Lymphoma Review: ASH 2024

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Disclosures

- Consultancy: AbbVie, ADC Therapeutics, Merck, Roche-Genentech, AstraZeneca, GenMab

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Outline

- Follicular lymphoma
  - inMIND trial: Tafa + R2 in R/R FL

- Mantle cell lymphoma frontline treatment
  - TRIANGLE overall survival update, data for rituximab maintenance
  - EA4151 use of MRD to guide autoSCT
  - ENRICH in transplant ineligible patients

Follicular Lymphoma

inMIND trial for treatment of R/R FL

Landscape of treatment in RR FL

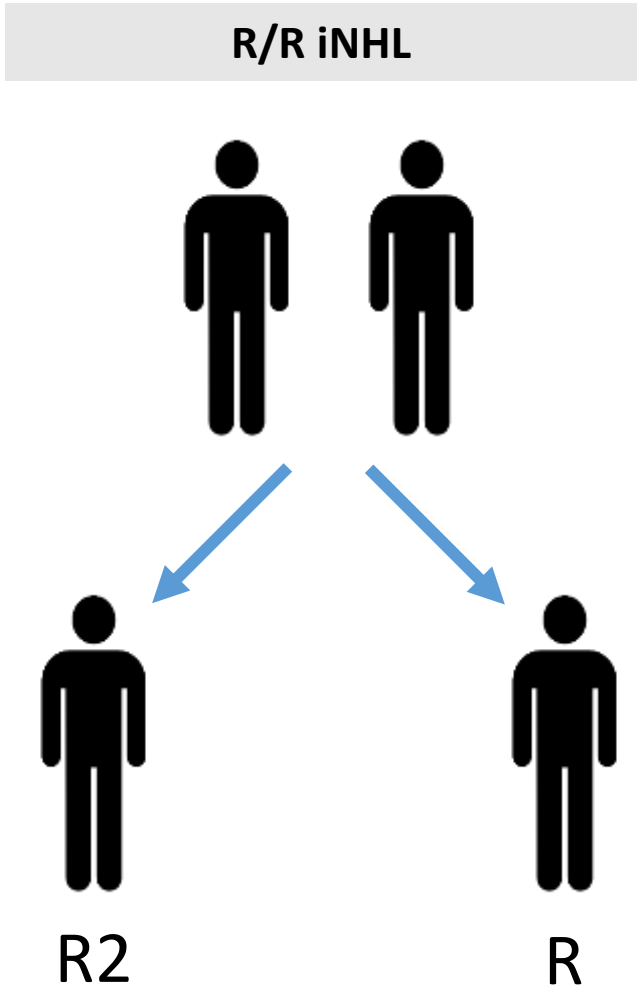
- Most common indolent non-Hodgkin B cell lymphoma (22% of adult NHL)
  - Generally incurable, with most patients experiencing multiple relapses

- 2nd line treatment:
  - Lenalidomide + rituximab (R2)
  - Chemo immunotherapy

- 3rd line treatment:
  - Tazemetostat
  - Zanubrutinib + obinutuzamab
  - Mosunetuzumab
  - Epcoritamab
  - CD19 CART (Axi-cel, Tisa-cel, Liso-cel)

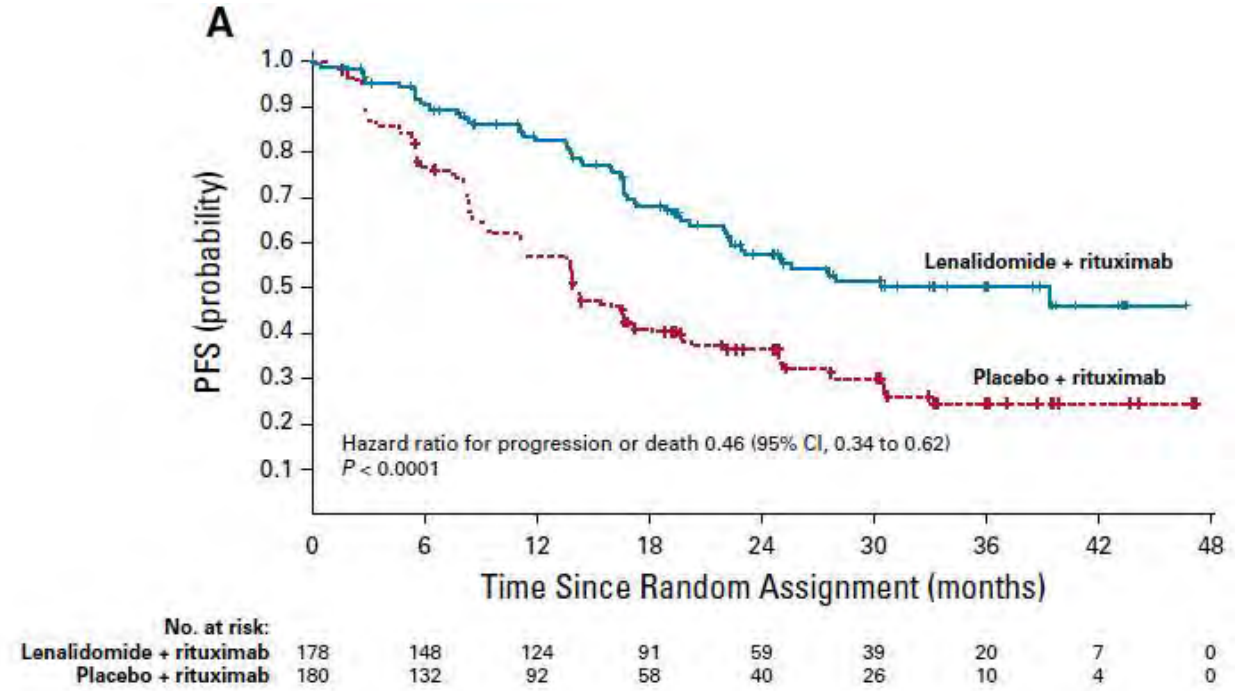
AUGMENT trial in RR FL

- ≥ 1 prior line of treatment
  - Required treatment per investigator
- NOT rituximab refractory
  - 84% received prior rituximab
- Lenalidomide 20 mg daily D1-21 q28 days + Rituximab C1-6



Improved ORR, CR and PFS with R2

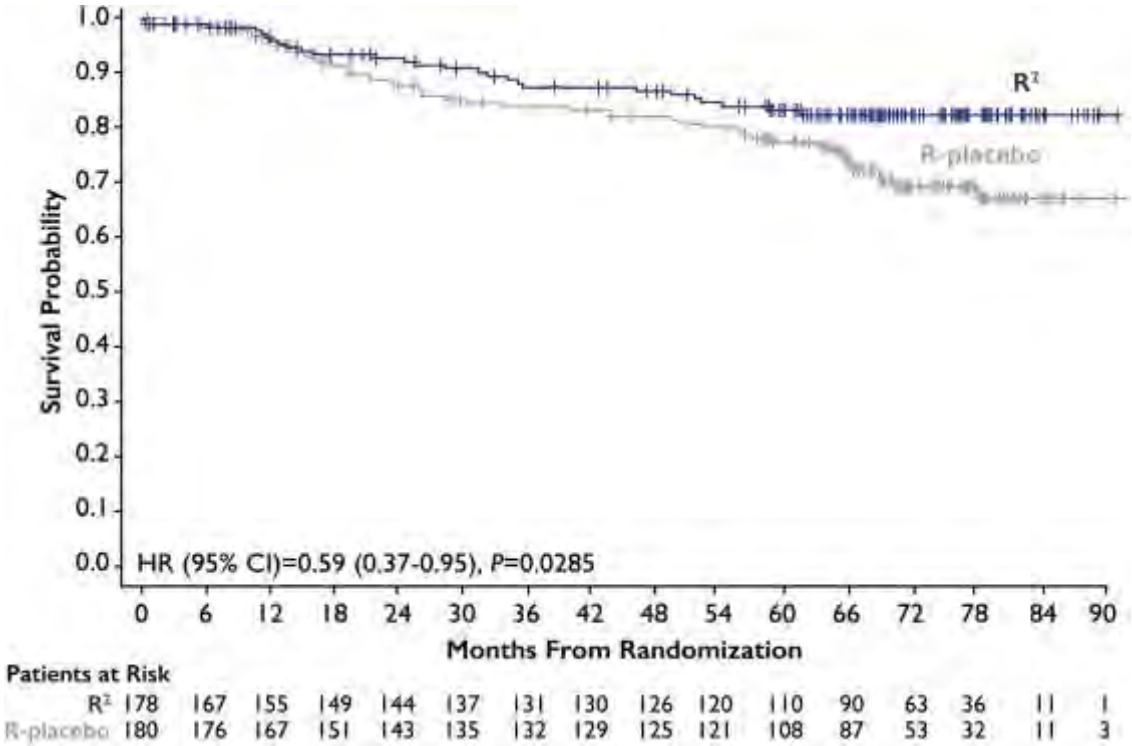
- ORR 78% (34%) vs. 53% (18%)
- PFS significantly improved for R2: HR 0.46 (0.34 – 0.62)
  - Median PFS 39.4 vs 14.1 mo
- Median duration of response: 39.4 mo vs. 14.1 mo



Leonard et al. JCO 2019

OS survival benefit with R2

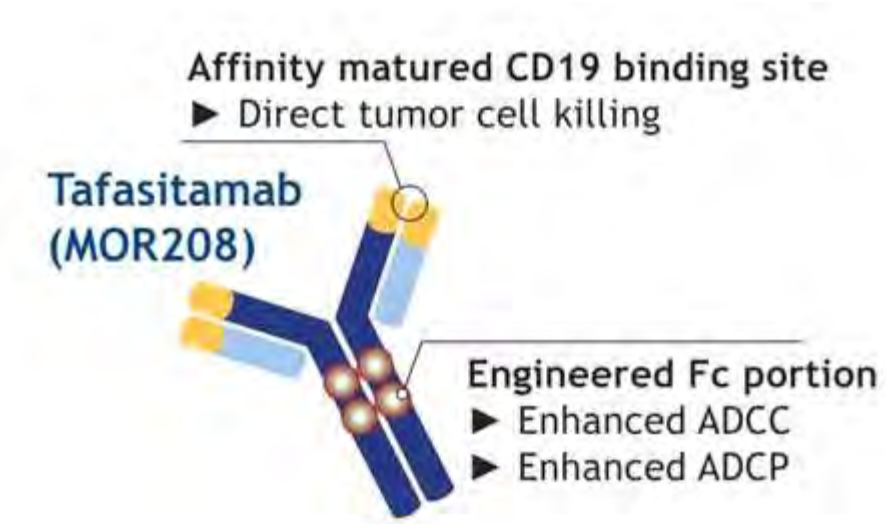
- Median follow up 65.9 months
- Improvement in median OS with R2 (HR 0.59, 95% CI 0.37 – 0.95, p = 0.0285)
- 5 year OS with R2 83.2% vs. 77.3% for rituximab alone
- Median TTNT 73.1 mo vs. 31.8 mo for R2 vs. rituximab alone



Leonard et al. ASH 2022 Oral Presentation

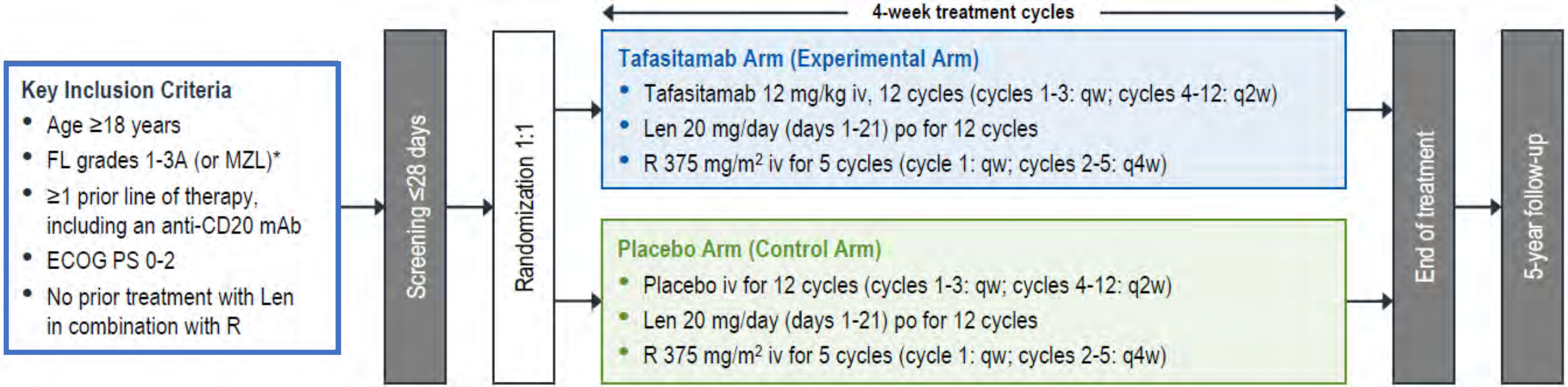
Tafasitamab: CD19 monoclonal Ab

- Mechanism of action: induces direct cytotoxicity and enhances NK cell and macrophage immune-mediated mechanisms
- Single agent: ORR 29% in FL
- FDA approved in combination with lenalidomide for 2nd line + R/R DLBCL



Jurczak et al Ann Onc 2018; Sehn et al ASH 2022

inMIND trial: Phase III RCT in RR FL



Stratification Factors (Patients With FL)

- POD24
- Refractoriness to prior anti-CD20 mAb therapy
- Number of prior lines of therapy (1 or ≥2)

Study Endpoints in FL Population (Investigator Assessed Unless Specified)

