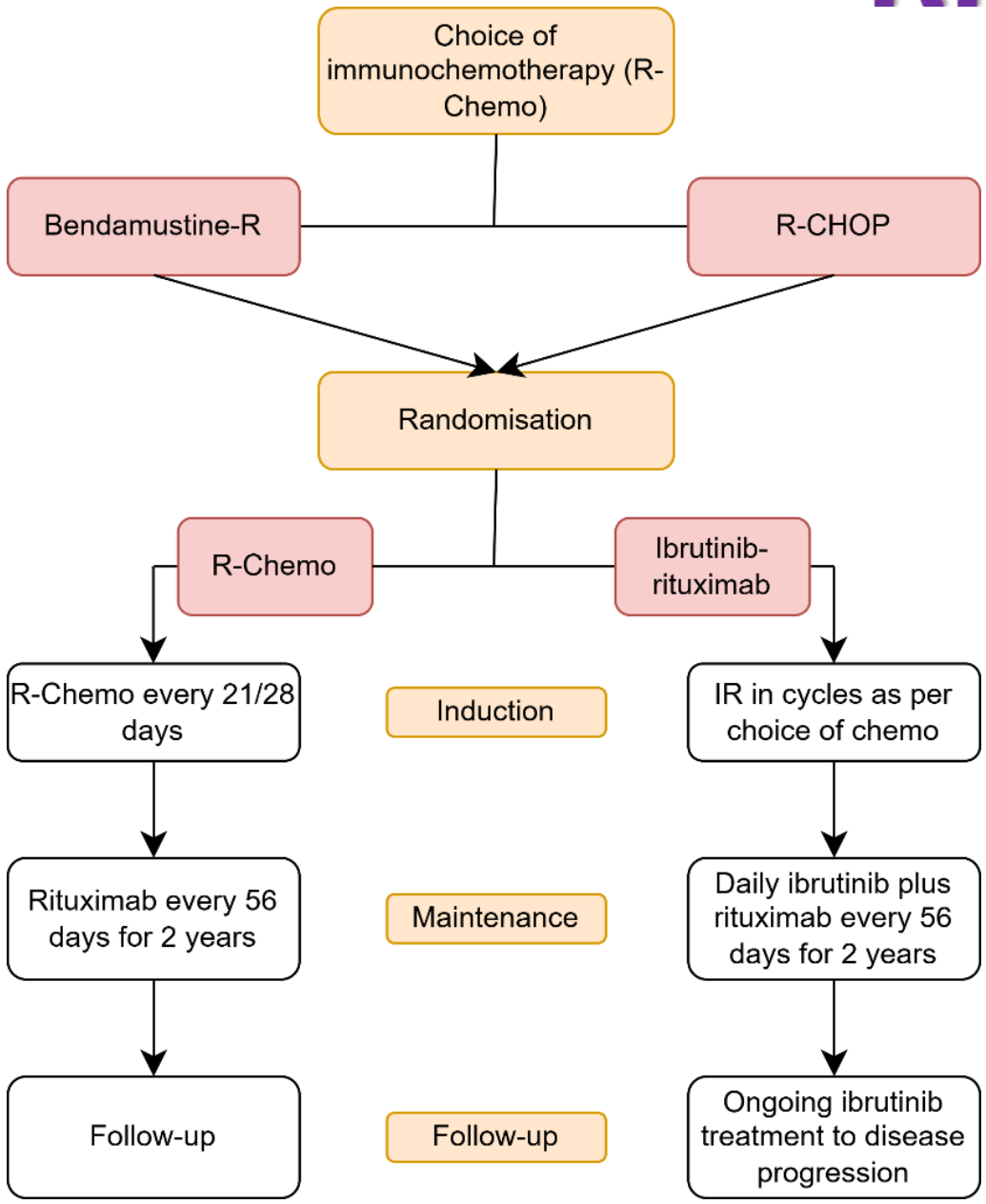
Median follow-up of 45 months.
ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PBR, placebo + bendamustine + rituximab.

- Ultimately this study demonstrated some of the cost w/ increased toxicity in the experimental arm
  - Additionally, data suggested that combination was no more durable than sequential
  - Benefit of BTKi in those who would fail to get to 2L????
    - How many of those need the chemotherapy portion?
      - Blastoid…..maybe

Trial design

Inclusion criteria
- 60 years or older
- Pathologically confirmed MCL, including either cyclin D1 overexpression or t(11;14)(q13;q32)
- Previously untreated, measurable (>1.5cm), stage II-IV MCL in need of treatment
- ECOG 0-2

