Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

66th ASH Meeting 2024

San Diego & virtuell

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Expert:innen berichten zu Lymphomen & Leukämien

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Klinikum der Universität München

Mantelzell-Lymphom (MCL)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2024 wird in Kooperation mit sieben unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Research Support (institution)	**Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche**
Employee	**-**
Major Stockholder	**-**
Speakers Bureau	**-**
Speakers Honoraria	**Astra Zeneca, Beigene, Gilead/Kite, Janssen, Lilly, Novartis, Roche**
Scientific Advisory Board	**Abbvie, Astra Zeneca, Beigene, BMS/Celgene, Gilead/Kite, Janssen, Lilly/Loxo, Novartis, Roche**

Kapitel 1

Erstlinientherapie.

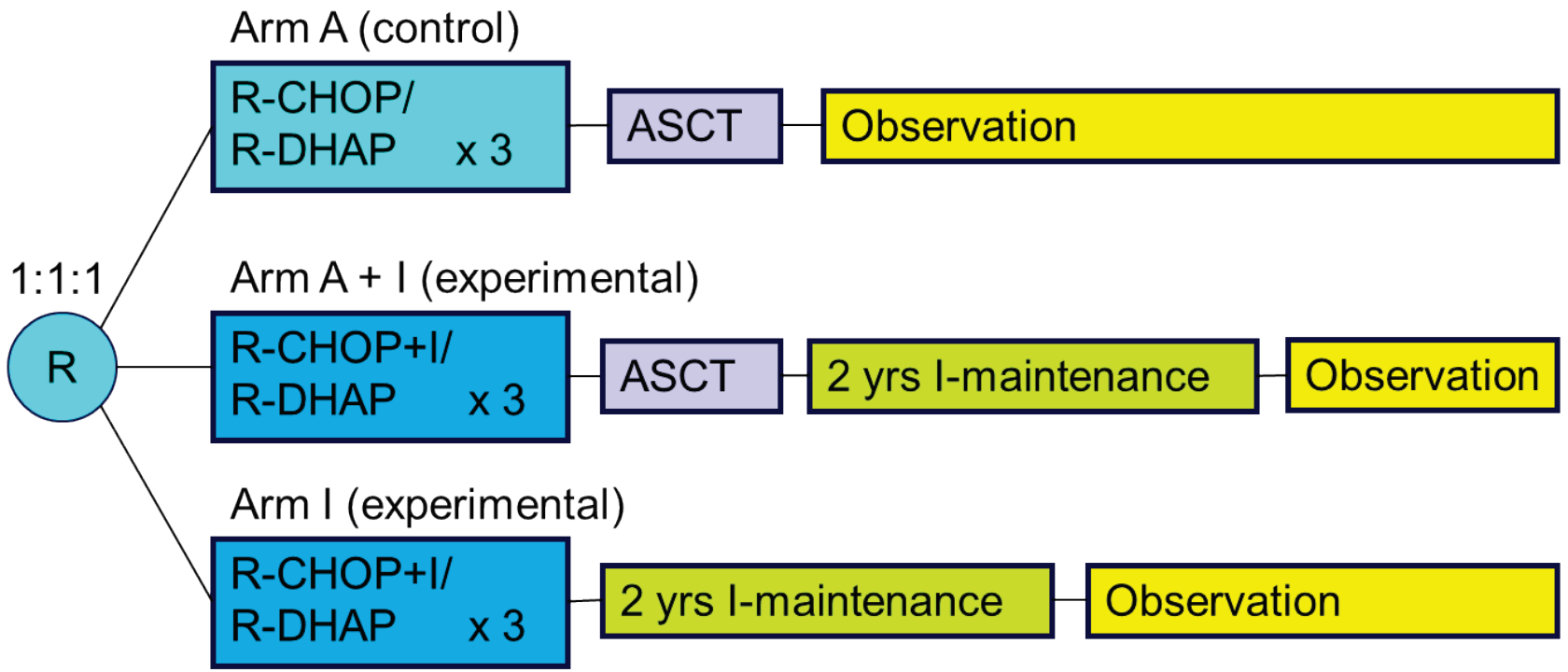
Immun-Chemotherapie & targeted Therapie

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



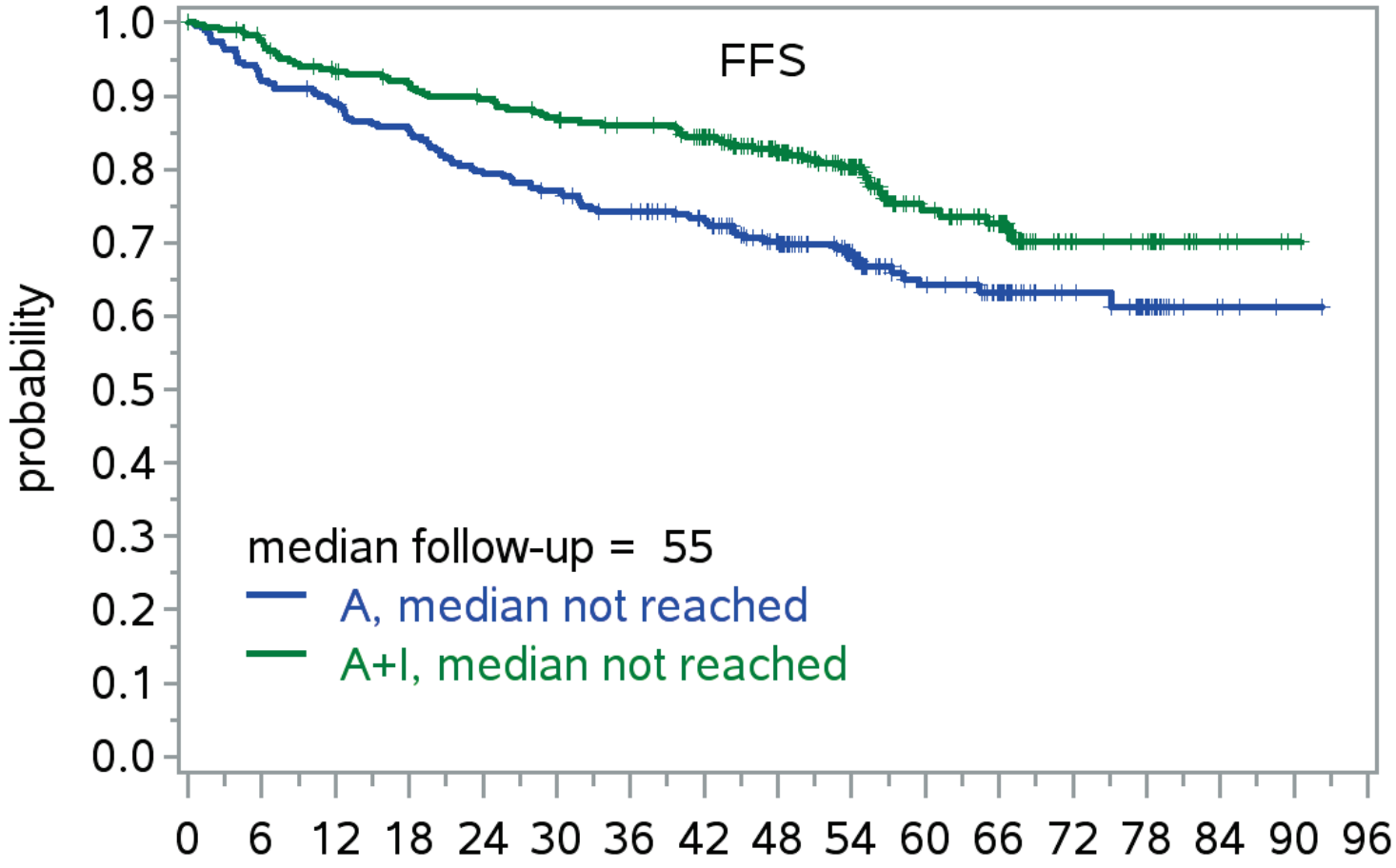
- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

Dreyling, ASH 2022: #1

Mantle cell lymphoma ASH 2022
Open questions

- longer follow-up (from 31 to 55 months)
- significance of OS ?
- ASCT in the era of ibrutinib containing regimens ?
- R maintenance in the era of ibrutinib containing regimens ?