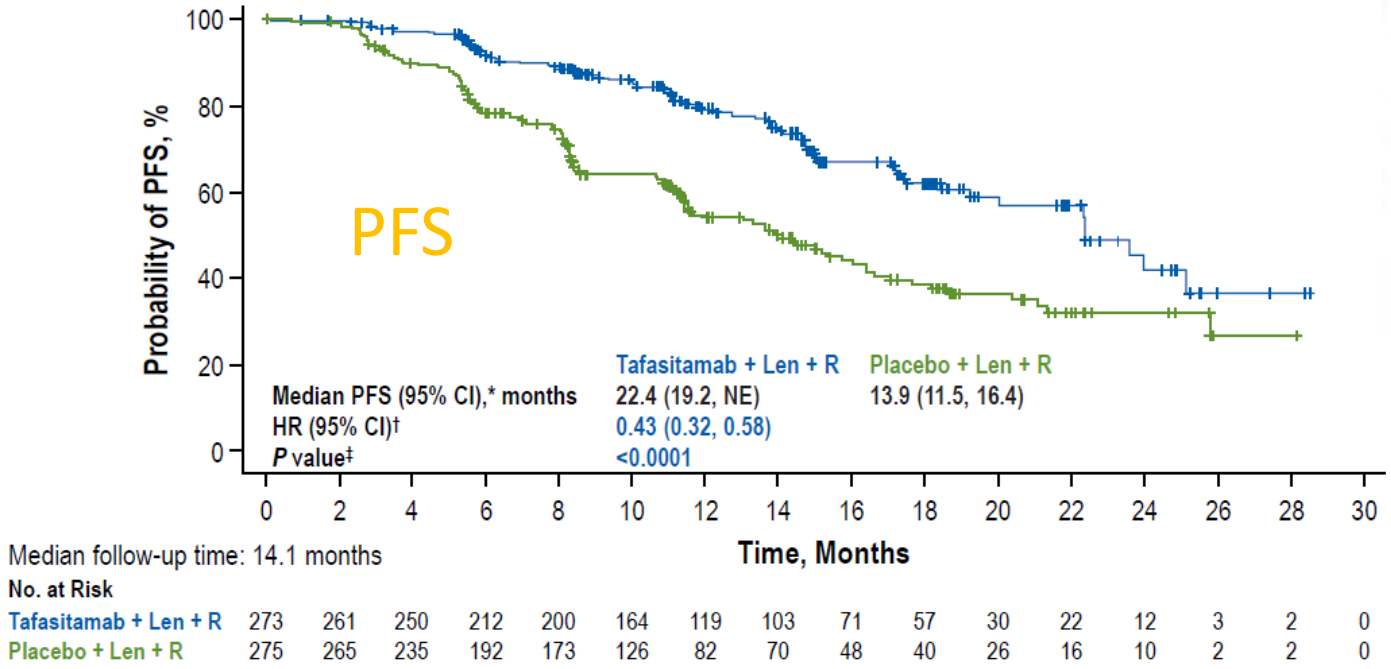
- Primary study endpoint: PFS
- **Key secondary:** PET-CR rate in the FDG-avid population, OS
- **Select other secondary:** PFS by IRC, ORR, DOR, safety, QoL, MRD
- **Exploratory:** TTNT, B-cell recovery, Ig levels, CD19 expression

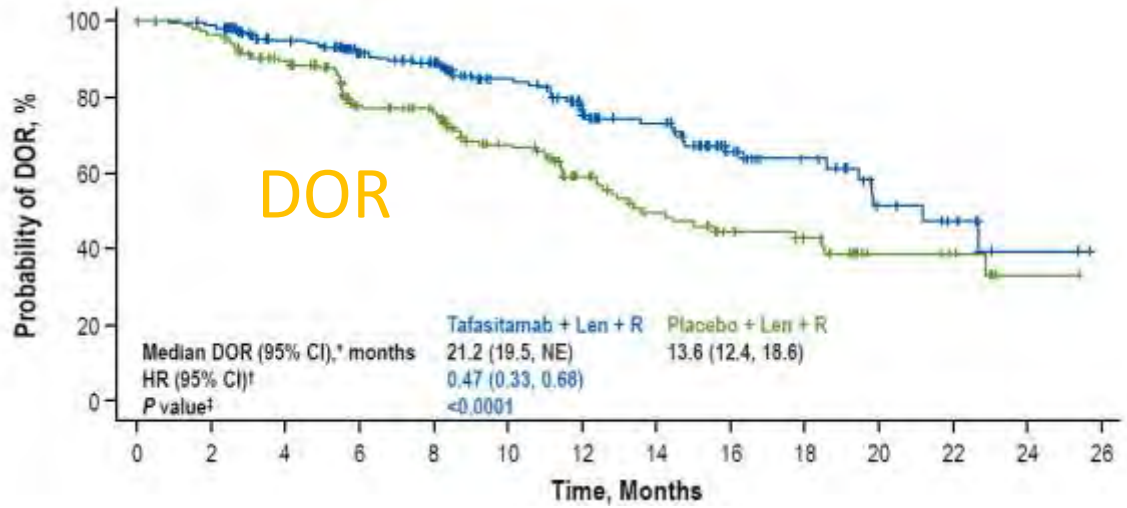
Improved ORR & CR rates with TafaR2

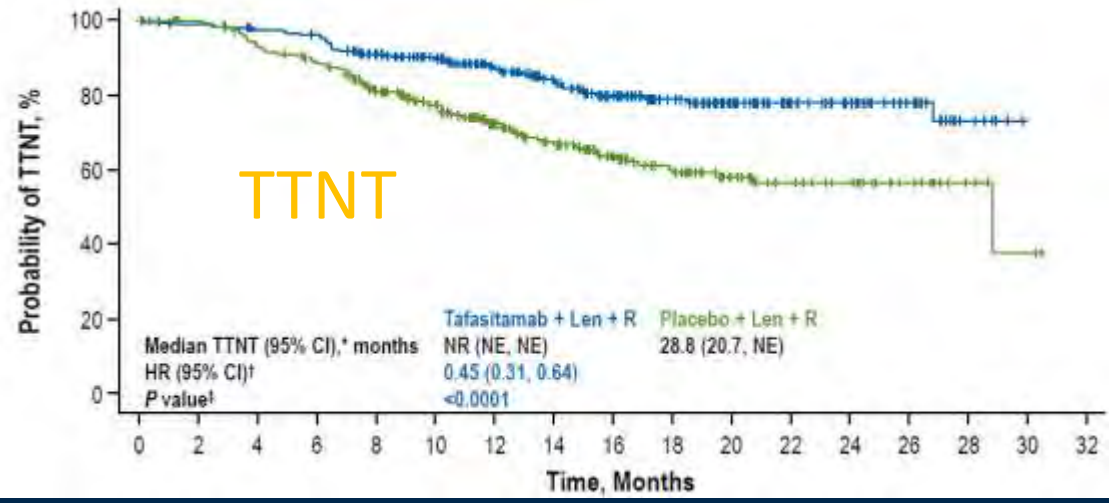
- N = 548
  - Groups well balanced for age, sex, FL G1-2 vs. G3A, B symptoms, FLIPI score, meeting GELF criteria, number of PLOT, refractory to prior anti CD20 therapy

- ORR 83.5% (CR 52%) for TafaR2
  - vs. ORR 72.4% (CR 40.7%) for R2
  - Statistically significant

Improved PFS, DOR, TTNT with TafaR2

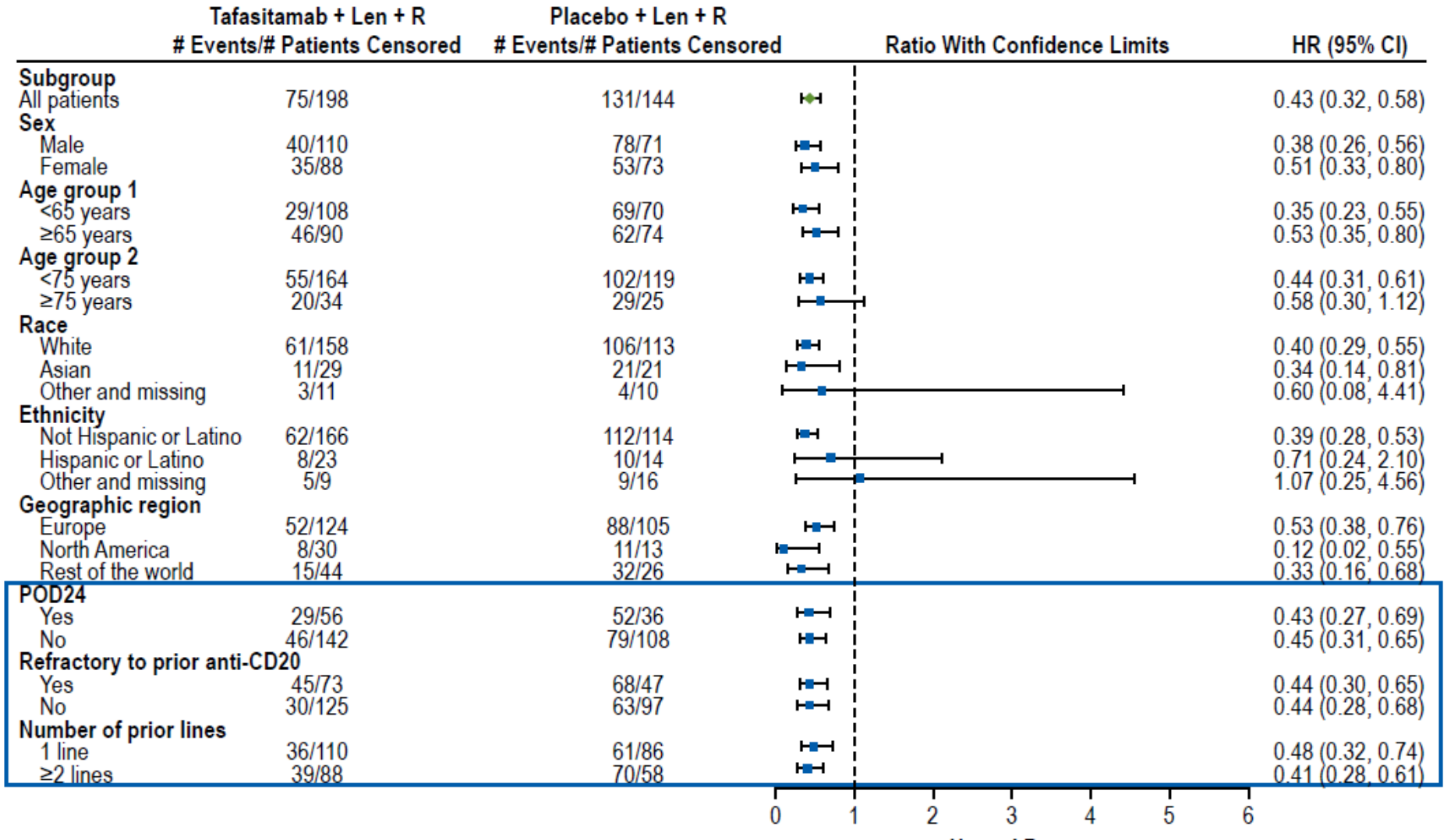






Median FU 14. 1 mo

Consistent PFS benefit across all high risk subgroups



Mild increased toxicity with TafaR2

Preferred Term, n (%)	Tafasitamab + Len + R (n=274)*	Placebo + Len + R (n=272)†
Any adverse event	272 (99.3)	270 (99.3)
Neutropenia	133 (48.5)	123 (45.2)
Diarrhea	103 (37.6)	77 (28.3)
COVID-19	86 (31.4)	64 (23.5)
Constipation	80 (29.2)	67 (24.6)
Rash	60 (21.9)	58 (21.3)
Fatigue	58 (21.2)	43 (15.8)
Cough	52 (19.0)	47 (17.3)
Pyrexia	52 (19.0)	44 (16.2)
Muscle spasms	49 (17.9)	49 (18.0)
Nausea	49 (17.9)	38 (14.0)
Infusion-related reaction	43 (15.7)	41 (15.1)
Thrombocytopenia	37 (13.5)	42 (15.4)
Pruritus	44 (16.1)	28 (10.3)

- No significant increase in G3/4 cytopenias
- Similar dose interruptions/discontinuations due to toxicity
- Similar len discontinuations and dose reductions
- Median len dose intensity 86 vs. 87%

InMIND vs. AUGMENT

Variable	inMIND Tafasitamab + Len + R (n=273)	inMIND Placebo + Len + R (n=275)	AUGMENT[1] R + Len (n=147)
Median age, years	64	64	62
Male, %	55	54	42
Ann Arbor stage IV at enrollment, %	55	59	30
FL grade 3A, %	25	26	12
FLIPI high risk (score 3-5) , %	50	55	37
ECOG PS 0, %	66	70	67
ECOG PS 1-2, %	34	30	33
B symptoms present, %	23	24	8
High tumor burden per GELF (yes), %	81	84	52
Refractory to last prior regimen, %	41	35	18
Refractory to anti-CD20, %	43	42	–

Management of RR FL

- Summary of inMIND trial:
  - Tafa + R2 improved ORR, CR, PFS, DOR, TTNT. No difference in overall survival.
  - Minimal increase in toxicity without affecting lenalidomide dose intensity
  - Cumbersome infusion schedule of Tafa: weekly C1-3, q2w C4-12

- My approach: Consider addition of Tafa to R2 in 2nd line + setting in patients who are able to manage the travel/frequency of infusion schedule

- Eagerly await results of CD20/CD3 bispecific antibodies + lenalidomide:
  - CELESTIMO: Mosun + len
  - EPCORE FL-1: Epco + R2

Mantle cell lymphoma

Rapidly evolving frontline treatment landscape

MCL: remains incurable but outcomes improved with Tx advances

- Represents 5-7% of all lymphomas
- Median PFS/OS varies based on MIPI score
- Predictors of worse outcomes:
  - Blastoid/pleomorphic variants
  - Ki67 >30%
  - TP53 mutations/deletions