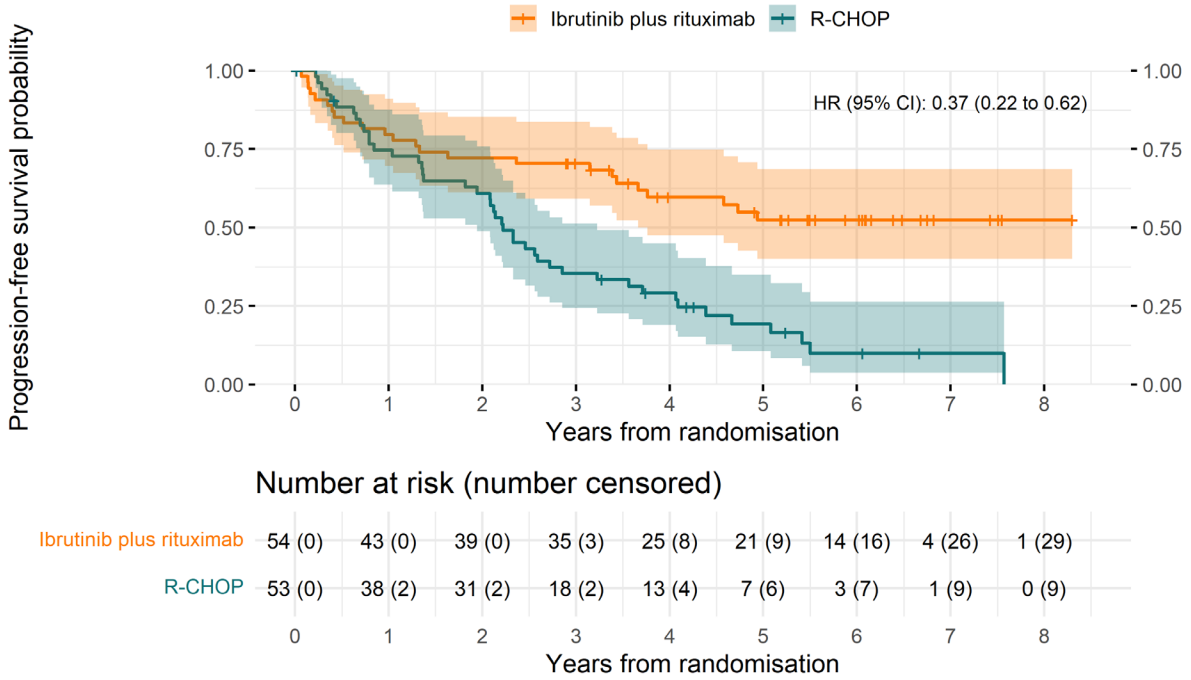
Exclusion criteria
- Considered fit for stem cell transplantation
- CNS involvement
- Known serological positivity for HBC/HCV/HIV



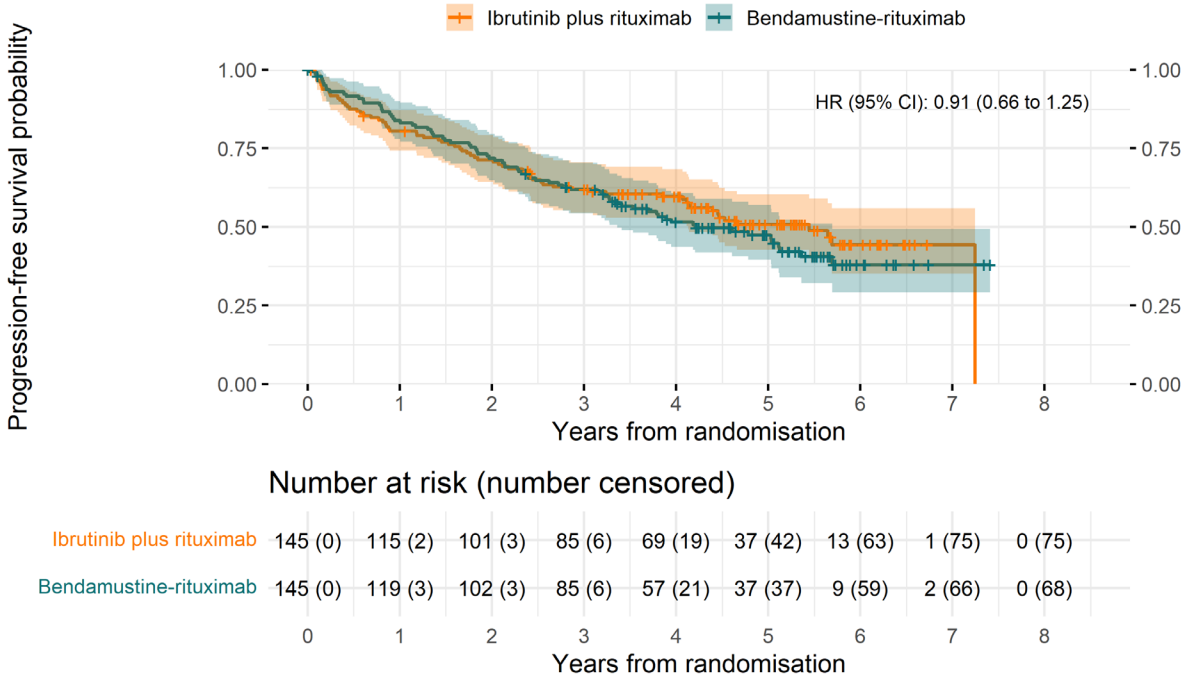
Rituximab 375mg/m^2
Ibrutinib - 560mg od
Bendamustine 90mg/m^2 D1+D2 of 28 day cycle
CHOP - (Cyclophosphamide 750mg/m^2, Doxorubicin 50mg/m^2, Vincristine 1.4mg/m^2, Prednisolone 100mg *5 days) 21 day cycle
Maintenance rituximab - 1400mg sc every 56 days