TRIANGLE: FFS Superiority of A+I vs. A

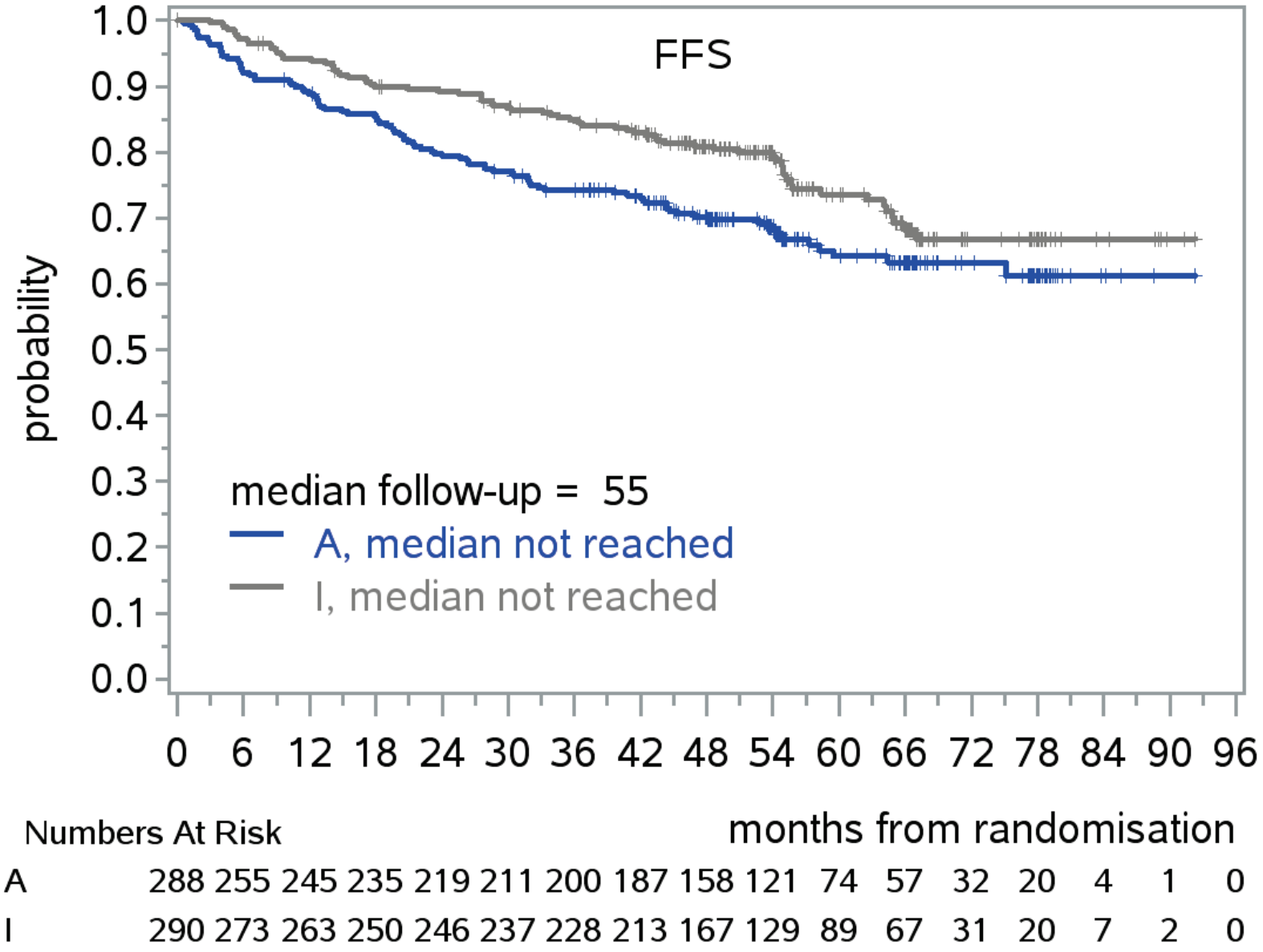


Numbers At Risk

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

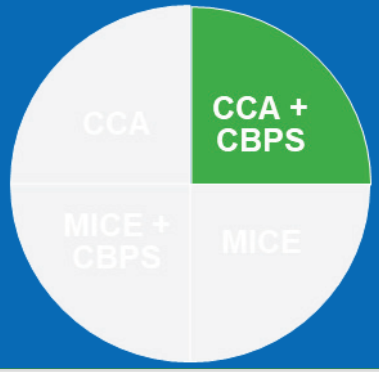
- Superiority of A+I vs. A
  - 4-year FFS A+I: 82%
  - 4-year FFS A: 70%
- p-value (overrunning, one-sided): p=0.0026
- HR (A+I vs. A): HR=0.64

TRIANGLE: No FFS Superiority of A vs. I

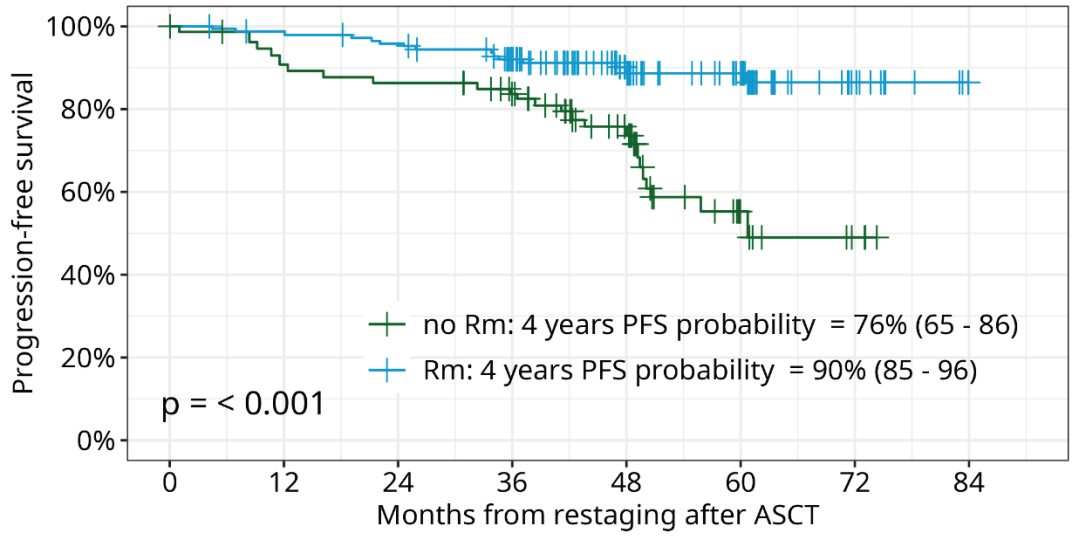


- Superiority of A vs. I rejected
  - 4-year FFS A: 70%
    (MCL Younger: 70%)
  - 4-year FFS I: 81%
- p-value (overrunning, one-sided):
  p=0.9890
- HR (A vs. I): HR=1.29
- Superiority of I
  (two-sided, retrospective)
  p=0.0208

Primary endpoint: Progression-free survival Weighted Kaplan-Meier curves*

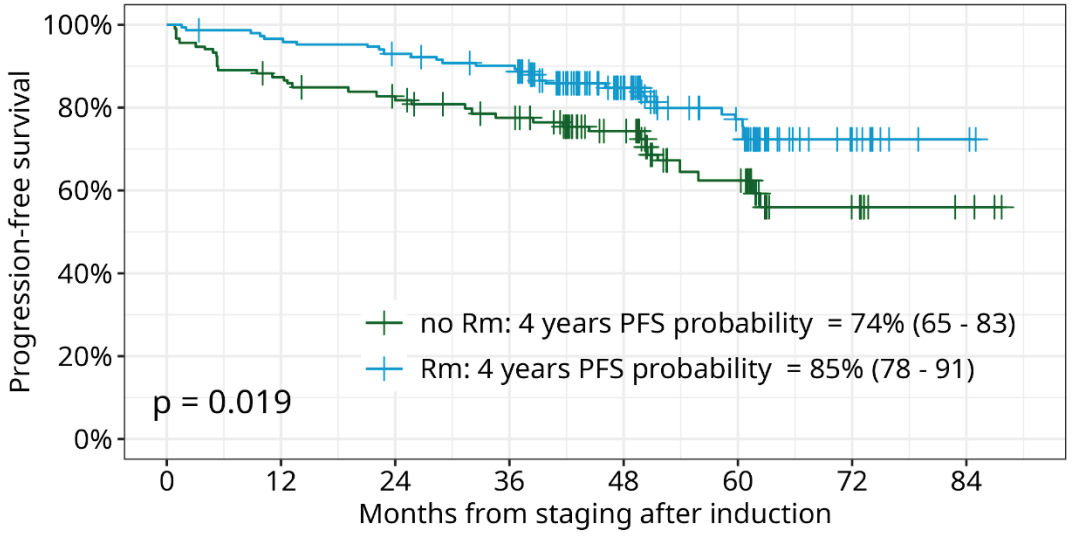


Arm A+I: PFS



noRm group								
At risk	85.3	75.1	71.6	63.8	41	12.9	6	0
Event	0	8.1	11.5	13.5	19.5	28.7	29.7	29.7
Rm group								
At risk	151.8	146.9	142.1	125.8	85.7	63	24.5	0
Event	0	3.1	6.9	12.8	14.6	15.5	16.6	16.6