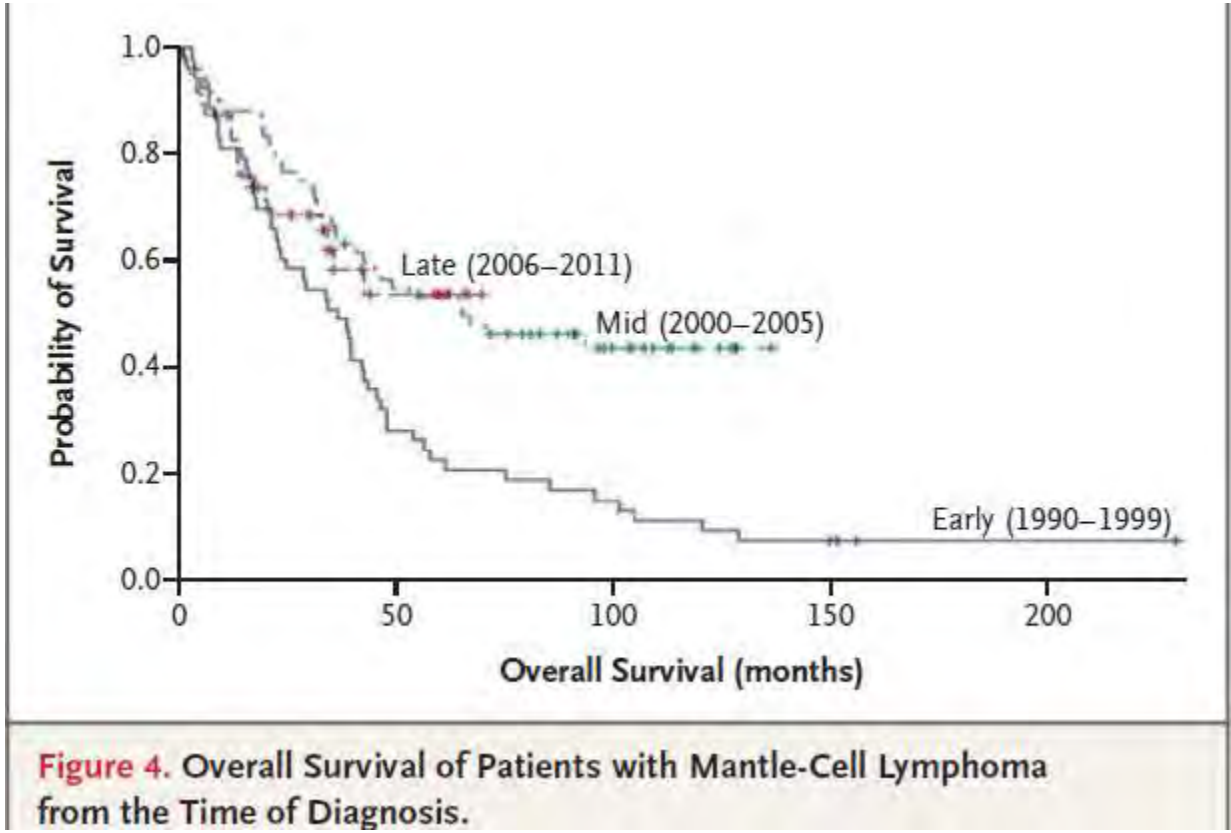
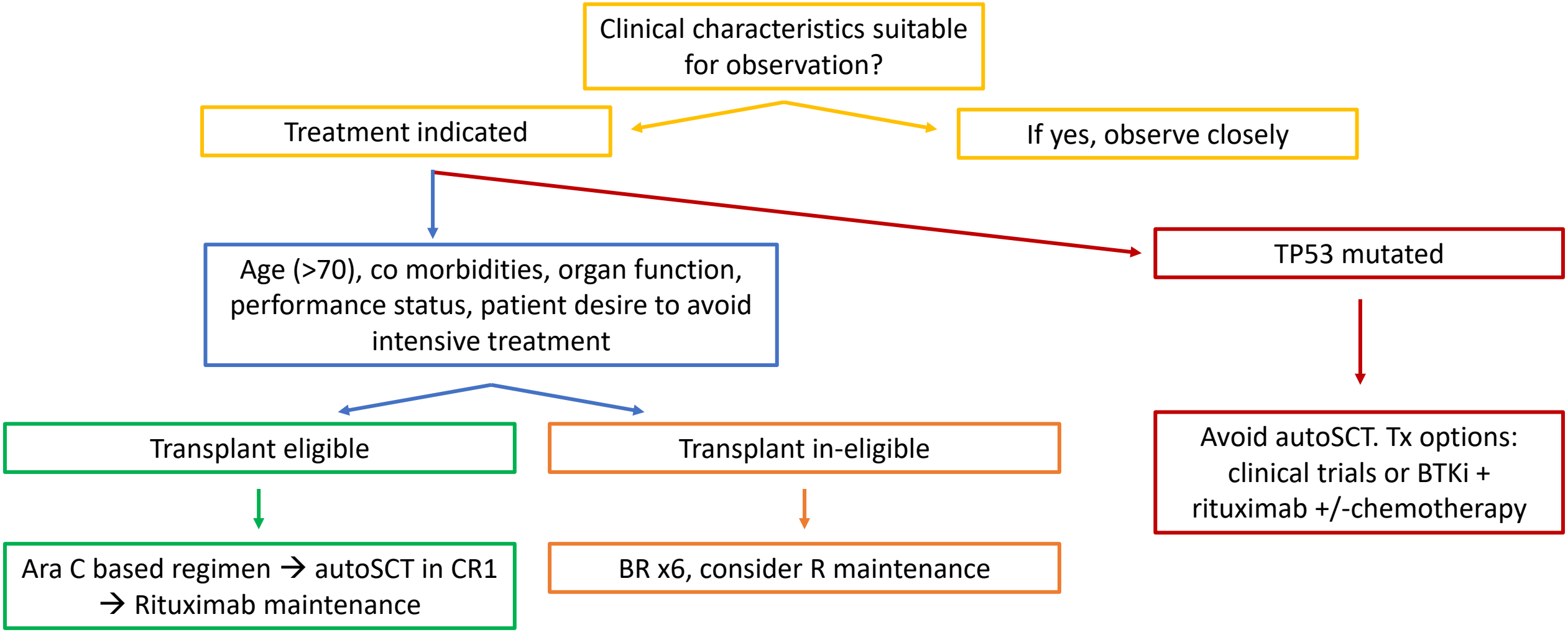


Figure 4. Overall Survival of Patients with Mantle-Cell Lymphoma from the Time of Diagnosis.

Hoster et al Blood 2008 ; Dreyling et al NEJM 2022

Frontline MCL Treatment pre 12/2023



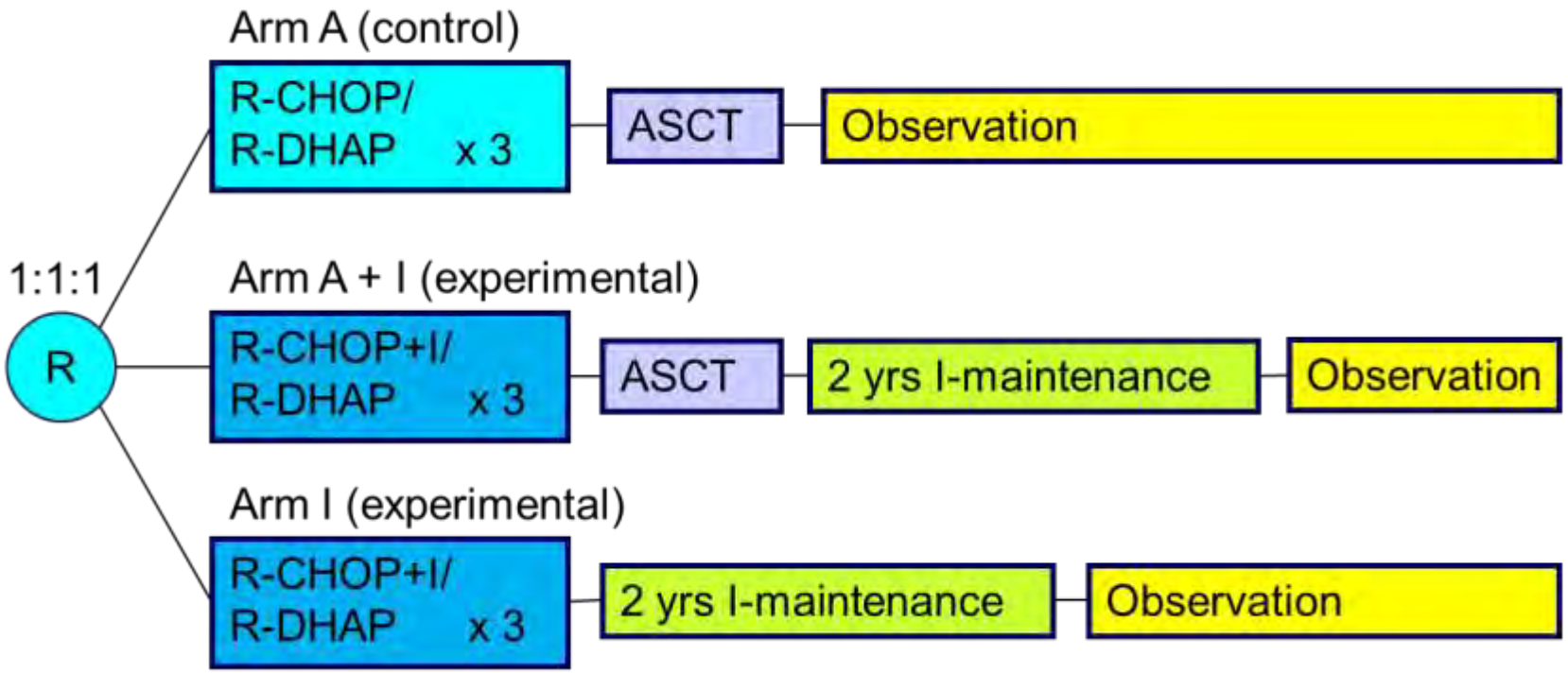
Frontline MCL data

- Transplant eligible: questioning the role of autoSCT
  - TRIANGLE updated data
    - Role for rituximab maintenance with or without BTKi
  - EA4151 MRD guided autoSCT

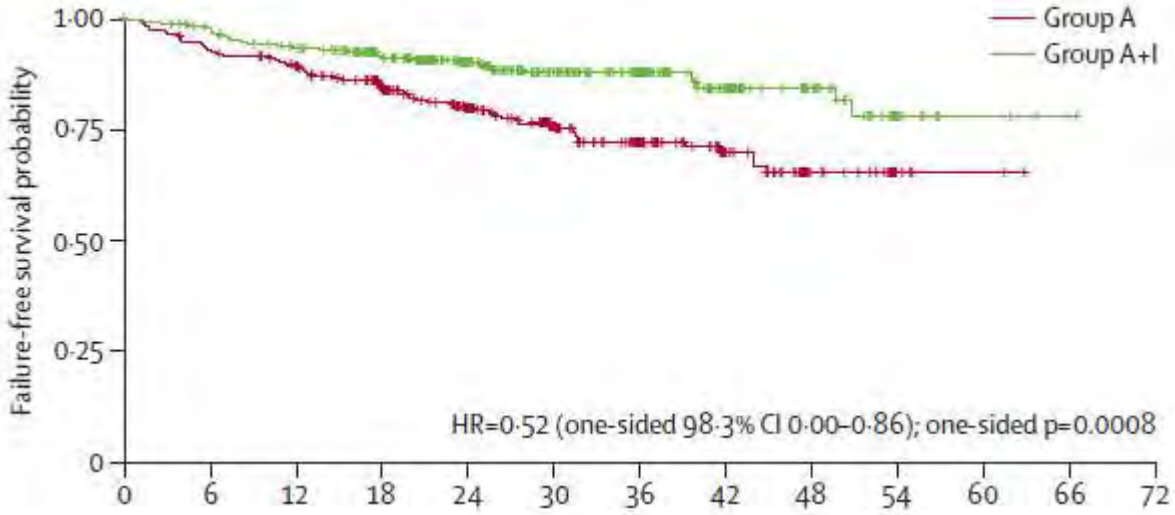
- Transplant ineligible: questioning the role for chemoimmunotherapy
  - ENRICH: Ibrutinib + Rituximab (IR) vs. chemoimmunotherapy