Progression-free survival

ENRICH



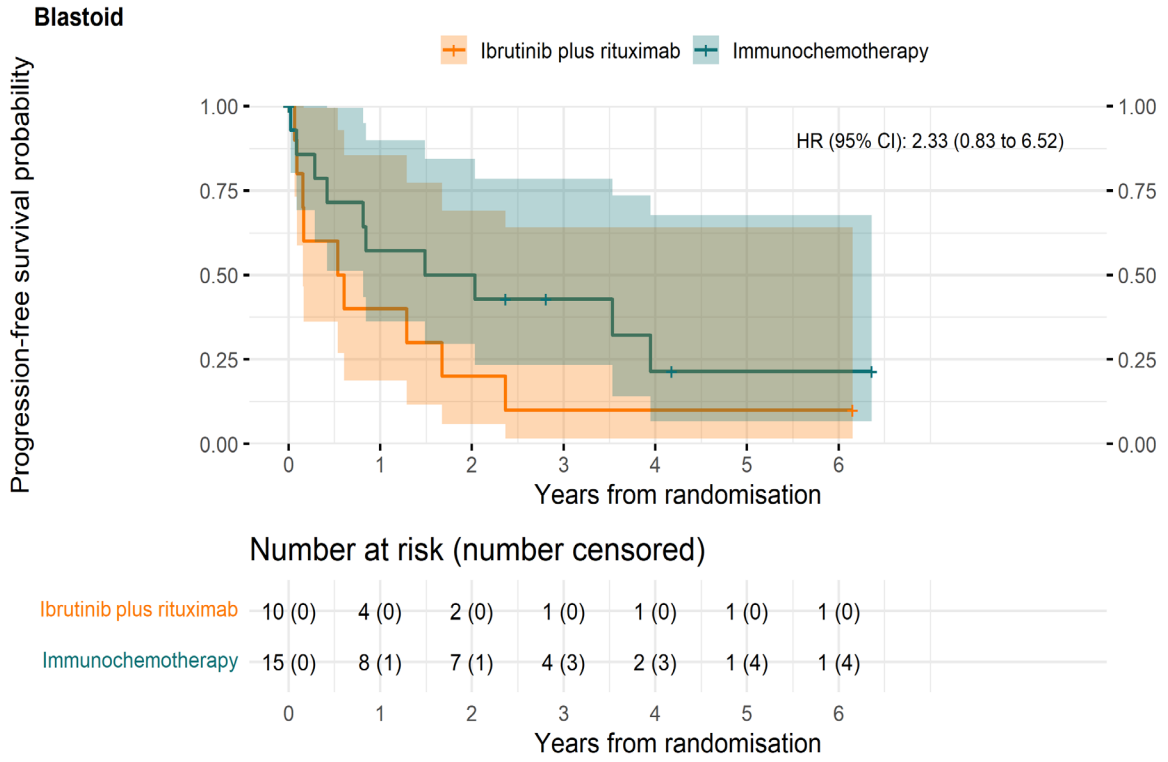
5-year PFS (95% CI)
IR: 52.4% (40.0% to 68.6%)
R-CHOP: 19.2% (10.6% to 35.1%)

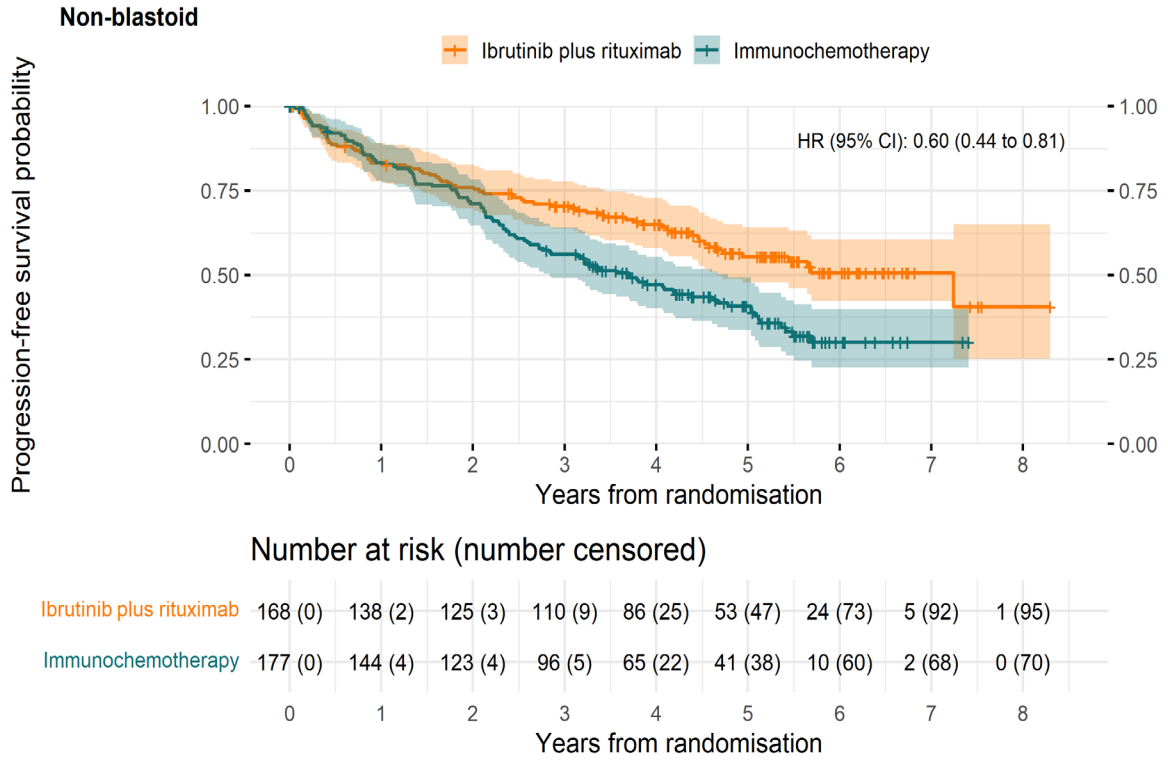


5-year PFS (95% CI)
IR: 50.8% (42.8% to 60.4%)
BR: 47.4% (39.5% to 56.9%)