Arm I: PFS

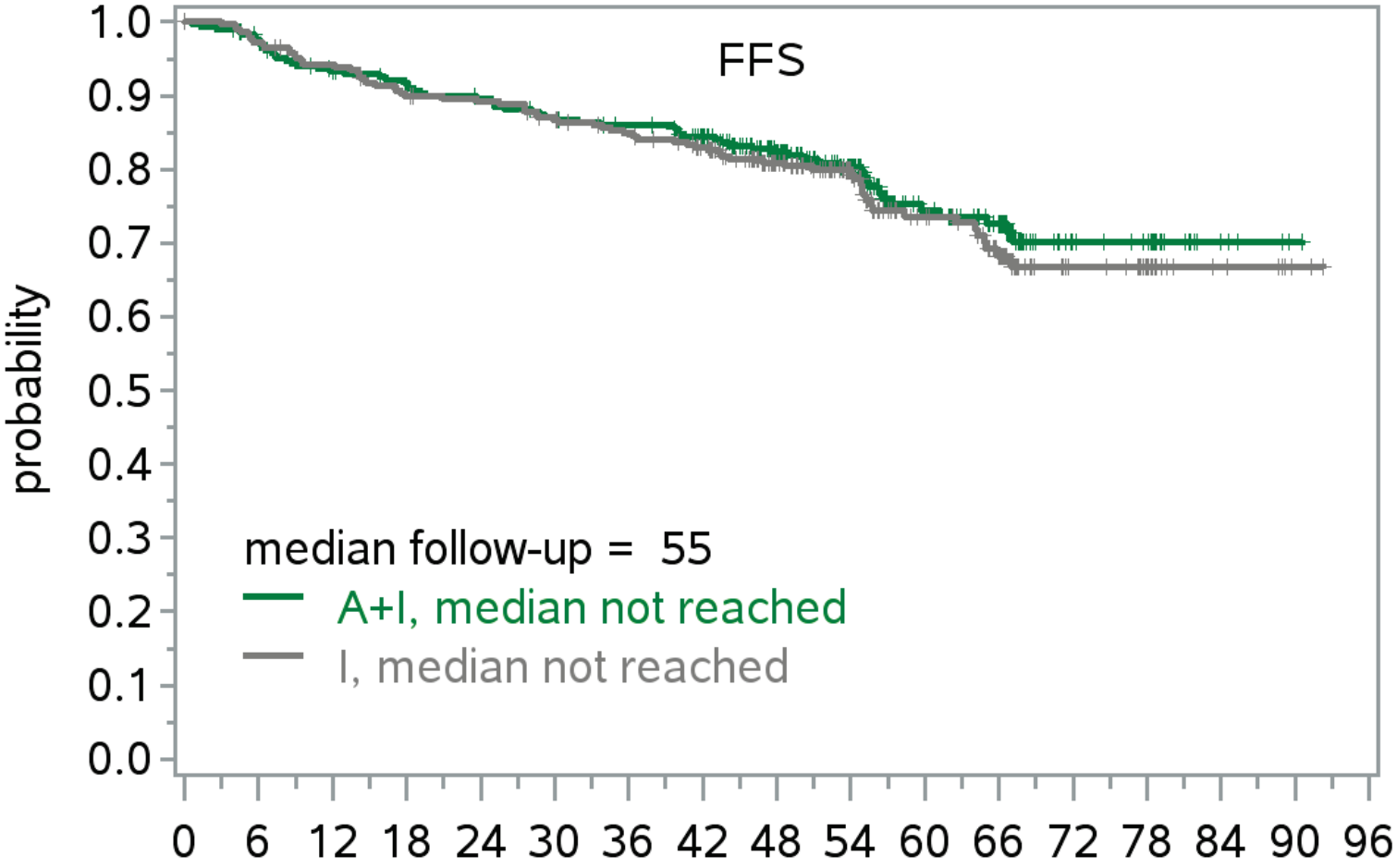


noRm group								
At risk	116.7	100.7	92.5	82.6	59.8	38.2	19.3	6
Event	0	14.1	20.2	26.2	29.2	35.8	37.7	37.7
Rm group								
At risk	157.2	148.3	141.5	135.3	87.3	57.9	23	3.9
Event	0	7	12.8	16.9	22.8	28.7	30.6	30.6

*Propensity Score including MIPI single variables, response after induction (arm I)/ after ASCT (arm A, A+I), Ki67, cytology