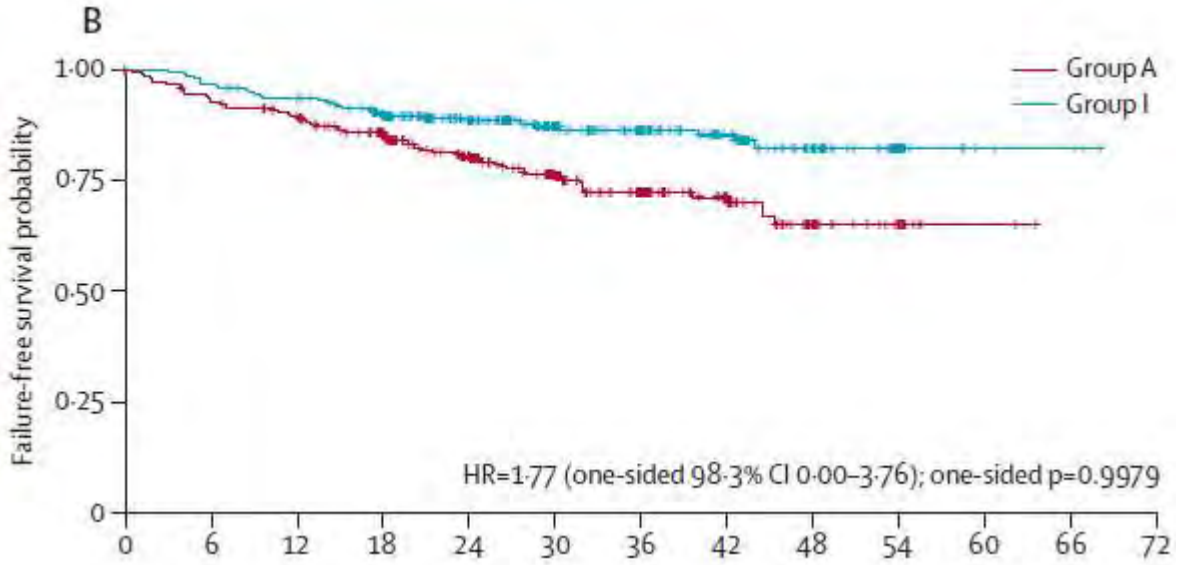
Transplant Eligible MCL

TRIANGLE: role of ASCT and BTKi in frontline MCL treatment



Improved FFS with BTKi maintenance

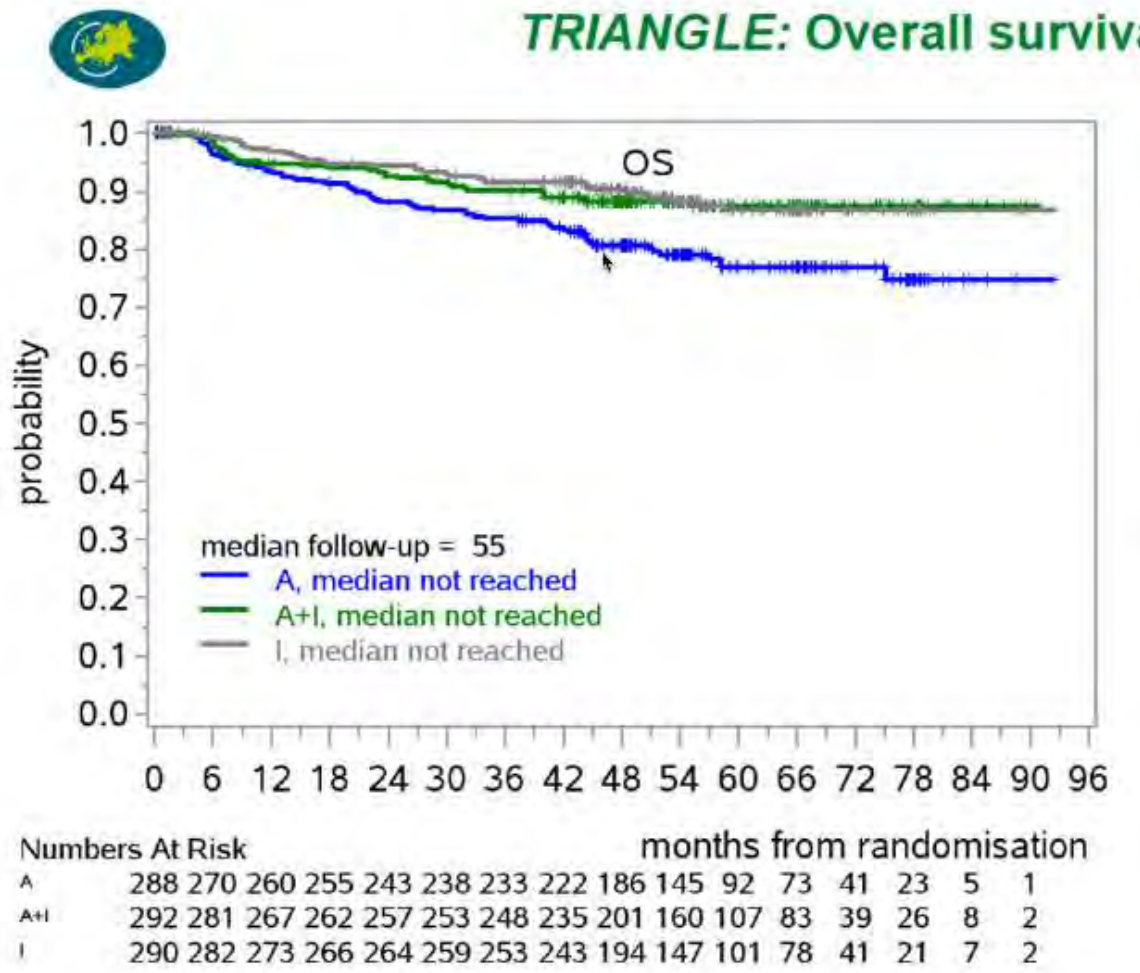




- Improve FFS in Groups A+ I and I
- No difference in OS at last publication

Dreyling et al. Lancet 2024

OS Benefit to BTKi maintenance



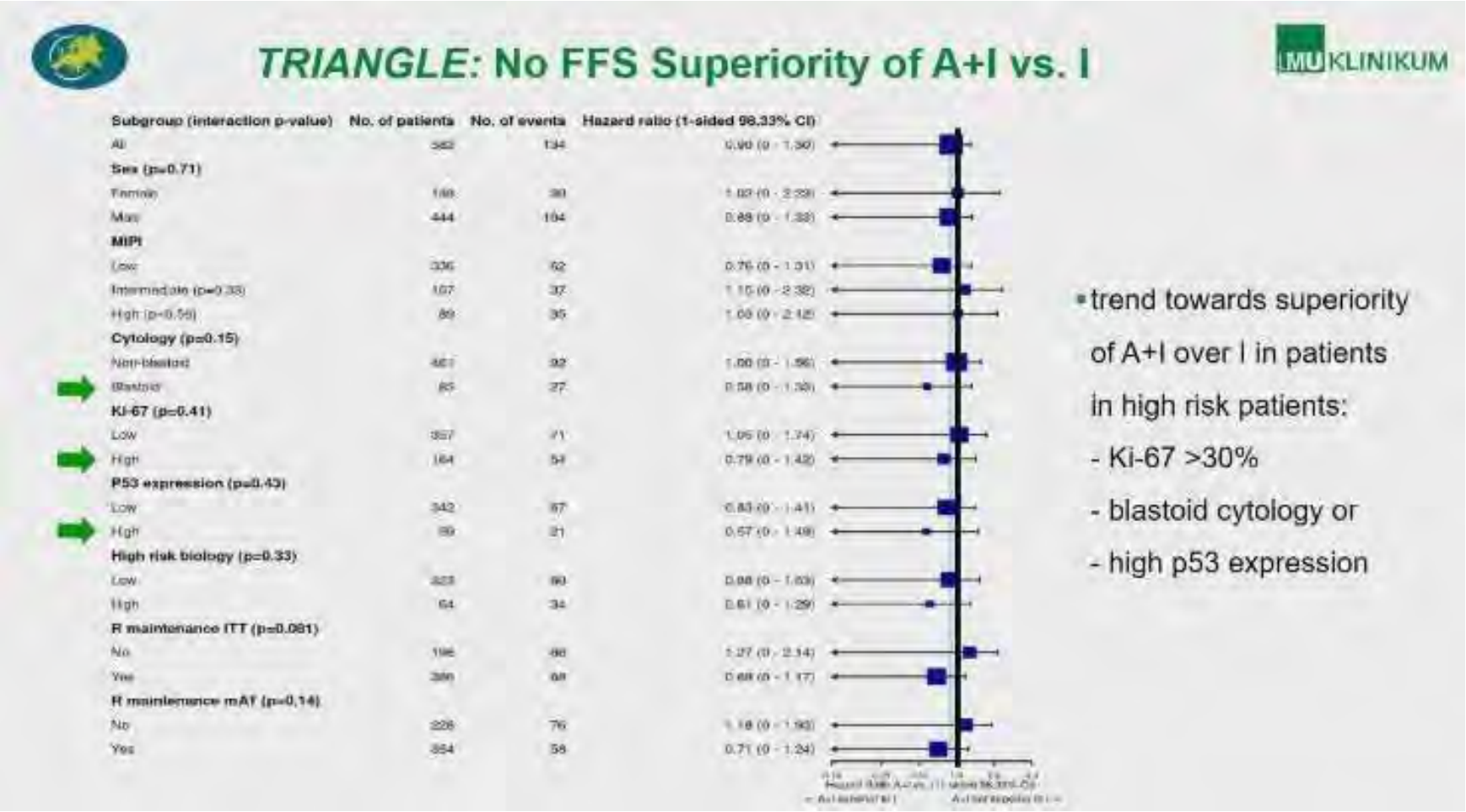
- 4-year OS:
  - A: 81%
    (MCL Younger exp.: 80%)
  - A+I: 88%
  - I: 90%
- two-sided test, (α = 5%):
  - A vs. I: p=0.0019, HR: 0.565
  - A vs. A+I: p=0.0036, HR I: 0.587
  - A+I vs. I: ongoing

Medan follow up 55 months

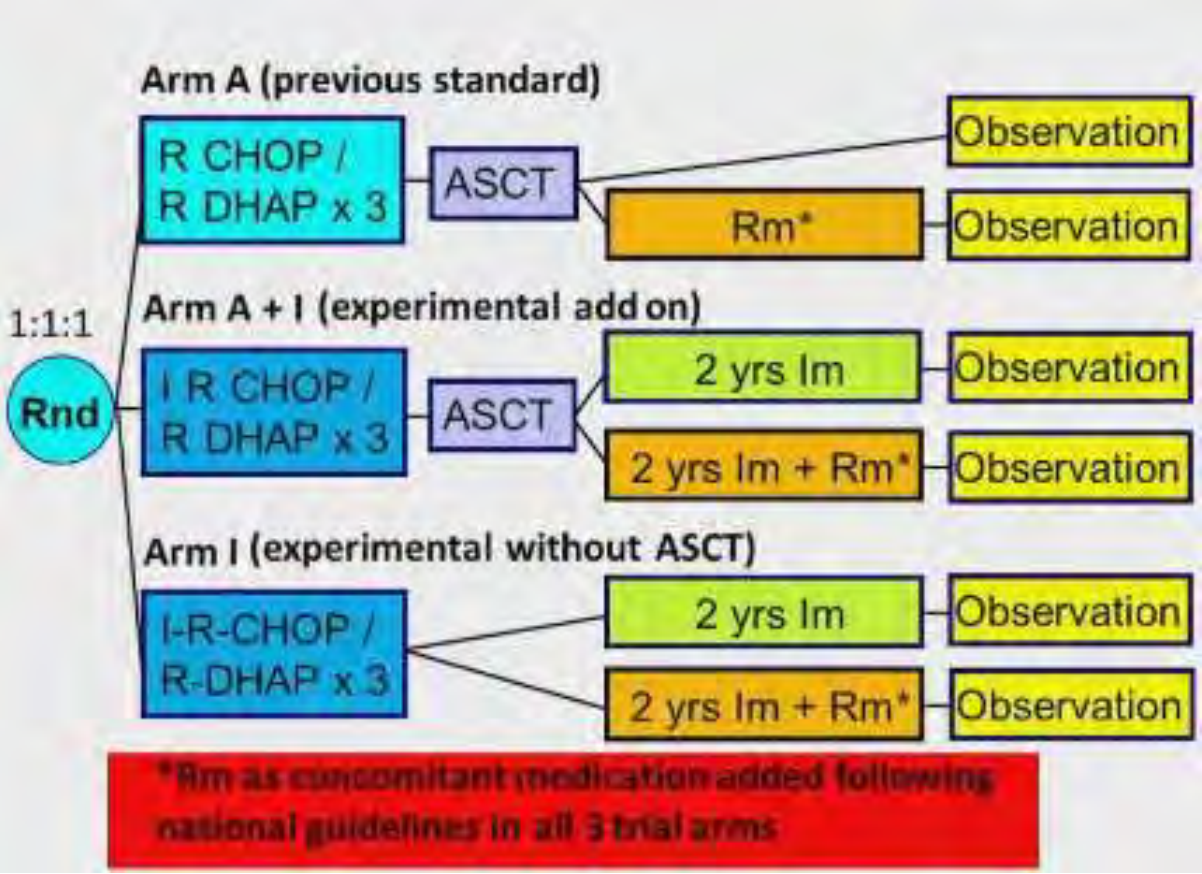
- 30% received BTKi on relapse

Dreyling et al. ASH 2024 oral presentation: Abstract 0240

No specific population that benefited from Auto + I



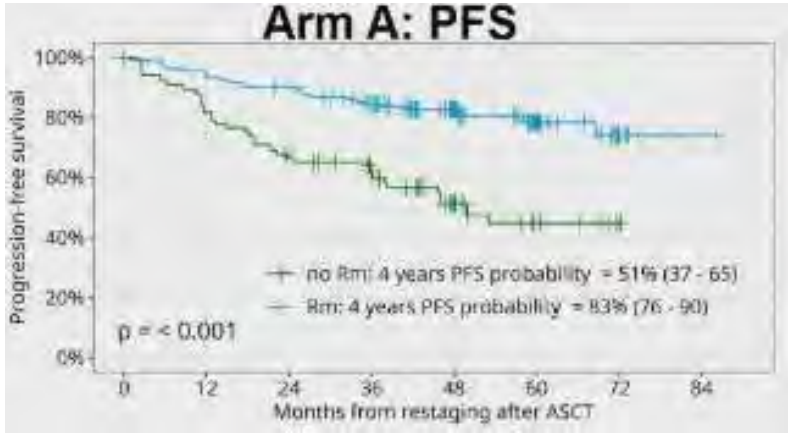
Maintenance BTKi +/- rituximab

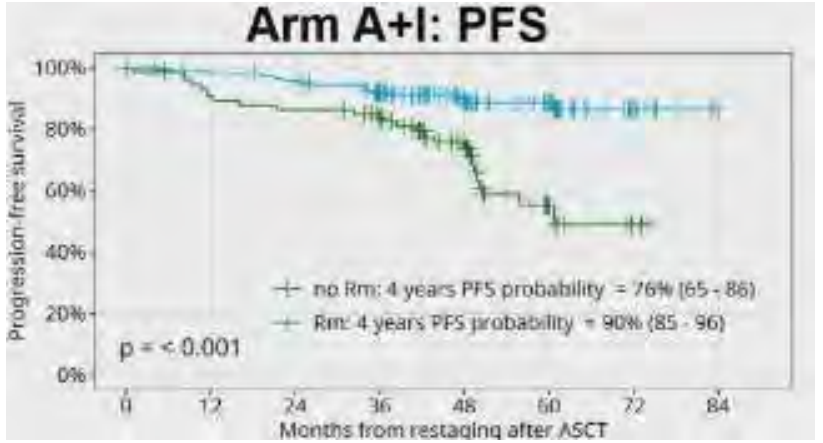


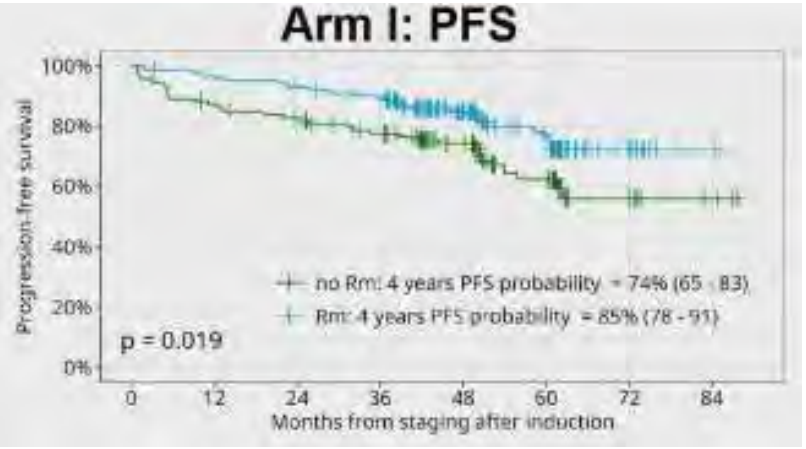
- Retrospective analysis of RM outcomes in TRIANGLE study
  - Non randomized use of rituximab on study
  - No significant diff in baseline characteristics between groups