Blastoid disease

Suggestion of inferior PFS for blastoid disease for those ran

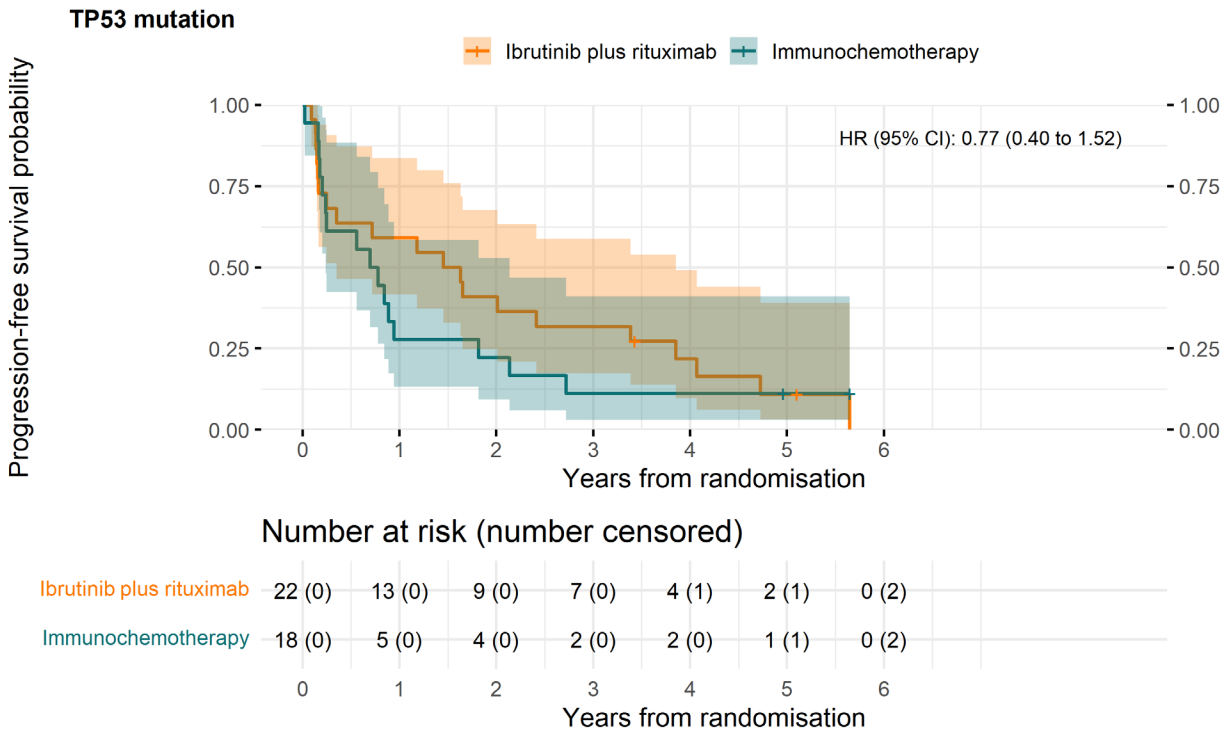


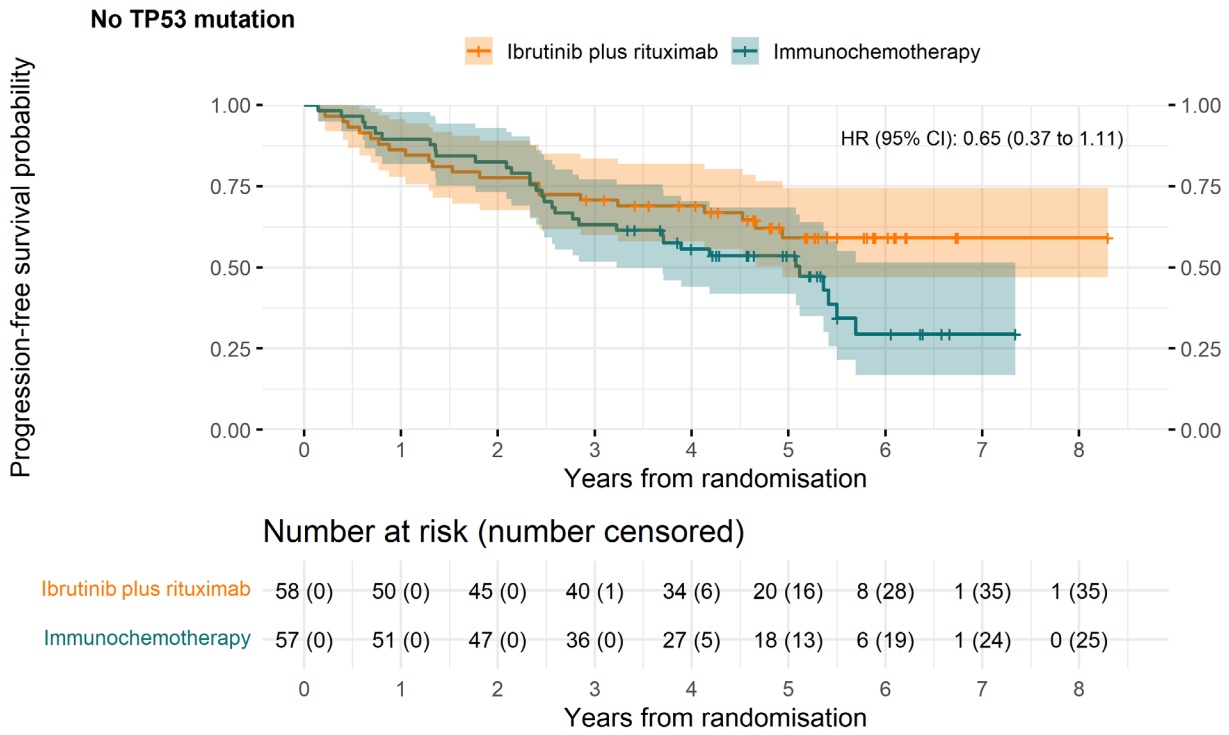


Blastoid subgroup (n=25) PFS 6.9 (95% CI 1.9 to NE) months for IR vs 21.1 (95% CI 9.8 to NE) months for immunochemotherapy)