Ladetto, ASH 2024, #237

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

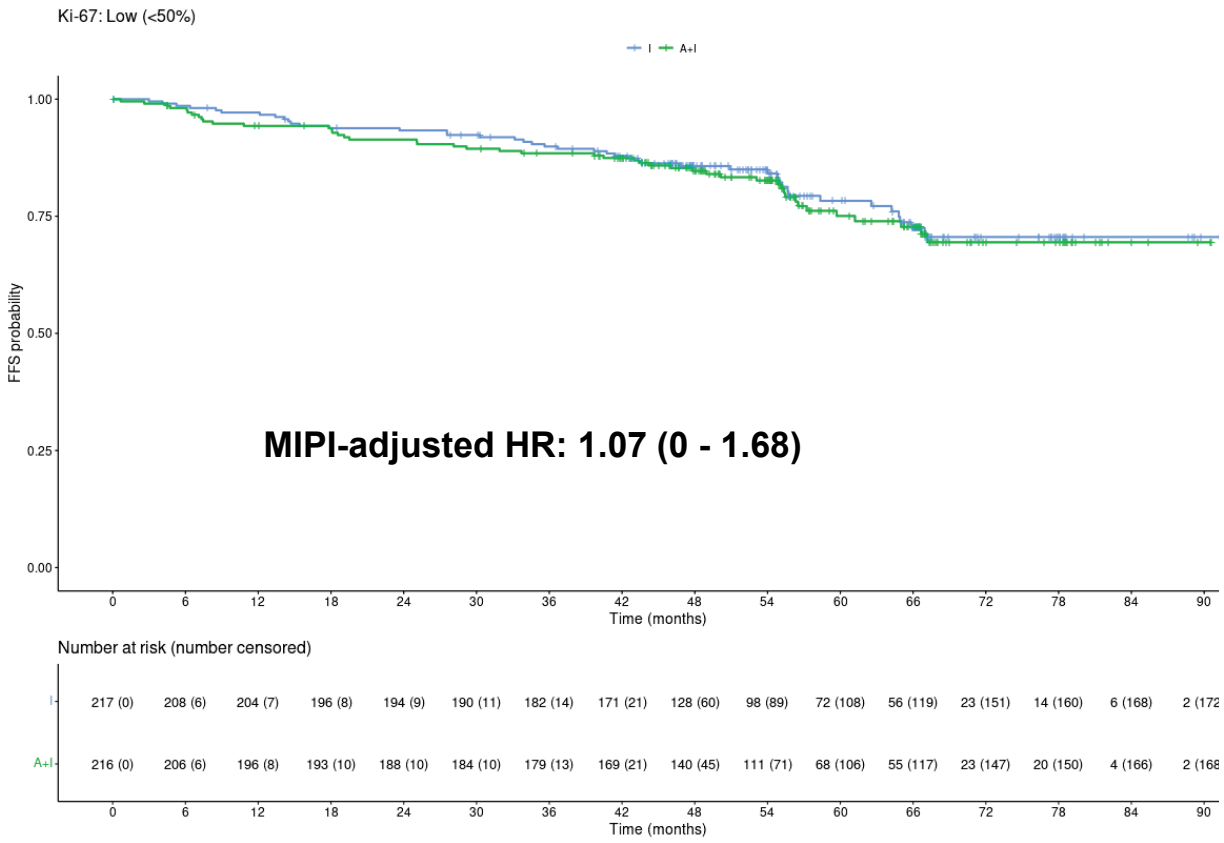


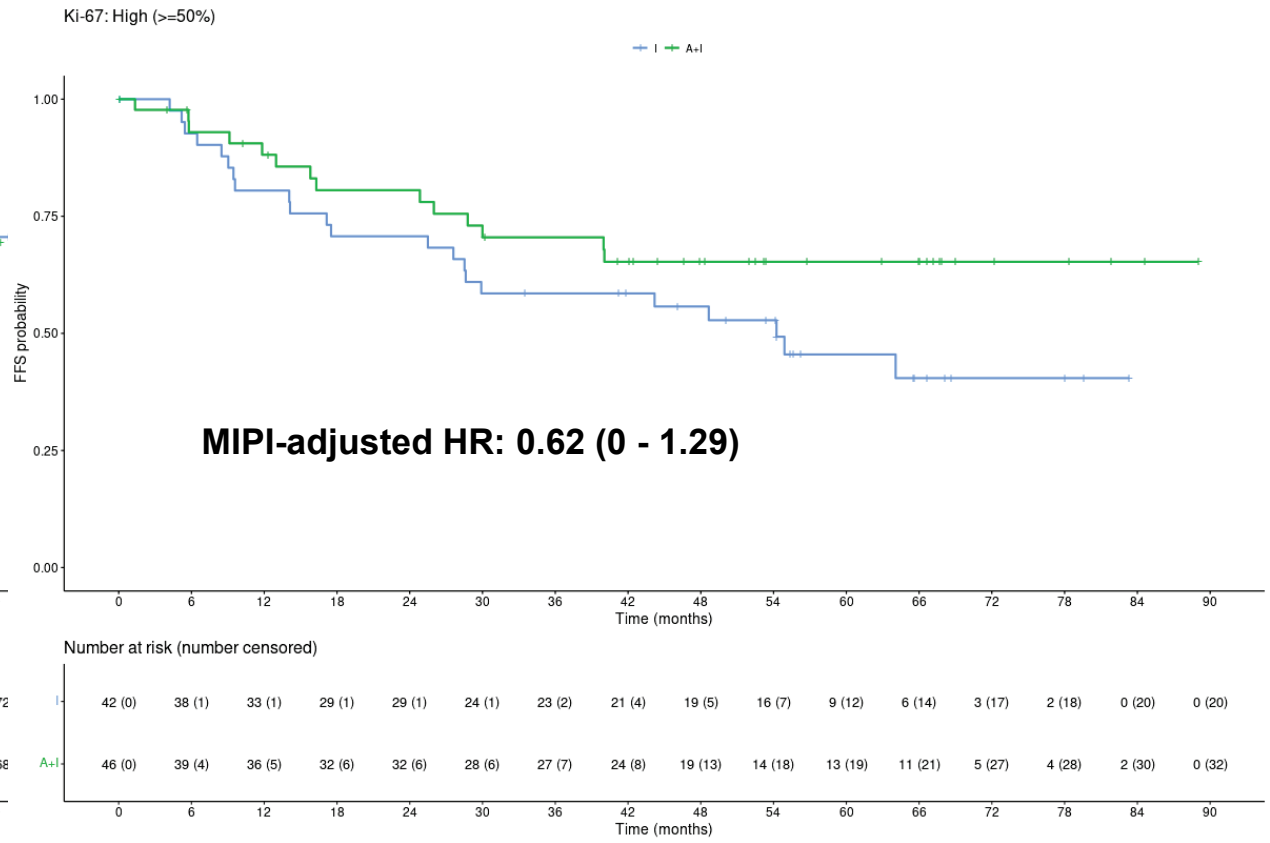
Numbers At Risk

A+I	292	274	259	252	245	236	230	217	180	141	89	70	28	24	6	2	0
I	290	273	263	250	246	237	228	213	167	129	89	67	31	20	7	2	0

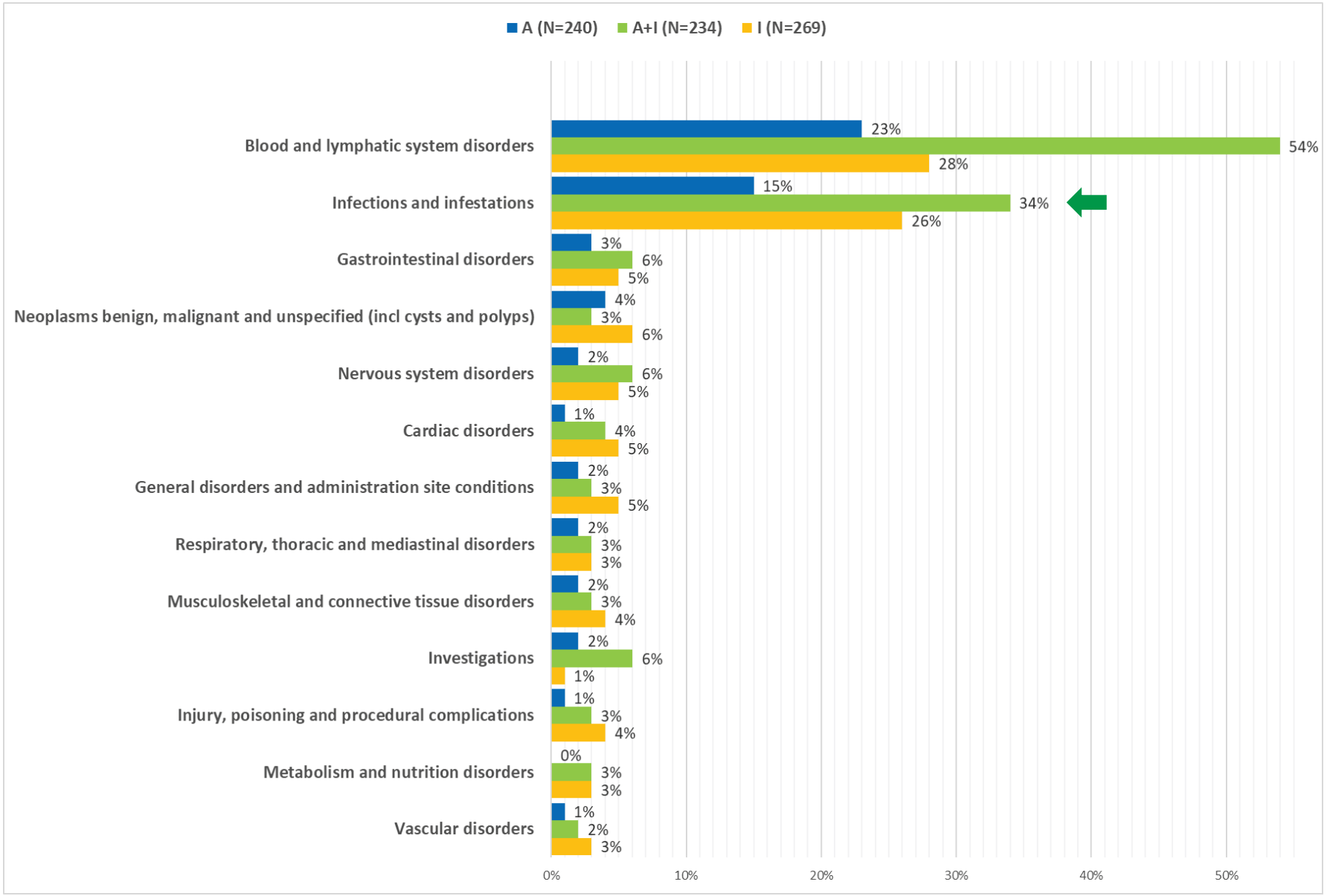
- Superiority of A+I vs. I rejected
  - 4-year FFS A+I: 82%
  - 4-year FFS I: 81%
- p-value (overrunning, one-sided): p=0.21
- HR (A+I vs. I): HR=0.83

TRIANGLE: A+I vs. I (FFS) and Ki-67 (50% cut-off)