- Use of RM:
  - A: 68%
  - A+I: 64%
  - I: 61%

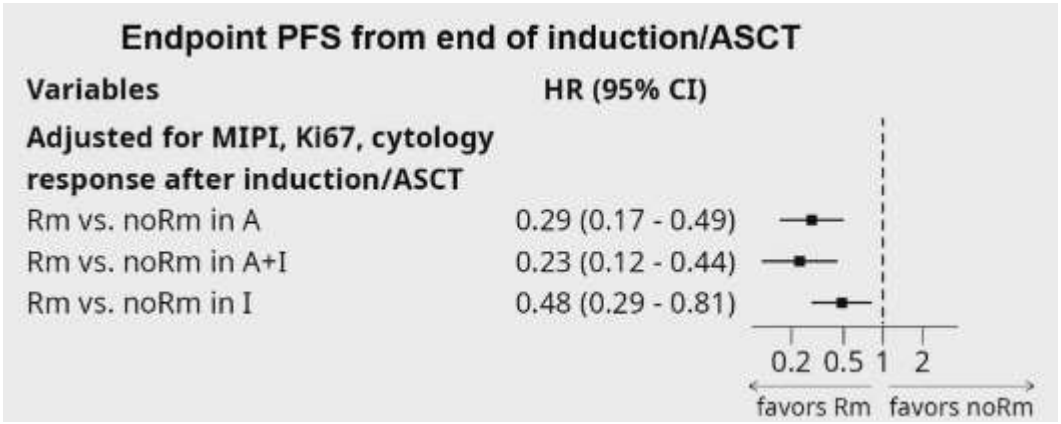
PFS benefit to RM in all arms







- Improvement in 4 years PFS with use of RM in all arms
  - Slightly greater benefit in ASCT containing arms (A and A+I)

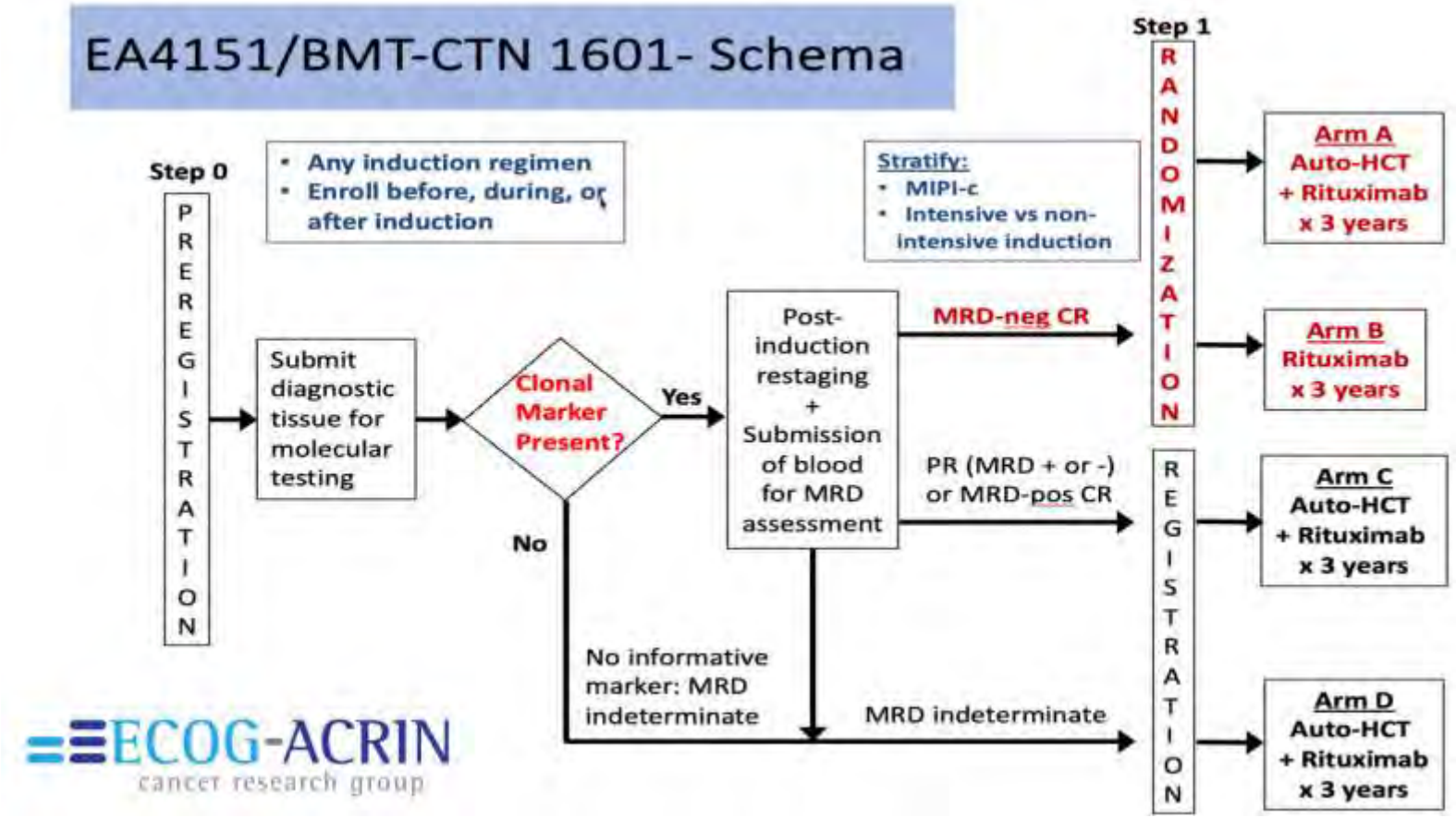


Cost of RM: increased toxicity

- Higher rate of G3-5 AE
  - Infections
  - Increased neutropenia only in ASCT arm
- No diff in death due to toxicity
- No diff in OS with RM in all groups

EA4151: role for autoSCT in MRD- CR1

- Transplant eligible
  - Age 18 - 70
- ClonoSeq 1x10 -6
- N = 650
  - 257/259 randomized
  - Arm C, N = 49
  - Arm D, N = 85

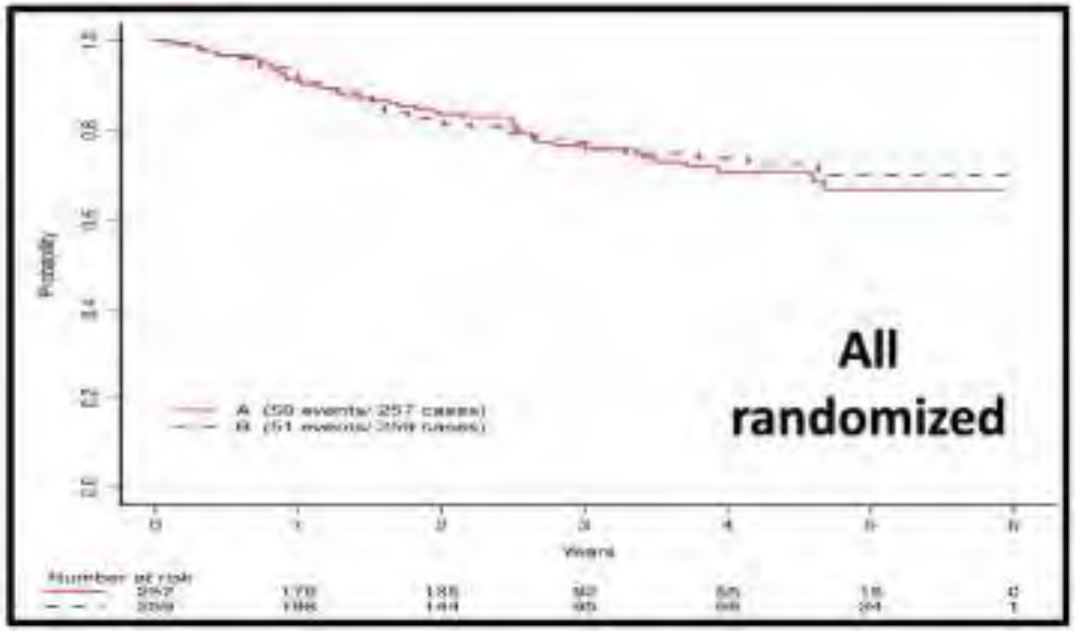


Fenske et al. ASH 2024 oral LBA-6

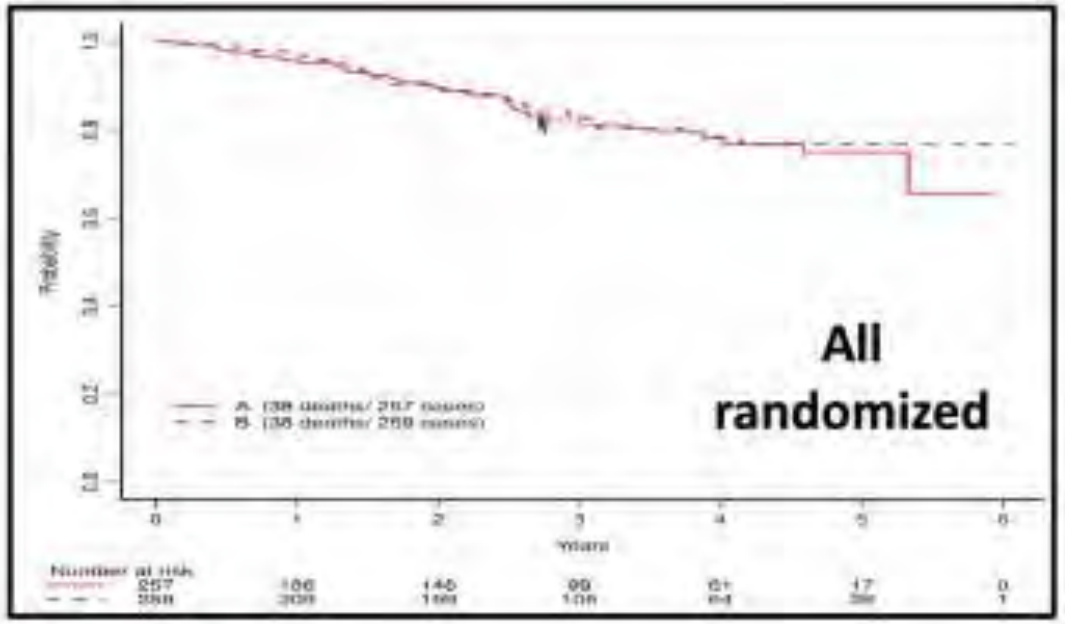
No diff in PFS and OS for arms A and B

MRD negative: with (A) or without (B) autoSCT

- 3 year PFS
  - 76.6% vs. 77.4%

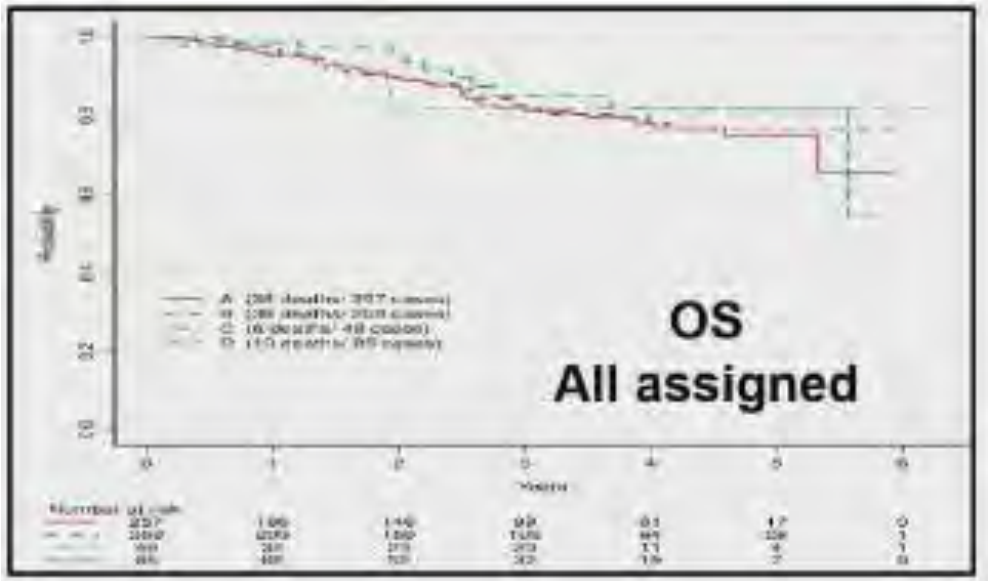


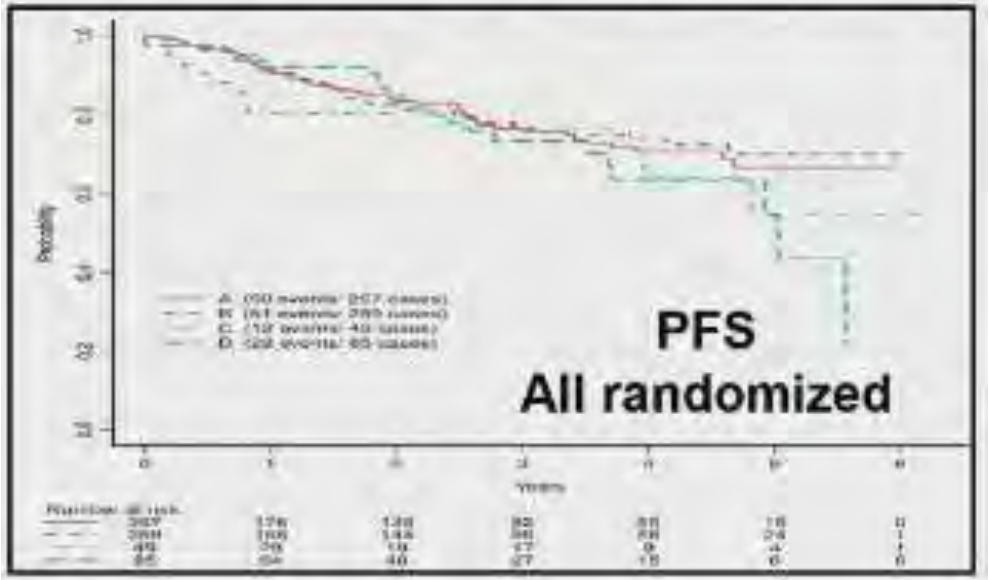
- 3 year OS:
  - 82.1% vs. 82.7%



Outcomes in Arms C & D

- Arm C: PR or MRD +
  - 3 year PFS: 76.9%
  - 3 year OS: 81.9%
- Arm C: MRD indeterminate
  - 3 year PFS: 73.4%
  - 3 year OS: 85.1%
- Outcomes of C/D appear similar to A/B!