HR 2.33, 95% CI 0.83 to 6.52

TP53 mutation





Median PFS for those treated with IR was 18.5 (95% CI 4.2 to 46.2) months versus

8.9 (95% CI 2.9 to 25.7) months for those treated with immunochemotherapy: HR of 0.77 (95% CI 0.40 to 1.52)

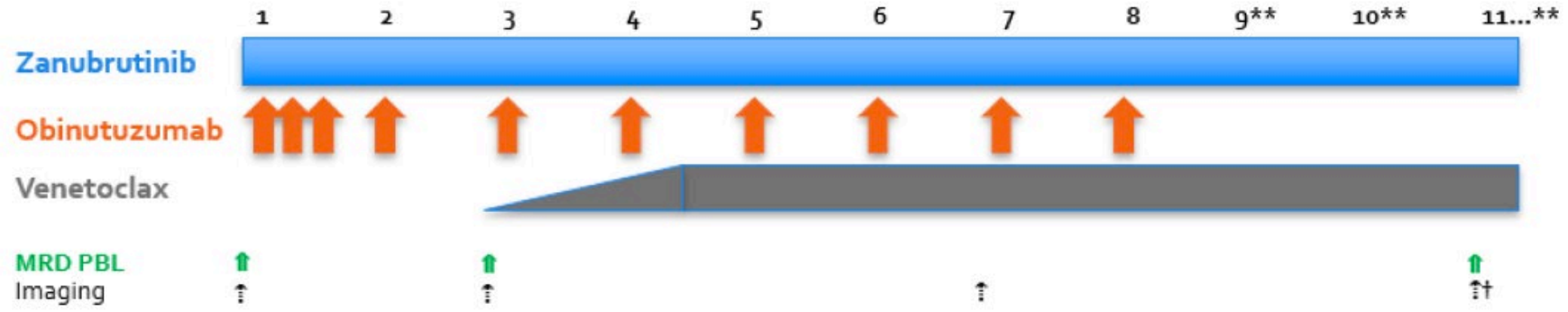
Older Patients

- Although ECHO w/ FDA does it fundamentally change the major question that arose after SHINE
  - Is combination better than sequential therapy…….
    - Data still doesn't support this argument.
      - PFS w/ ECHO was shorter than SHINE
  - What about BTKi plus R
    - ENRICH again a mixed bag w/ improvement in p53 mutated but worse in blastoid…..otherwise a wash……
      - With a few caveats
        - Continuous vs. fixed
        - What happens next?????

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:

Zanubrutinib 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 zanubrutinib and venetoclax.

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

Kumar et al. Blood 2021

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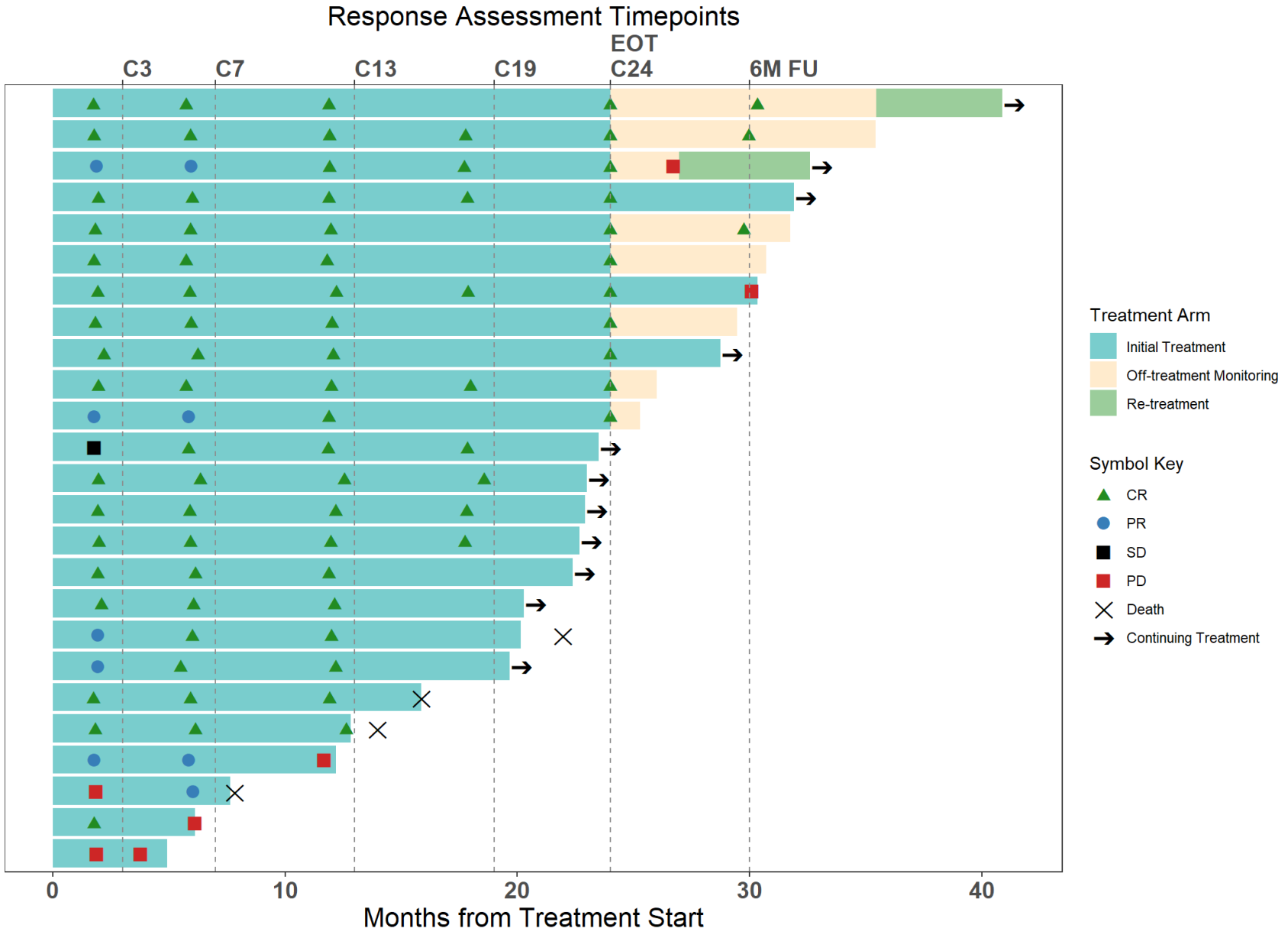
Response timing and duration