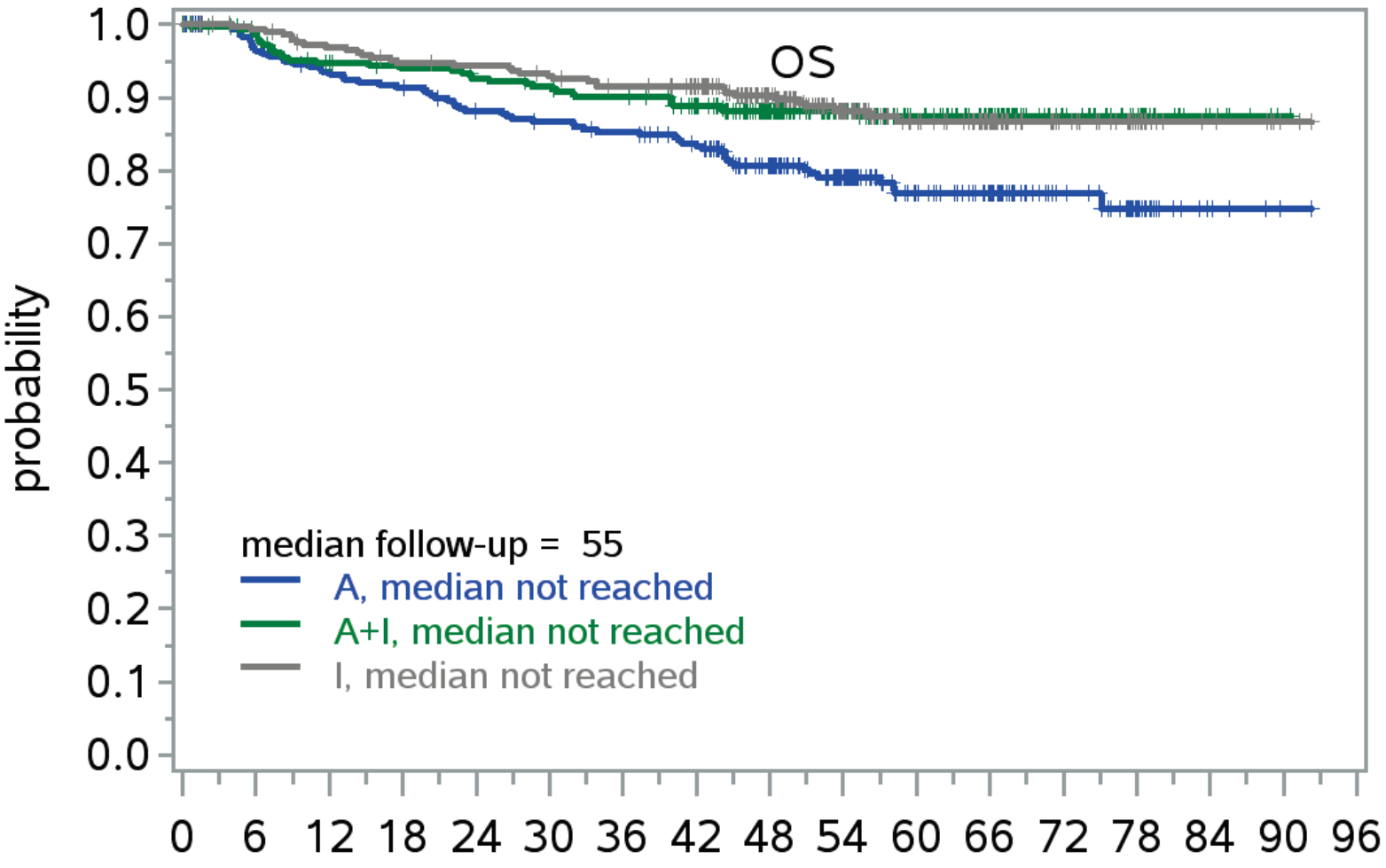




TRIANGLE: Grade ≥3 AEs (maintenance/follow-up)



TRIANGLE: Overall survival

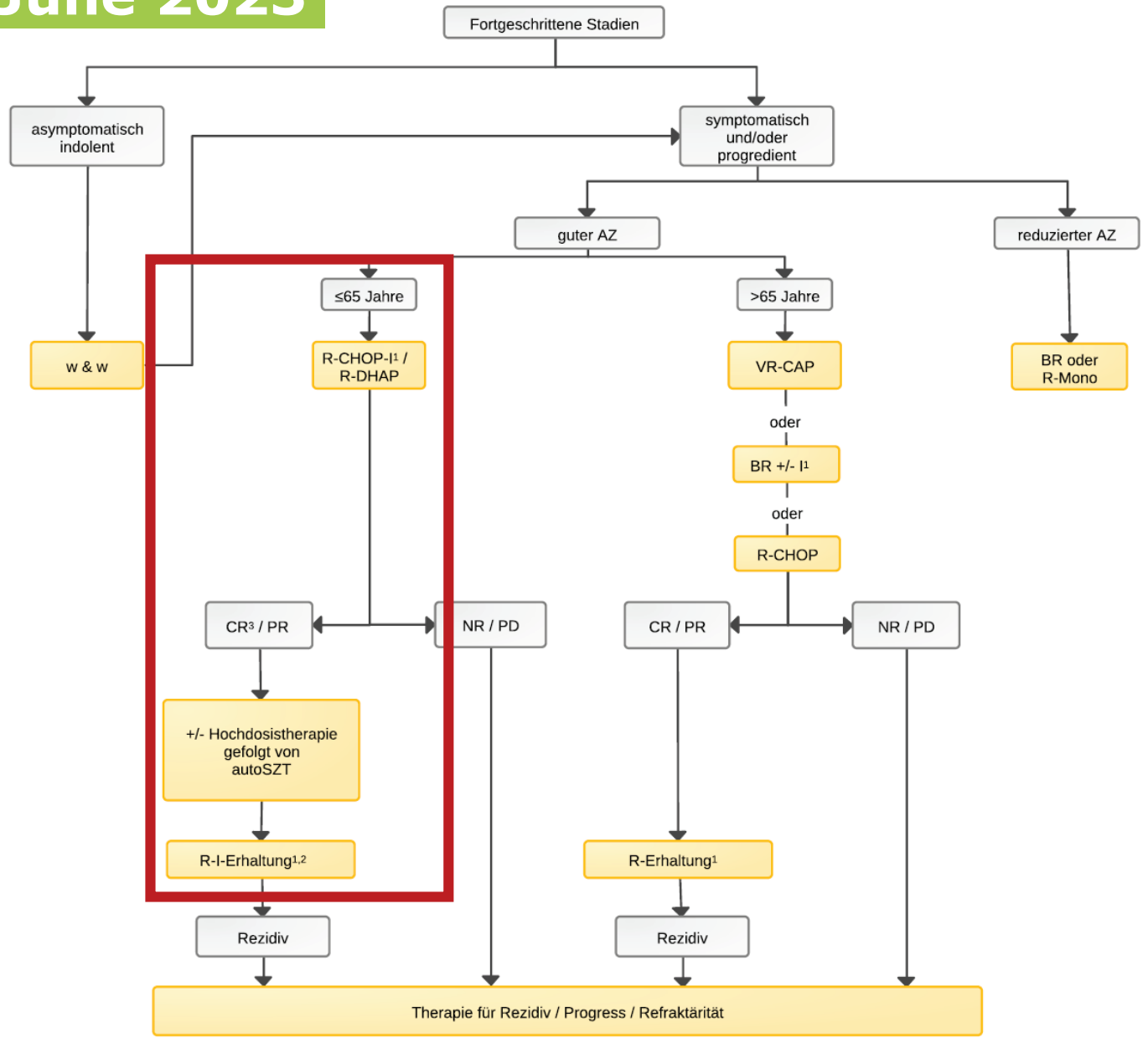


Numbers At Risk

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

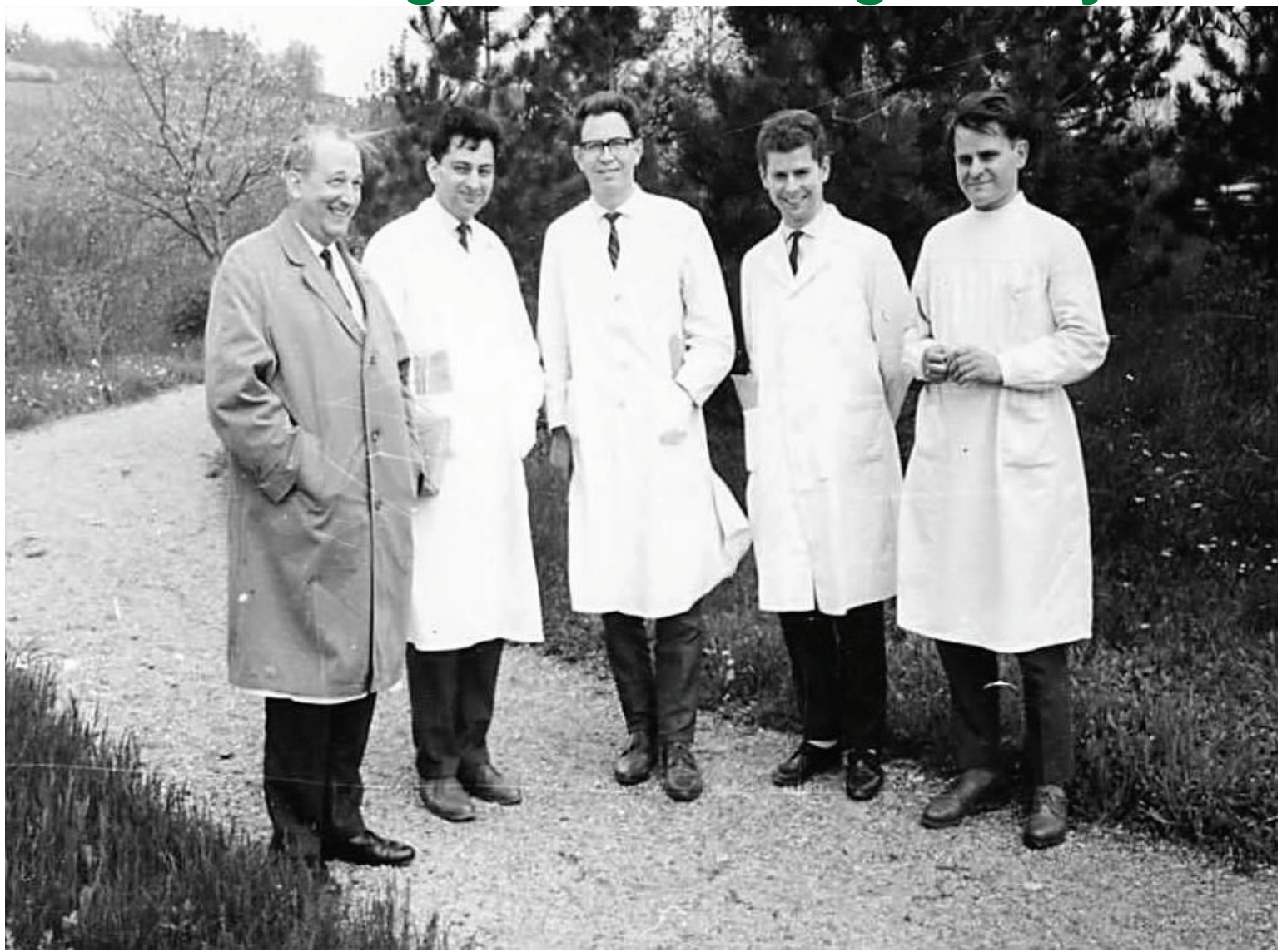
- 4-year OS:
  - A: 81%
    (MCL Younger exp.: 80%)
  - A+I: 88%
  - I: 90%
- two-sided test, (a = 5%):
  - A vs. I: p=0.0019, HR: 0.565
  - A vs. A+I: p=0.0036, HR I: 0.587
  - A+I vs. I: ongoing