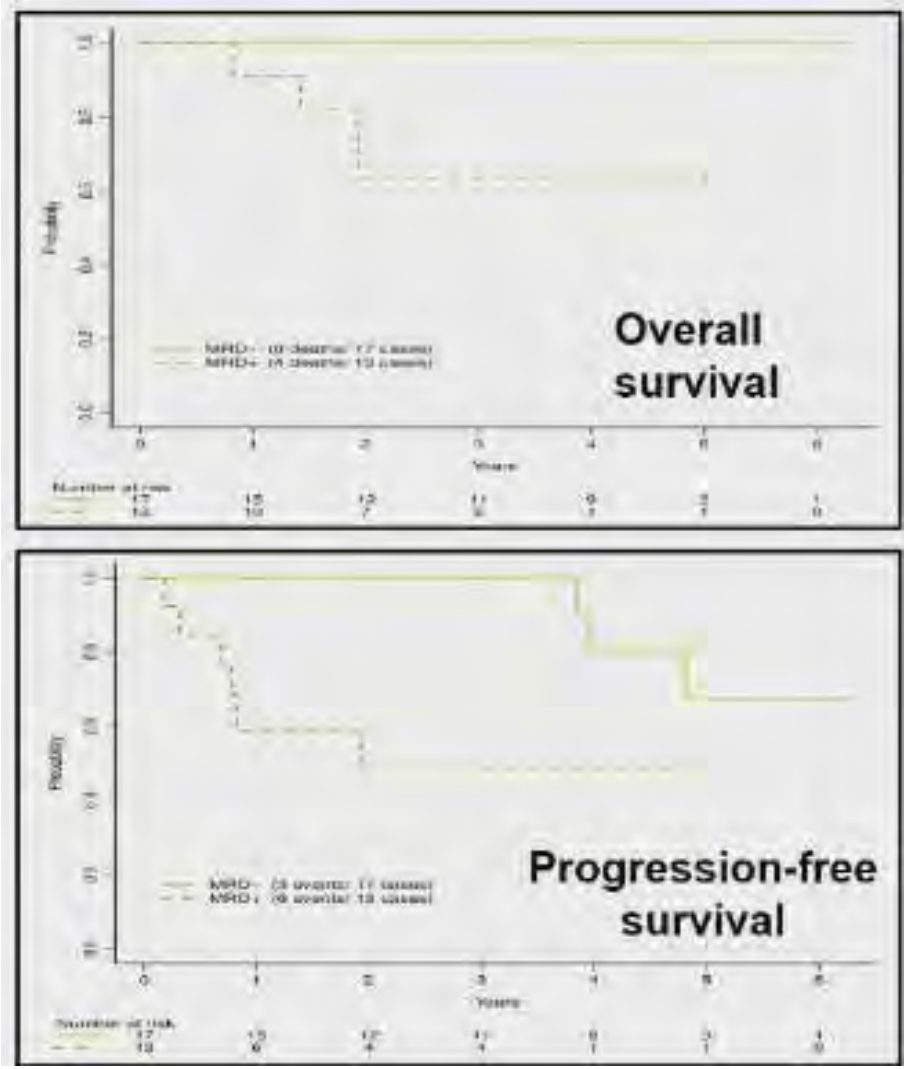




Arm C: Outcomes by MRD status post transplant

- If converted to MRD negative post auto, improved 3 year PFS and OS:
  - PFS: 100% vs. 48.8% in MRD+ vs. MRD- patients
  - OS: 63.6% vs. 100% in MRD+ vs MRD – patients

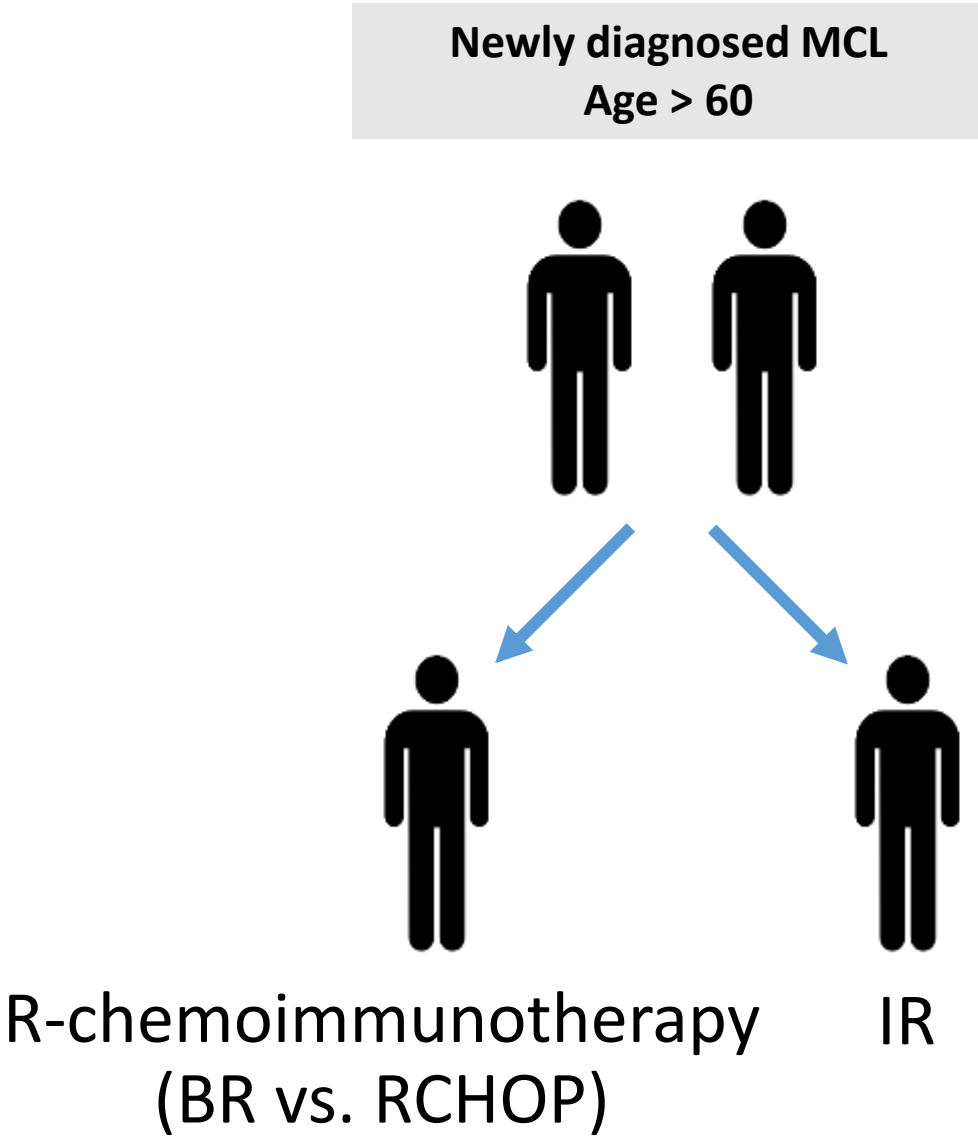
- Only 2 patients on the whole trial received BTKi maintenance
  - How much of this can negative impact of MRD + disease can be overcome by BTKi maintenance vs. autoSCT?



Transplant Ineligible MCL

ENRICH trial

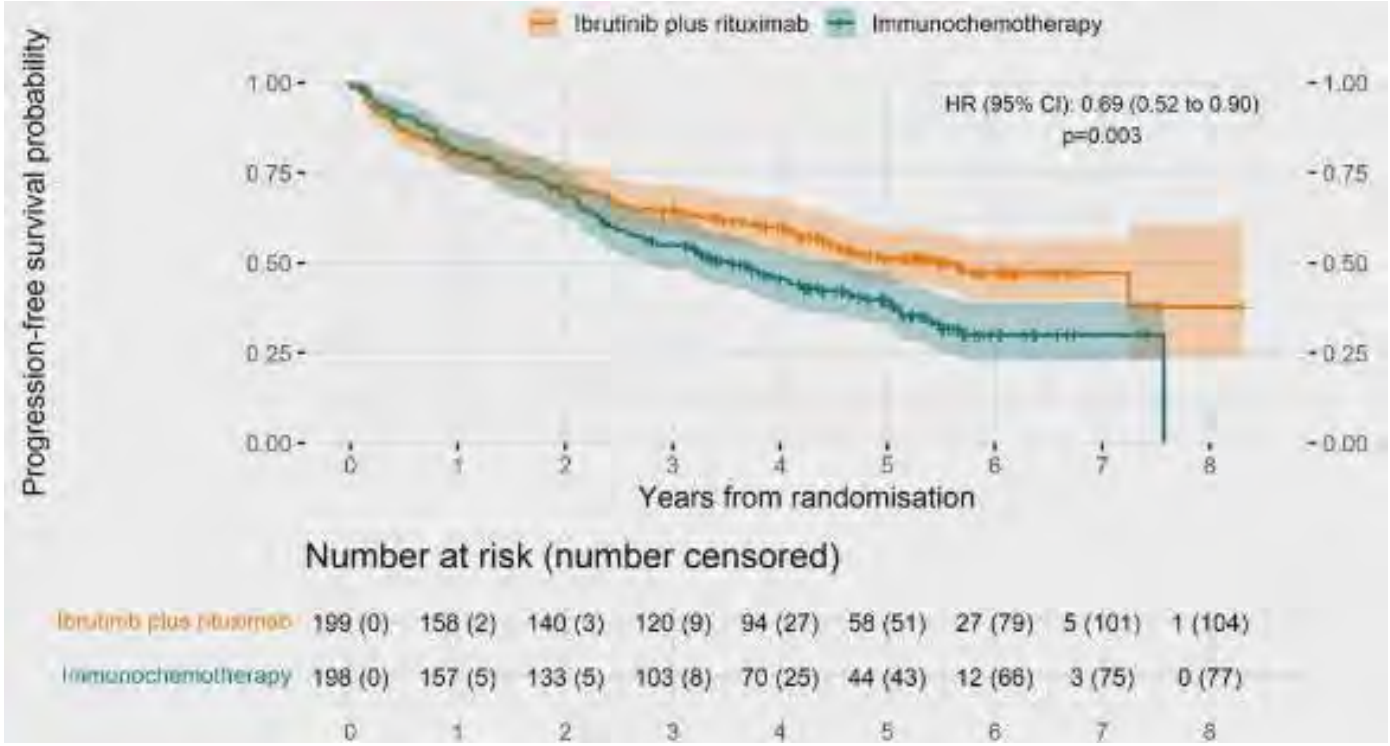
- Randomized Phase II/III trial
  - N = 397
- Stage II- IV MCL, in need of treatment
- Maintenance:
  - R-chemo: Rituximab q2 mo x 2 years
  - IR: Ibrutinib + rituximab q2 mo x2 years
  - Ibrutinib 560 mg daily until progression