- 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

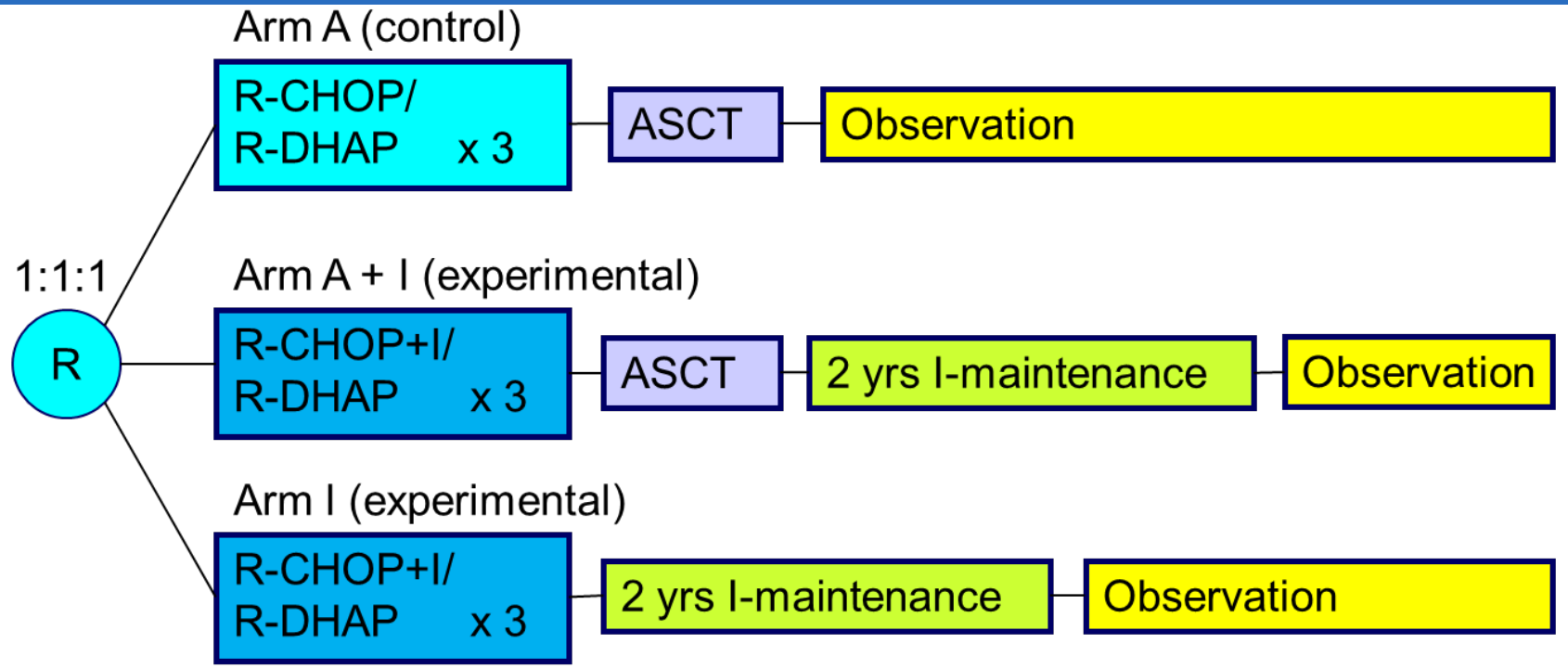
The Brick House

- Is BOVEN (combo targeted agents) the answer….
  - Treated what we believe is the worst of the worst
    - P53 mutated patients w/ marked improvement in 2-year PFS over CIT
  - Overall, well tolerated and can be given in older patients given it lacks CIT
    - BOVEN elderly patient data presented at EHA 2024
    - Currently in the NCCN guidelines for p53 mutated patients
  - We are still pending longer follow up
    - Are the responses durable
    - Fixed duration therapy so…..
      - What happens at relapse???
        - Can we retreat??

Younger Patients

TRIANGLE: Trial Design

- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2



- Primary outcome: FFS

- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety

- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

Dreyling, ASH 2022: #1

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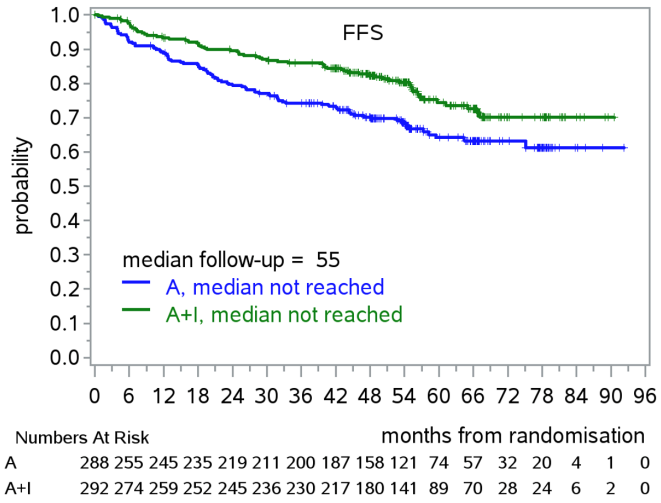
TRIANGLE: FFS Superiority of A+I vs. A