Mantle cell Lymphoma
Onkopedia June 2023



Bendamustine:

An ‘agent’ with a long history



- synthesis : W.Ozegowski, D.Krebs, Institute of Microbiology and Experimental Therapy, Jena (1962)
- Published in Journal für Praktische Chemie, Vol. 20, issue 3-4, 1963

Treatment Schema

Key Eligibility
- Untreated mantle cell lymphoma
- Age 18 - 70
- ECOG PS 0-2
- Adequate organ and marrow function

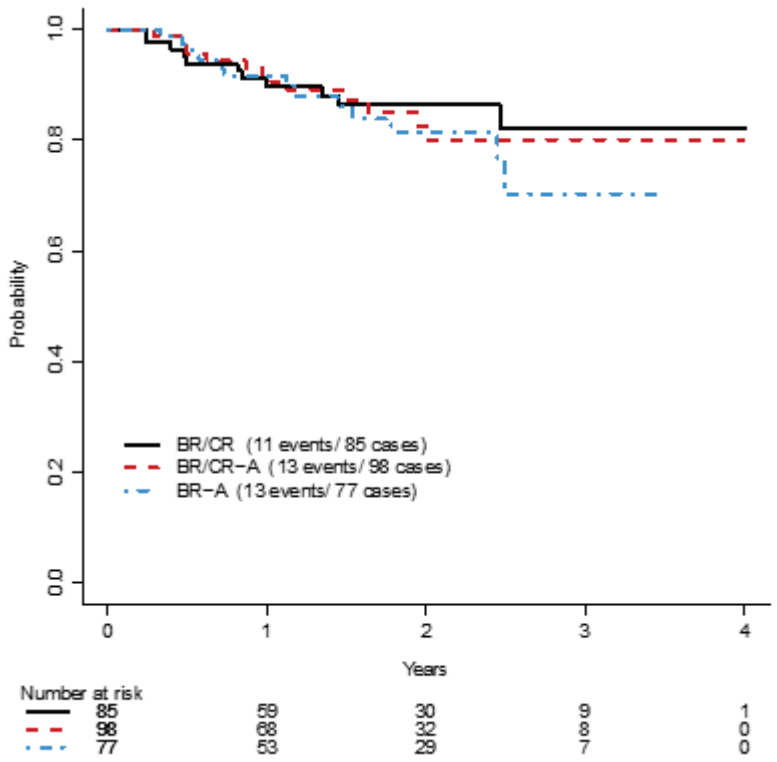
Randomization
1:1:1

BR/CR
- 3 cycles of Bendamustine/Rituximab
- 3 cycles of Cytarabine/Rituximab

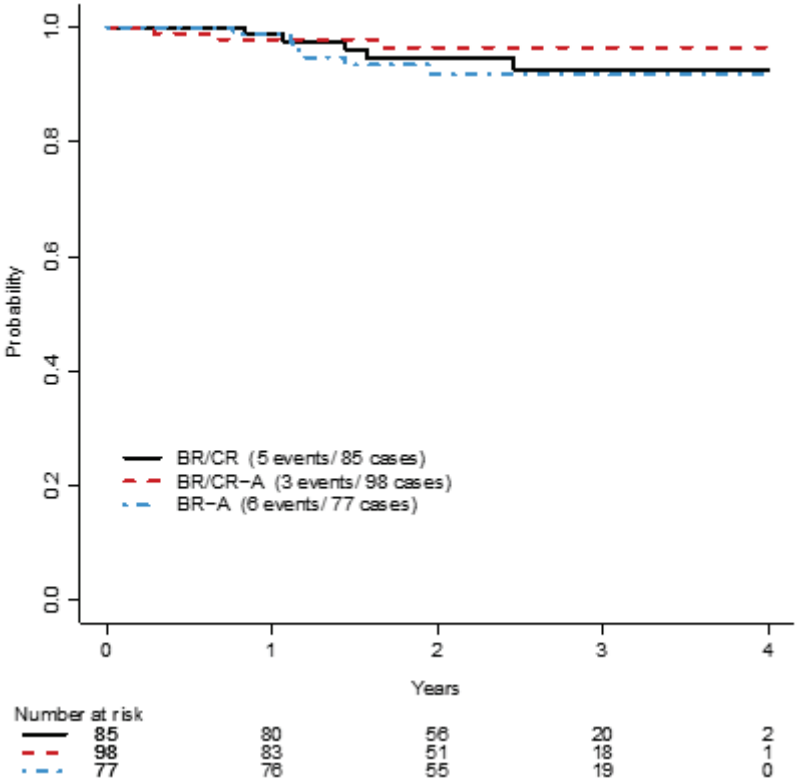
BR/CR-A
- 3 cycles of BR + Acalabrutinib continuous
- 3 cycles of CR + Acalabrutinib D1-7, 22-28

BR-A
- 6 cycles of BR + Acalabrutinib continuous

No Significant Difference in PFS/OS between Arms



PFS



OS

At median follow-up 27.9 mo, 12 mo PFS were 90% BR/CR, 91% BR/CR-A, and 92% BR-A

Safety Profile: Grade 3-5 TRAE in ≥ 5%

	BR/CR N = 124			BR/CR-A N = 129			BR-A N = 99		
%	G3	G4	G5	G3	G4	G5	G3	G4	G5
Anemia	22	1	0	31	1	0	3	0	0
Platelet count decreased	7	48	0	5	61	0	5	1	0
White blood cell decreased	7	42	0	2	45	0	16	6	0
Neutrophil count decreased	11	41	0	7	51	0	15	12	0
Lymphocyte count decreased	7	43	0	7	42	0	25	26	0
Febrile neutropenia	8	3	0	9	3	0	3	1	0
Infection	6	2	0	7	2	0	5	2	0
Rash	1	0	0	8	0	0	7	0	0
Worst degree	14	65	0	12	74	1.6	36	36	0

Kapitel 2

Erstlinientherapie.