PFS benefit with IR or R-chemo

- Median follow up 47.9 mo
- Median PFS 63.3 vs 42.4 mo

  Favoring IR

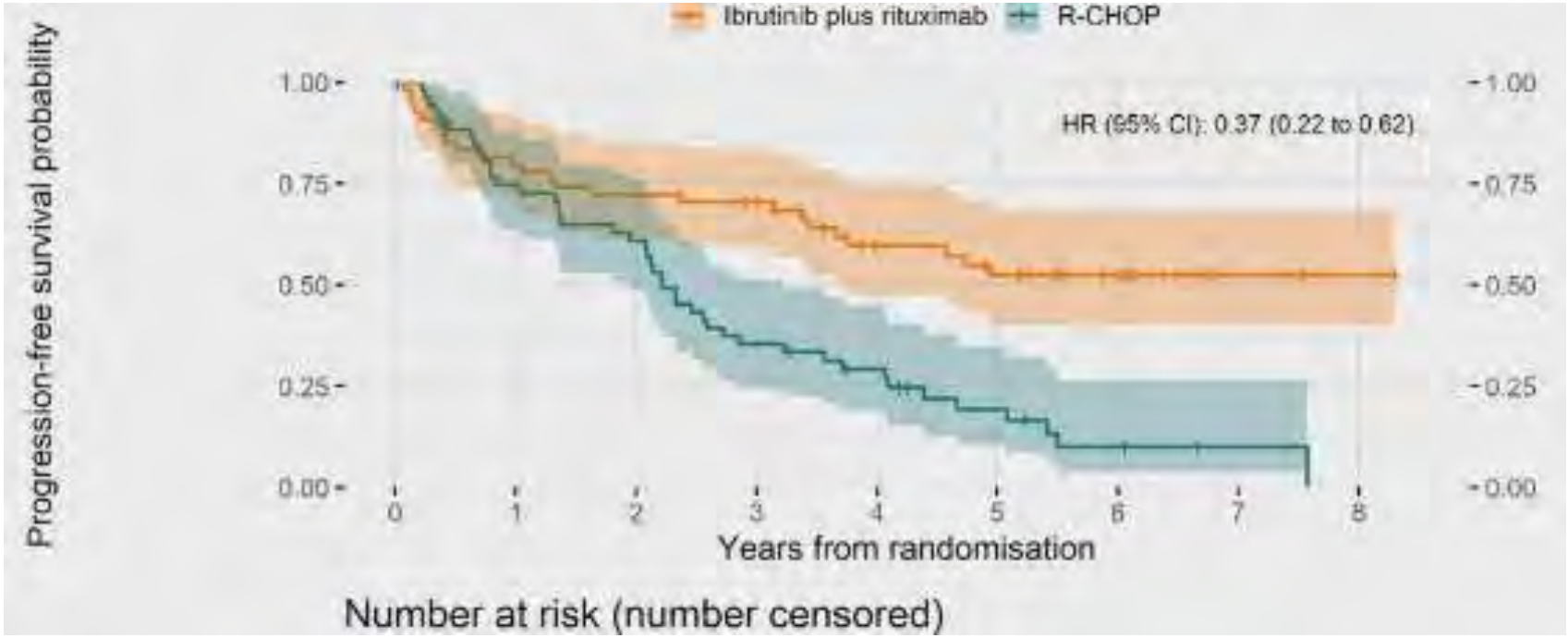


- Test of interaction for choice of chemotherapy regimen…

PFS benefit largely driven by poor performance of RCHOP arm

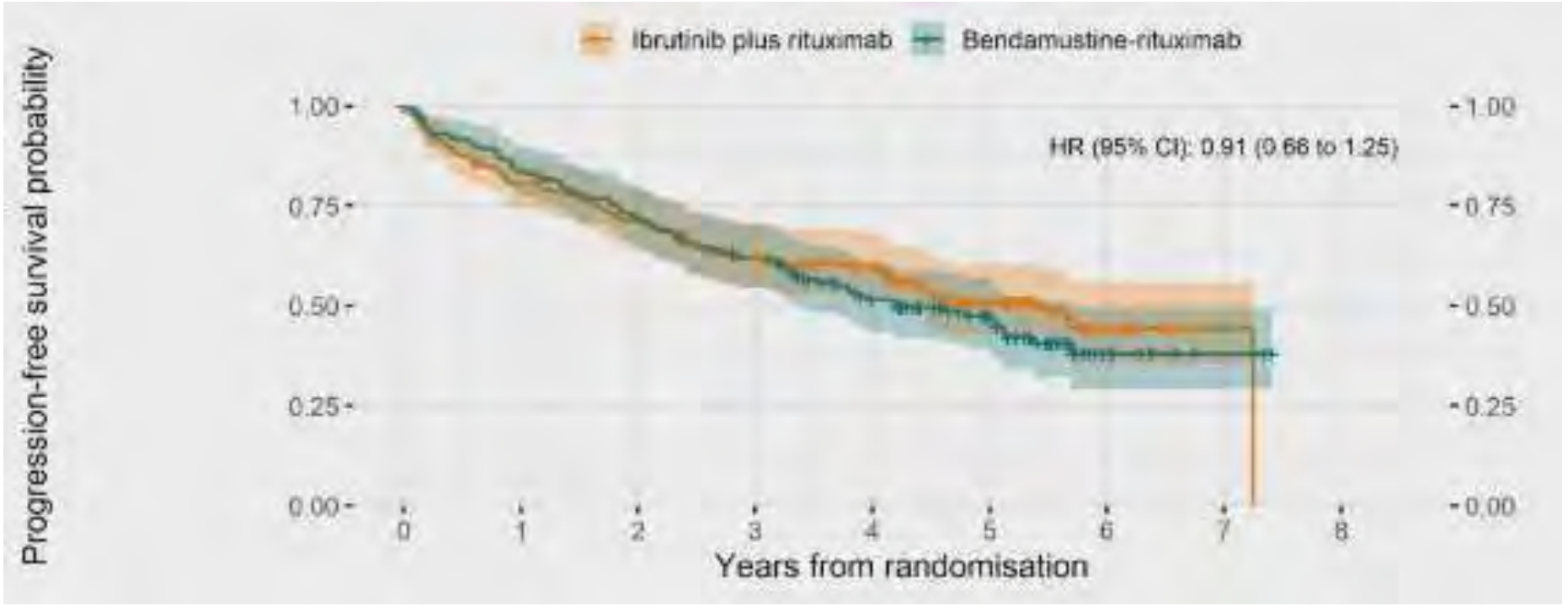
PFS for RCHOP choice

- SS difference in 5 year PFS:
  - IR 52.4%
  - RCHOP 19.2%



PFS for BR choice:

- No SS difference in 5 year PFS:
  - IR 50.8%
  - BR 47.4%

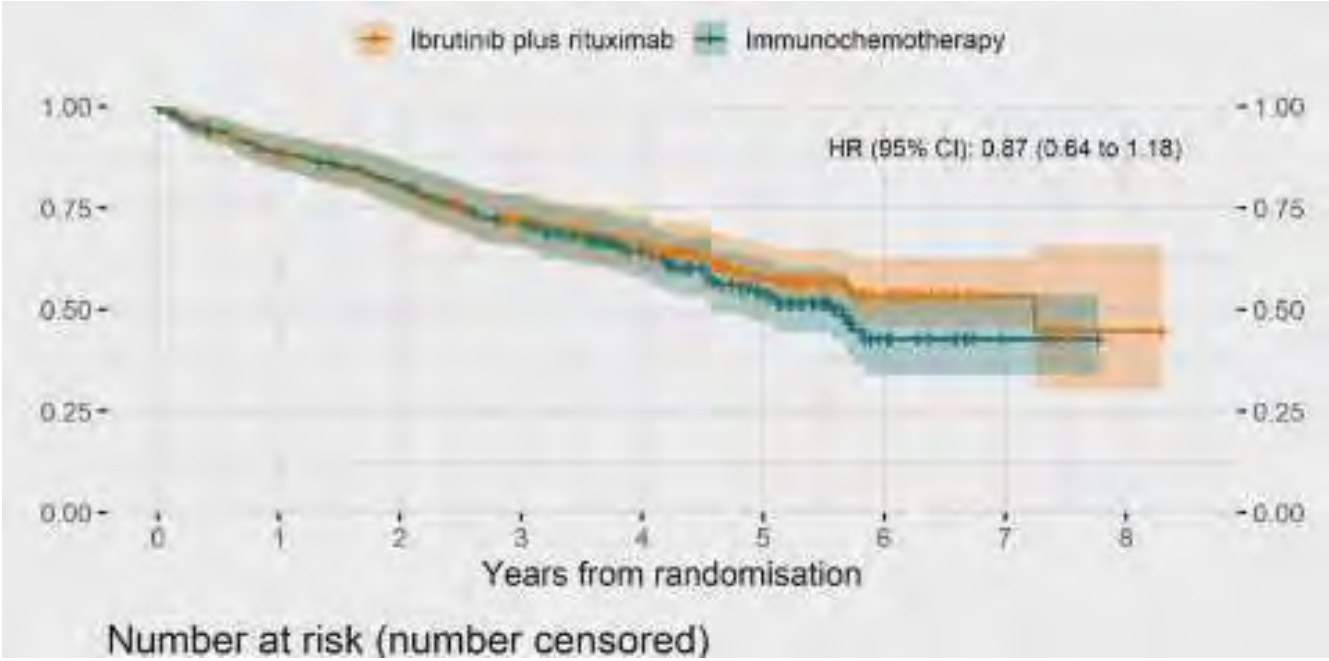


No SS difference in OS, similar toxicity

- 5 year OS:
  - IR 57.7%
  - R-chemo 54.5%

- Toxicity:
  - Similar G3/4 AE
  - 22% G3/4 cardiac toxicity with ibrutinib
  - Higher neutropenia with R-chemo (15% G3/4 NF with RCHOP)

- QOL: “Earlier improvement in QOL with IR treatment”
  - How will this hold up long term with time limited vs. ongoing treatment with IR



Summary of MCL at ASH 2024

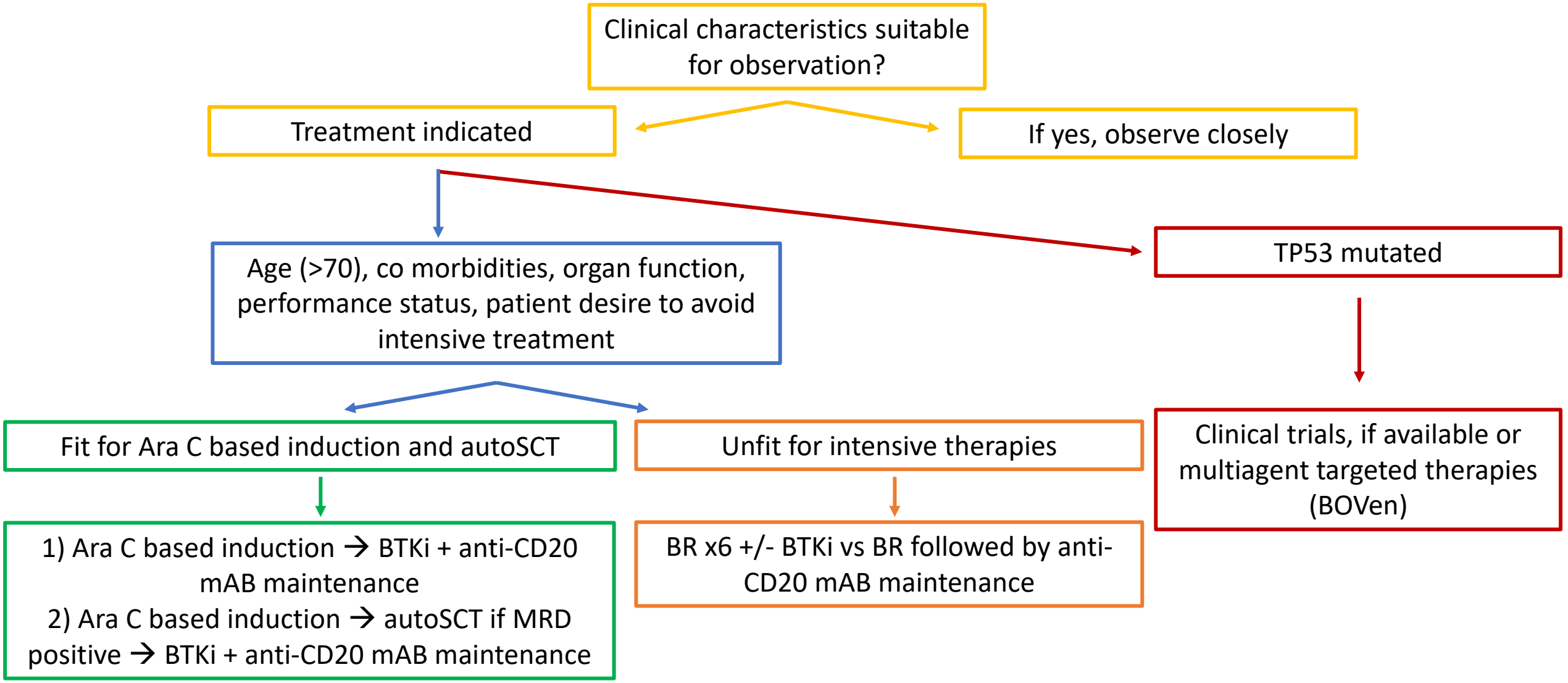
- BTKi and rituximab maintenance improves overall survival in young, transplant eligible patients
  - No difference in FFS or OS in patients who received auto vs. no auto (A+I vs. I)
- No benefit to transplant in MRD negative patients at end of induction
- Frontline treatment of elderly patient: R-BTKi superior to RCHOP, equivalent to BR
  - Ongoing MANGROVE study or R-zanu vs. BR in same population

Frontline MCL: Clear as mud

- Q: Which transplant eligible patients still may benefit from autoSCT?
- Q: In the era of BTKi maintenance, should we still use cytarabine based induction without autoSCT?
  - ECOG 4181 study: BR/RC vs. BR/RC + acala vs. BR + acala only
- Q: Which transplant ineligible patients should receive frontline BR vs. BTKi vs. combination BR + BTKi?
  - Trend towards worse outcomes in blastoid patients with IR treatment vs. R-Chemo in ENRICH trial
- Q: Which patients should be treated with frontline multiagent targeted therapy?
  - OASIS II trial: R + BTKi +/- Venetoclax, improved CR with ven addition but no diff in PFS
- A: Use 2nd generation BTKi in leu of ibrutinib: Acala vs. Zanu
  - Acalabrutinib now FDA approved for 1st line MCL (ECHO trial)

Wagner- Johnston et al. ASH 2024 Oral Abstract 0236; LeGouill et al. ASH 2024 Oral Abstract 0745

Frontline MCL Treatment in 2/2025



Tip of the lymphoma iceberg at ASH

- DLBCL:
  - Longer follow up with CD20/CD3 bispecifics as single agent in R/R DLBCL and combination treatment in FL with impressive DOR
  - Novel agents in RR disease: promising data for golcadomide and CD19/CD3 bispecifics
- FL:
  - Lonca in R/R disease
- Hodgkins:
  - ctDNA utility in prognostication
  - Pembro maintenance in leu of autoSCT in R/R setting
- PTLD:
  - Tab-cel for EBV+ disease

While I can’t bring you the warm San Diego beaches…

…hopefully brought you the practice changing lymphoma data from ASH 2024

Thank you!