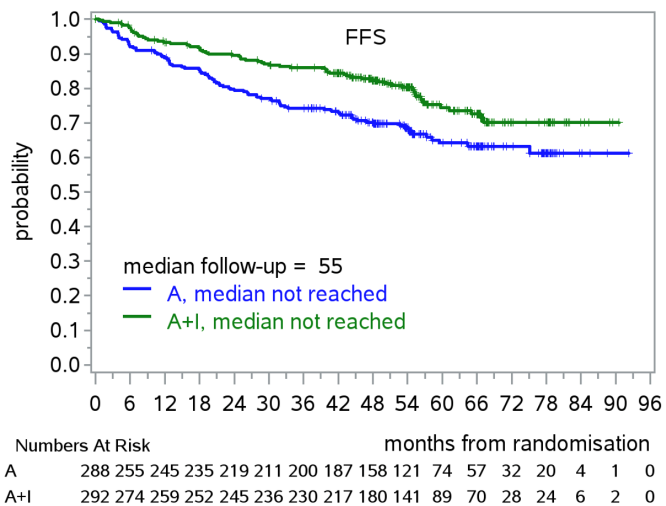


Numbers At Risk

A	288	255	245	235	219	211	200	187	158	121	74	57	32	20	4	1	0
A+I	292	274	259	252	245	236	230	217	180	141	89	70	28	24	6	2	0

- Superiority of A+I vs. A
  - 4-year FFS A+I: 82%
  - 4-year FFS A: 70%
- p-value (overrunning, one-sided): p=0.0026
- HR (A+I vs. A): HR=0.64

TRIANGLE: FFS Superiority of A+I vs. A

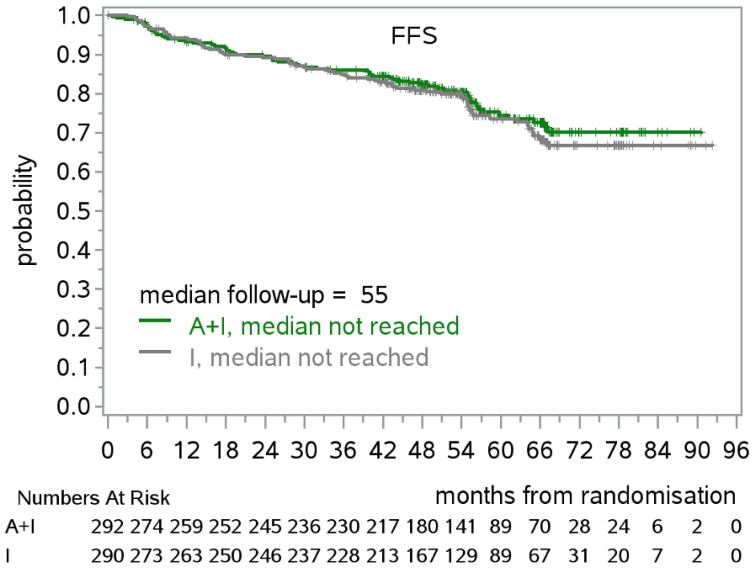


Numbers At Risk

A	288	255	245	235	219	211	200	187	158	121	74	57	32	20	4	1	0
A+I	292	274	259	252	245	236	230	217	180	141	89	70	28	24	6	2	0

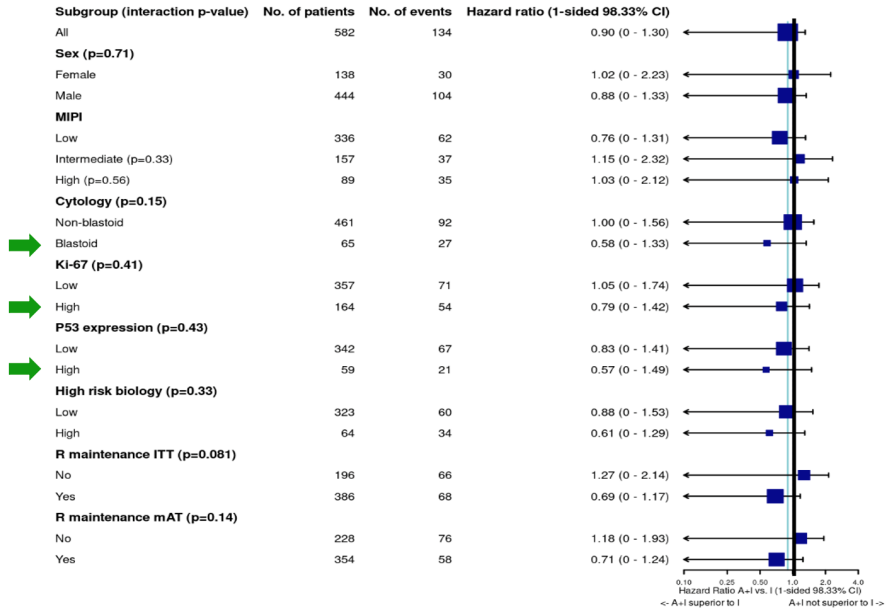
- Superiority of A+I vs. A
  - 4-year FFS A+I: 82%
  - 4-year FFS A: 70%
- p-value (overrunning, one-sided): p=0.0026
- HR (A+I vs. A): HR=0.64

TRIANGLE: FFS Superiority of A+I vs. I ?