(keine Immun-Chemotherapie &) targeted Therapie

Ibrutinib-rituximab versus Immunochemotherapy in previously untreated mantle cell lymphoma

Dr David J Lewis [1], Prof Mats Jerkeman [2], Dr Lexy Sorrell [3], Prof David Wright [4], Prof Ingrid Glimelius [5], Dr Christian B Poulsen [6], Dr Annika Pasanen [7], Prof Andrew Rawstron [8], Dr Karin Wader [9], Dr Nick Morley [10], Dr Catherine Burton [8], Prof Andrew J Davies [11], Dr. Ingemar Lagerlöf [12], Dr Surita Dalal [8], Dr Ruth De Tute [8], Dr Chris McNamara [13], Mrs Nicola Crosbie [1], Mrs Helle Erbs Toldbod [14], Dr Jeanette Sanders [3], Prof Victoria Allgar [3], Dr Sree Aroori [3], Mr Mark Warner [3], Ms Claire Scully [3], Mr Brian Wainman [3], Dr Jacob Haber Christensen [15], Dr Jon Riise [16], Dr Kristina Sonnevi [17], Dr Mark J Bishton [18], Dr Toby A Eyre [19], Prof Simon Rule [20] on behalf of the ENRICH investigators

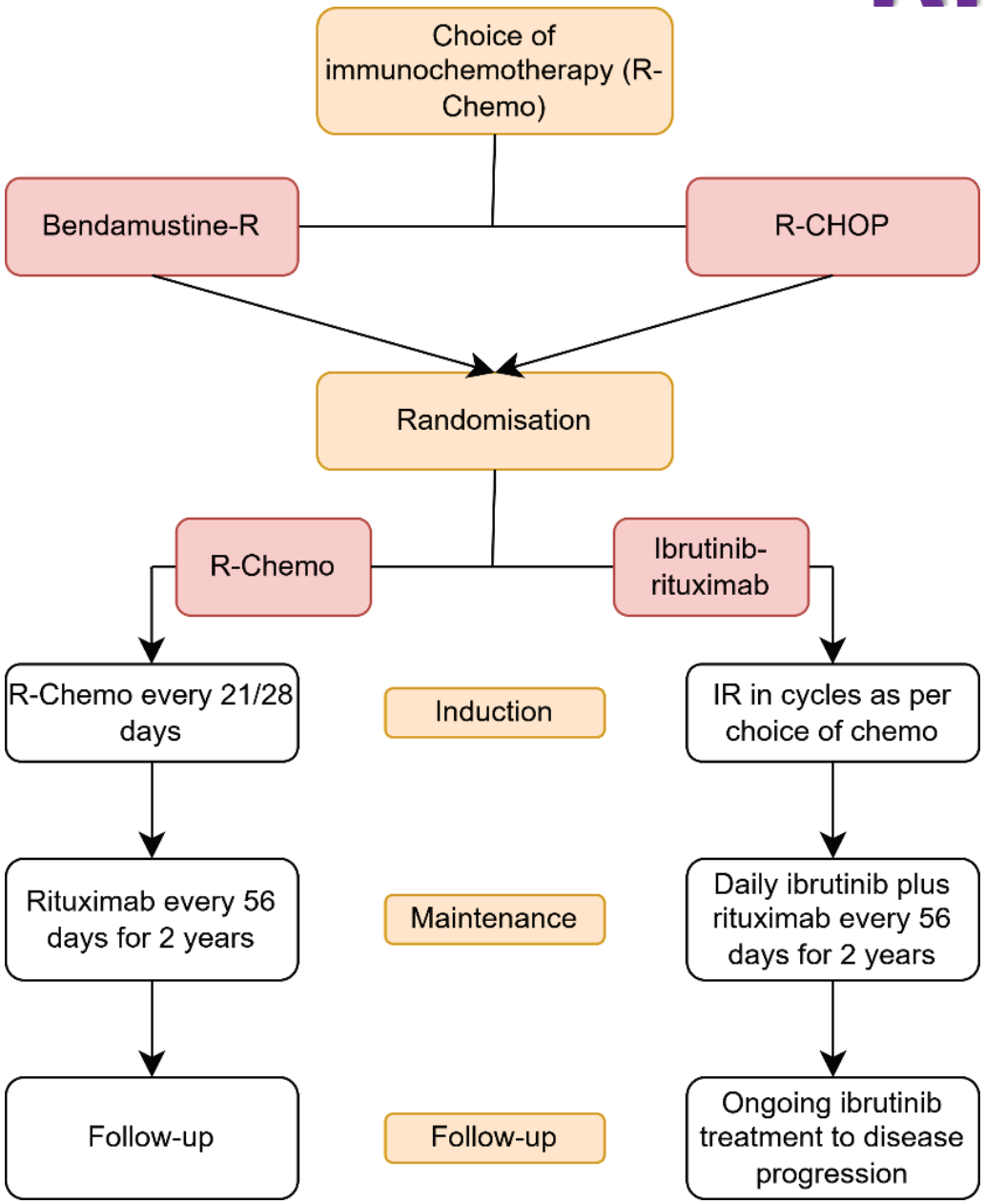
1 University Hospitals Plymouth NHS Trust, Plymouth, UK, PL6 8DH, 2 Lund University Hospital, 3University of Plymouth, 4University of Exeter, 5 Dept of Immunology, Genetics and Pathology, Uppsala University, 6 Zealand University Hospital Roskilde, 7 HUS Helsinki University Hospital, Helsinki, Finland, 8 Leeds Teaching Hospitals NHS Trust, 9 St Olav's Hospital HF, Trondheim, Norway, NO 700, 10 Sheffield Teaching Hospitals NHS Foundation Trust, 11 University of Southampton, 12 Linköping University Hospital, 13 University College London, 14 Aarhus University Hospital, 15 Odense Universitetshospital, 16 Oslo University Hospital,17 Karolinska University Hospital, 18 University of Nottingham, 19 Oxford University Hospitals NHS Trust, 20 AstraZeneca Mississaug

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



Grade 3-4 Adverse events

N participants (% of safety population)	Ibrutinib plus rituximab, N=198	Bendamustine-rituximab, N=143	R-CHOP, N=52
Total	125 (63.1%)	97 (67.8%)	36 (69.2%)
All Cardiac AEs	44 (22.2%)	7 (4.9%)	7 (13.5%)
All bleeding AEs	10 (5.1%)	3 (2.1%)	3 (5.8%)
Atrial Fibrillation	12 (6.1%)	1 (0.7%)	0
Neutropenia	18 (9.1%)	27 (18.9%)	11 (21.2%)
Neutropenic sepsis	6 (3.0%)	2 (1.4%)	8 (15.4%)
Corona virus infection	10 (5.1%)	10 (7.0%)	0

Grade 3 and 4 adverse events during induction treatment and maintenance

Safety population - patients who had at least one cycle of treatment

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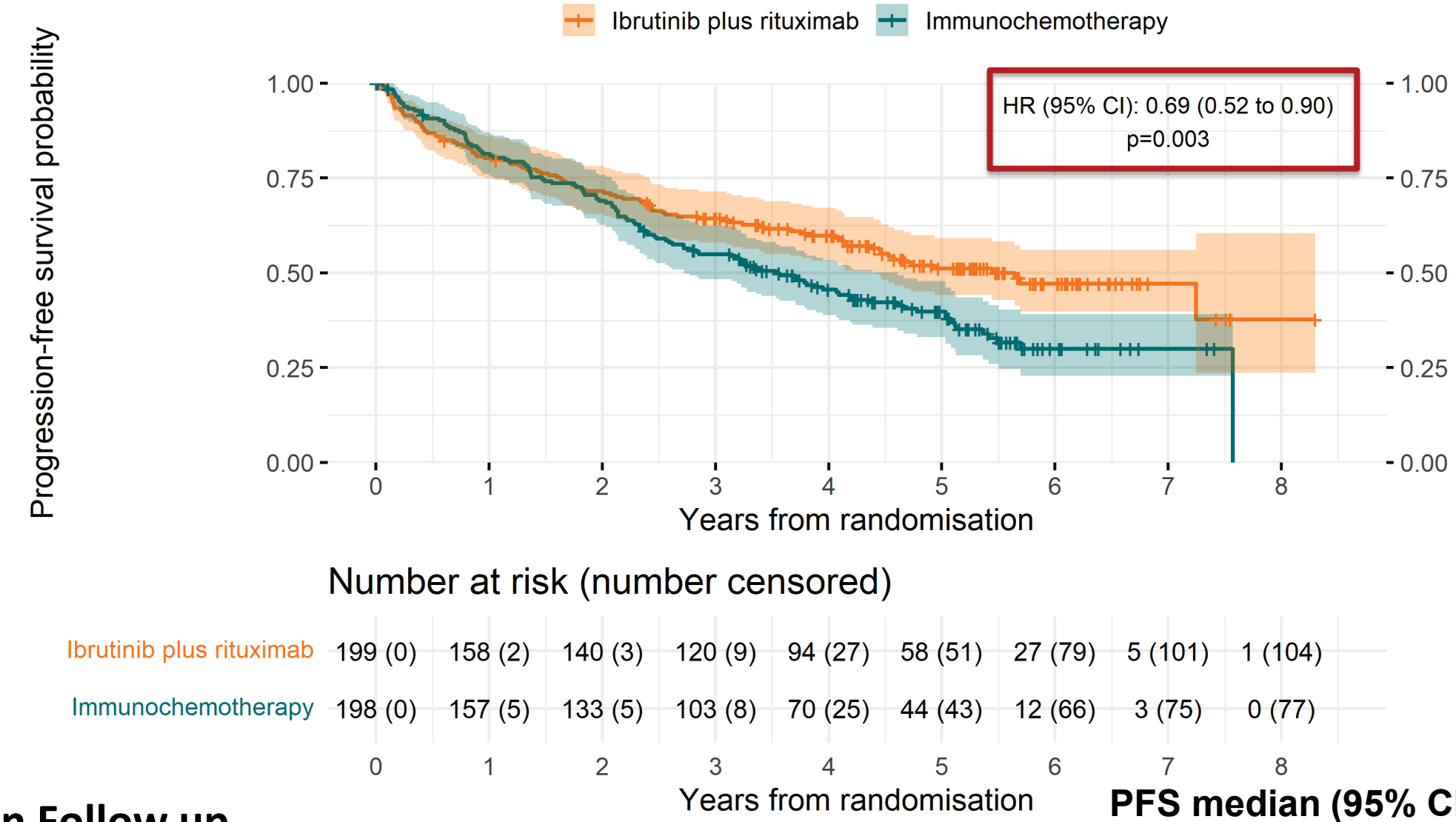
Grade 3 and 4 adverse events during induction treatment and maintenance