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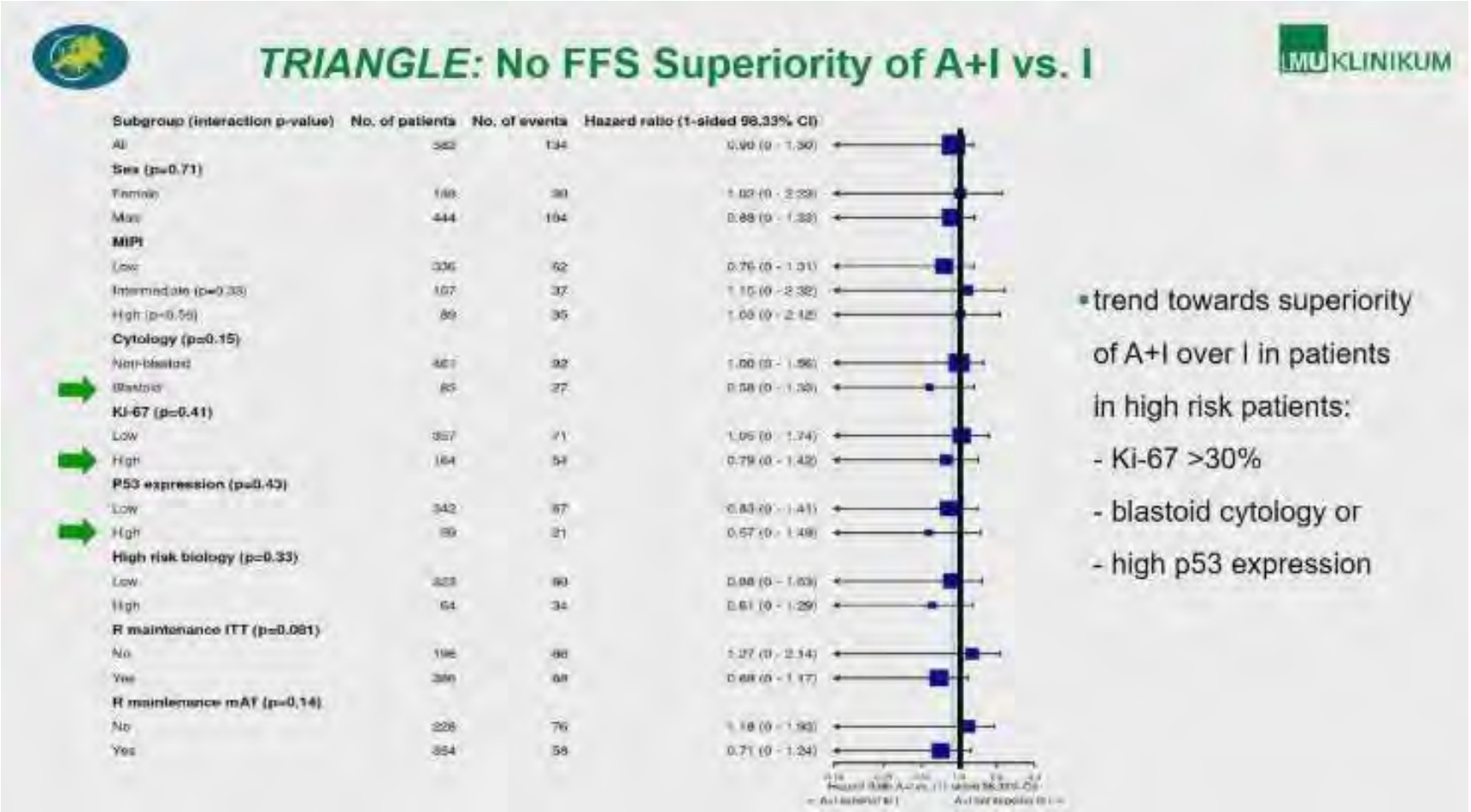
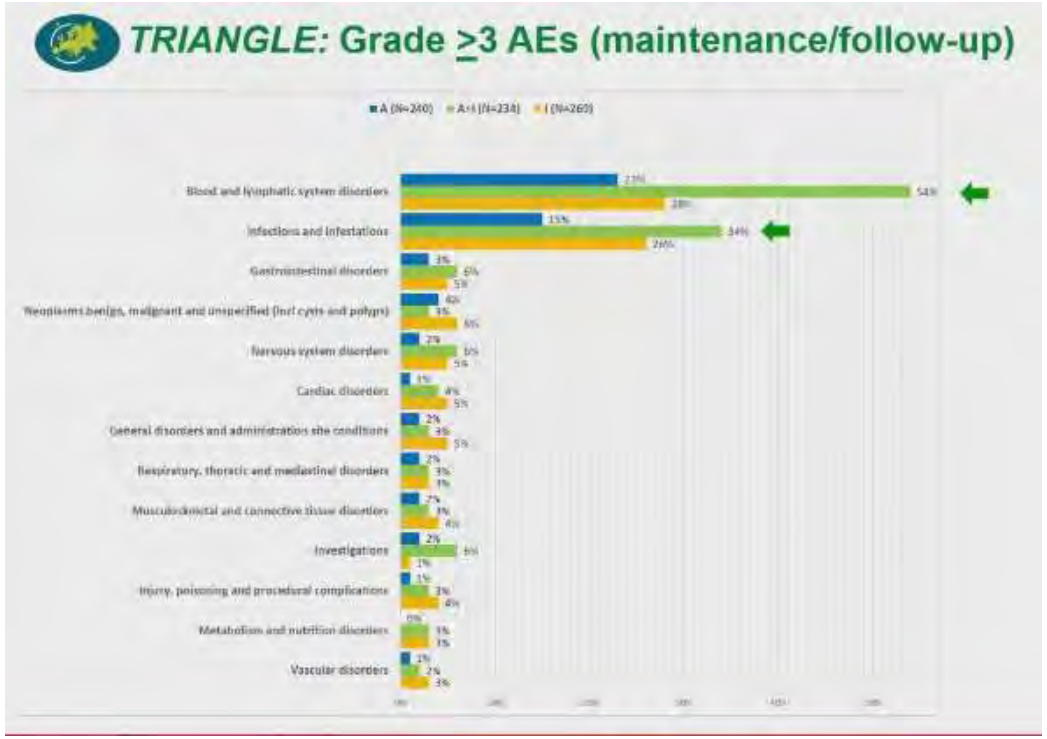
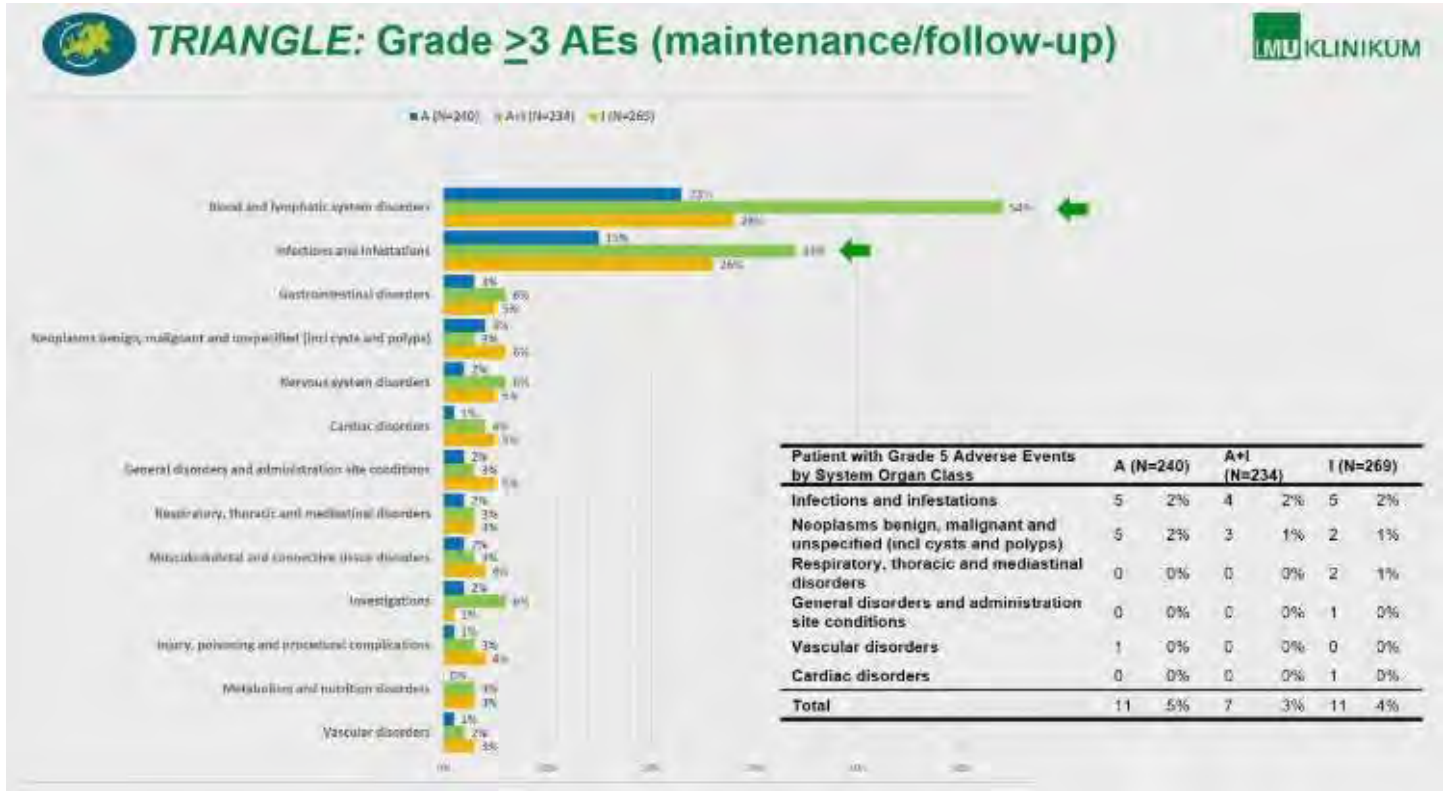
Extra Slides

Which patients benefit from ASCT?



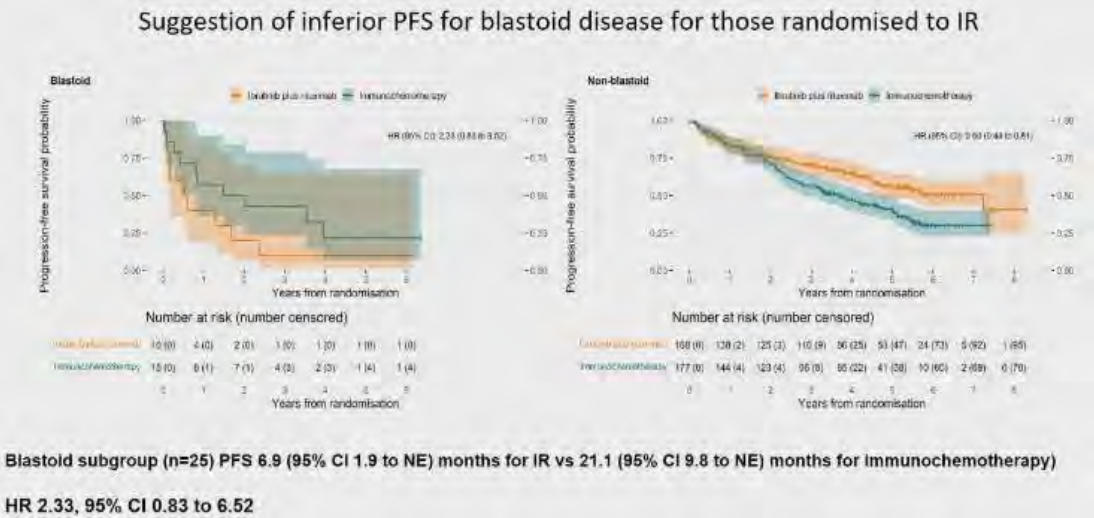
But again comes at a cost…

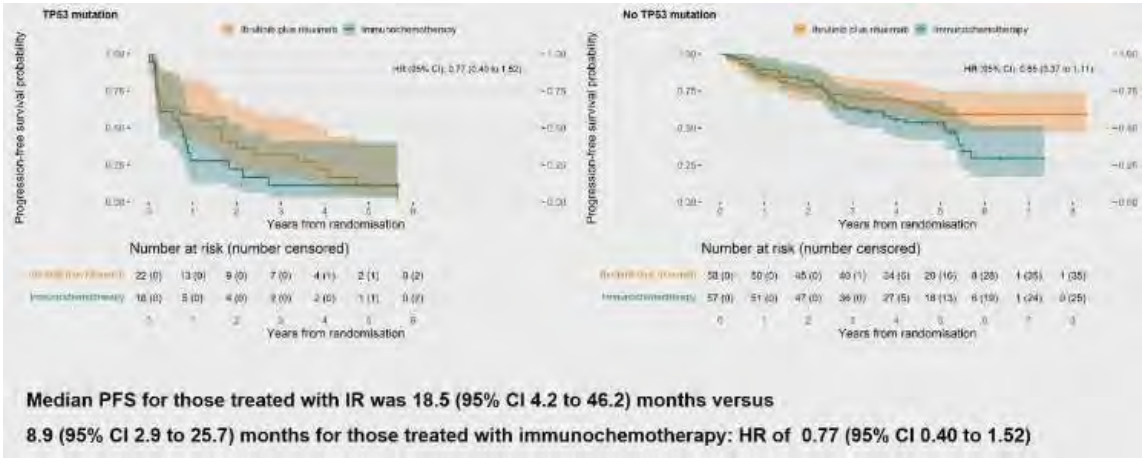


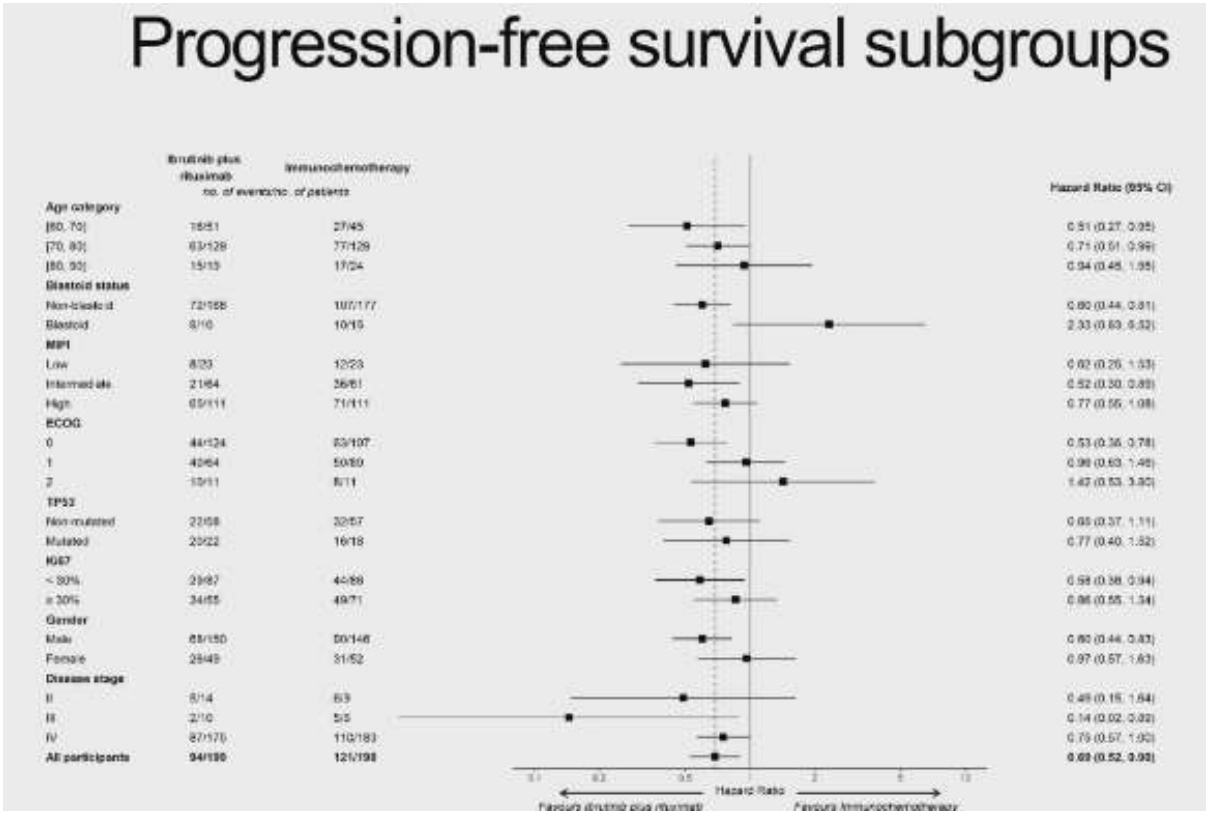


Patient with Grade 5 Adverse Events by System Organ Class	A (N=240)		A+I (N=234)		I (N=269)	
Infections and infestations	5	2%	4	2%	5	2%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	2%	3	1%	2	1%
Respiratory, thoracic and mediastinal disorders	0	0%	0	0%	2	1%
General disorders and administration site conditions	0	0%	0	0%	1	0%
Vascular disorders	1	0%	0	0%	0	0%
Cardiac disorders	0	0%	0	0%	1	0%
Total	11	5%	7	3%	11	4%

Which patients benefit most from IR?







Which patients benefit more from RM?

- More improvement with RM in low risk MIPI
- No diff based on classical/pleomorphic cytology or Ki67