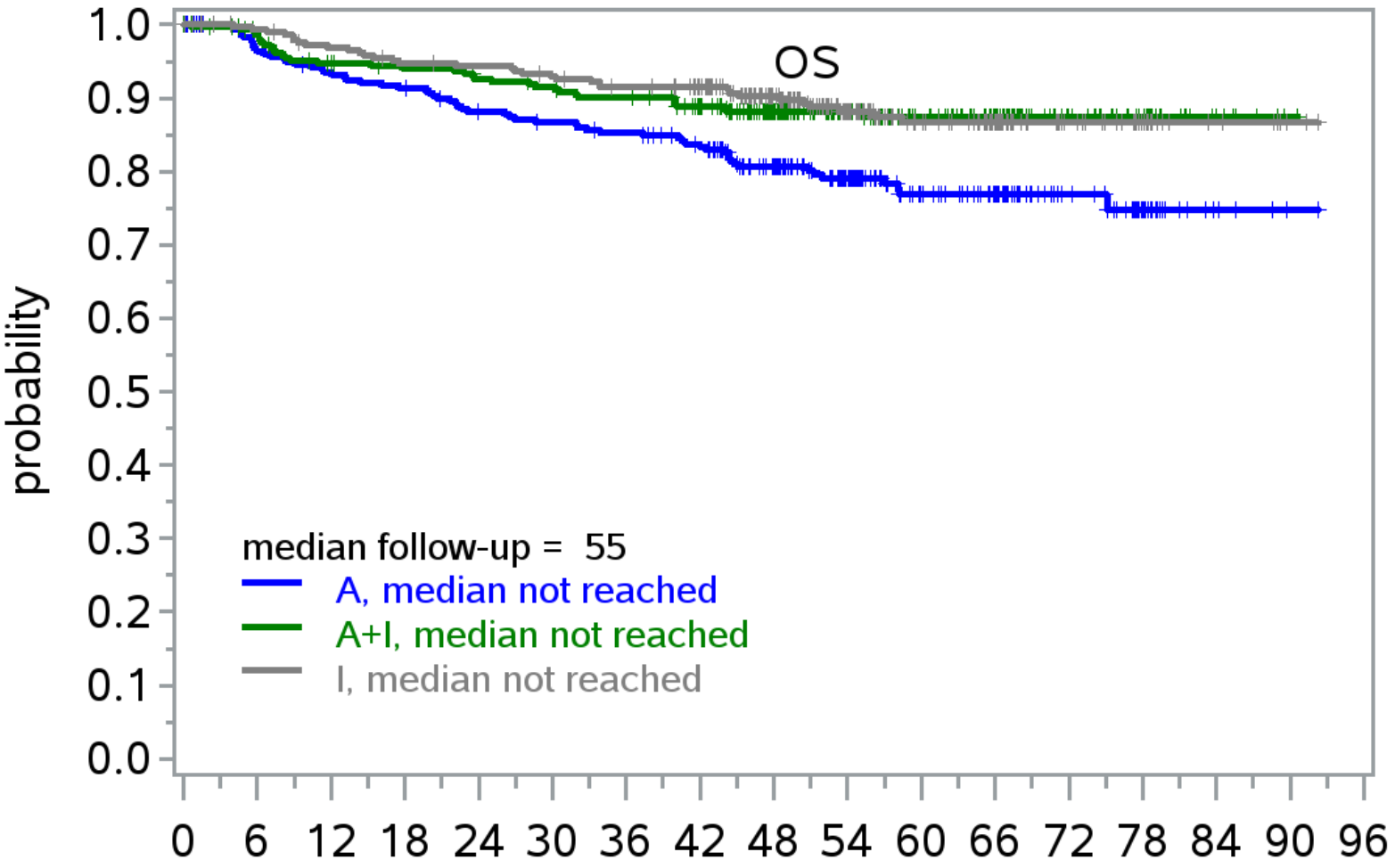
- Superiority of A+I vs. I rejected
  - 4-year FFS A+I: 82%
  - 4-year FFS I: 81%
- p-value (overrunning, one-sided): p=0.21
- HR (A+I vs. I): HR=0.83

TRIANGLE: No FFS Superiority of A+I vs. I



- trend towards superiority of A+I over I in patients in high risk patients:
  - Ki-67 >30%
  - blastoid cytology or
  - high p53 expression

TRIANGLE: Overall survival



Numbers At Risk

A	288	270	260	255	243	238	233	222	186	145	92	73	41	23	5	1
A+I	292	281	267	262	257	253	248	235	201	160	107	83	39	26	8	2
I	290	282	273	266	264	259	253	243	194	147	101	78	41	21	7	2

- 4-year OS:
  - A: 81%
    (MCL Younger exp.: 80%)
  - A+I: 88%
  - I: 90%
- two-sided test, (α = 5%):
  - A vs. I: p=0.0019, HR: 0.565
  - A vs. A+I: p=0.0036, HR I: 0.587
  - A+I vs. I: ongoing

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The Brick House

- Is BTKi in younger patients the answer….
  - TRIANGLE w/ OS benefit……
    - Does that hold if we removed patients, we wouldn't treat w/ CIT + ASCT (high-risk patients)
      - Early separation of EFS overall and wide gap in those w/ high expression of p53
      - How much do those patients influence this???
    - Still w/ same question overall.
      - What happens at relapse???
        - Can we retreat??
        - If not, is it worth it for all???

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Moving Forward

- With 2nd generation BTKi's fulfill the promise of the class
  - ECHO w/o the baggage of Shine and MDA study w/o significant toxicity
  - But still doesn't answer ? Of sequential vs. combo
- BTKi based regimens likely best for subset of high risk but is chemo needed in these cases……
  - Maybe blastoid patients.
  - What happens next?? (still the major issue)
  - Given none of the regimens discussed appear curative what happens in 2L
    - Can BTKi be given again?
      - Pirto vs. CAR-T
        - If CAR-t… can we live w/ brexu-cel

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Thank you

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