Safety population - patients who had at least one cycle of treatment

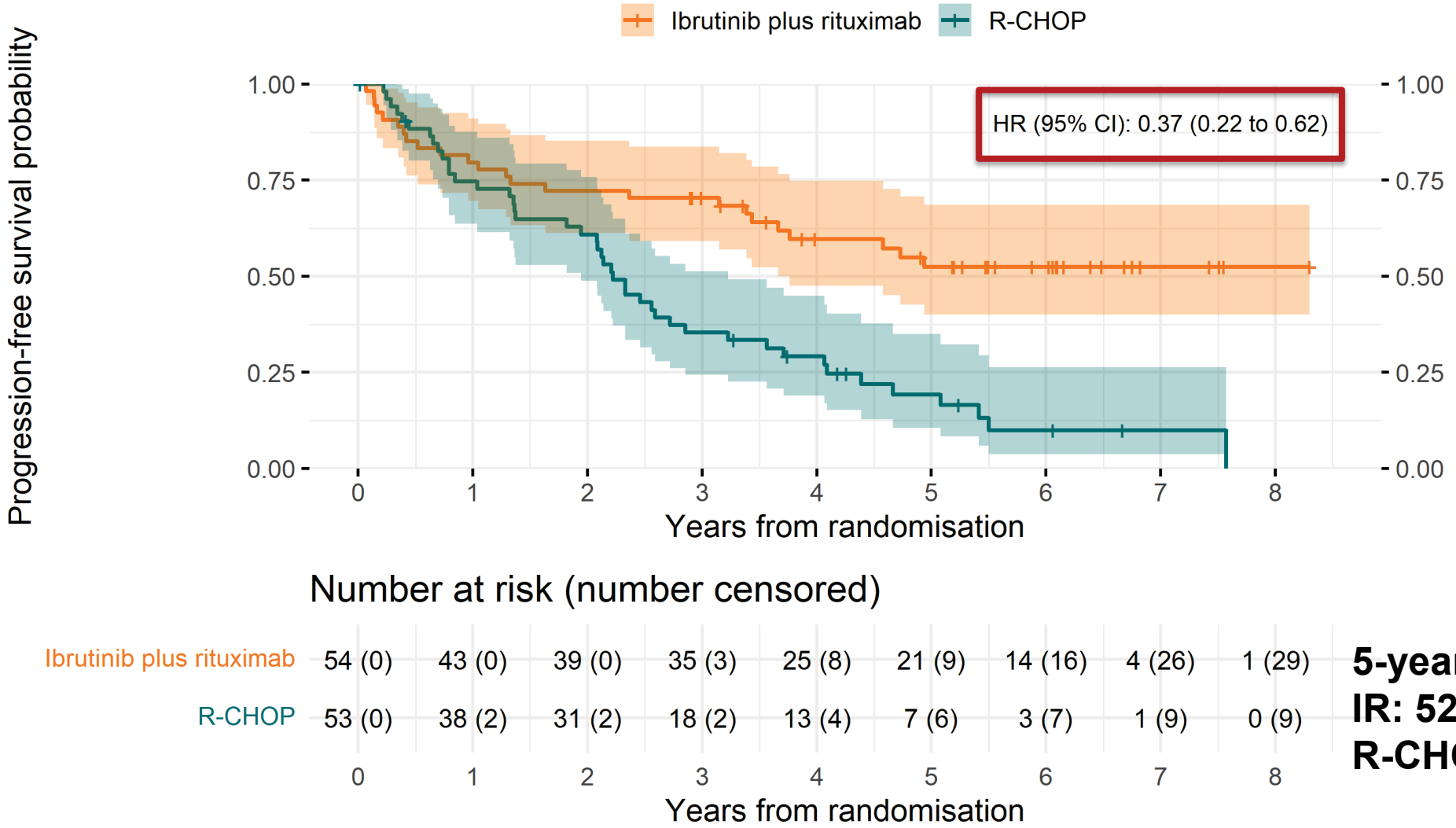
Progression-free survival



Median Follow up
47.9 months

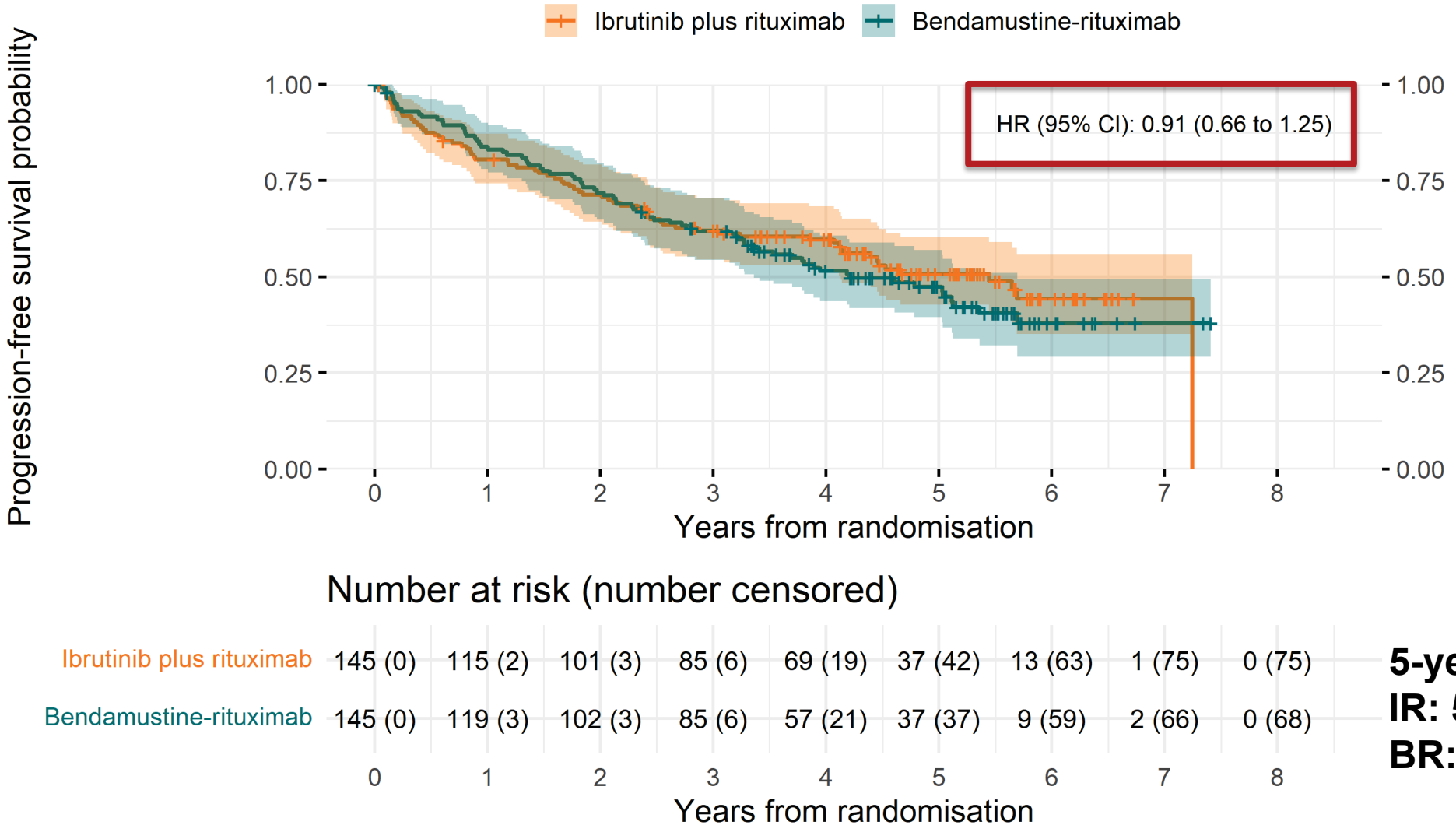
PFS median (95% CI)
IR: 65.3 mo (52.7 to not evaluable)
R-chemo: 42.4 mo (32.7 to 55.3)

PFS for R-CHOP choice



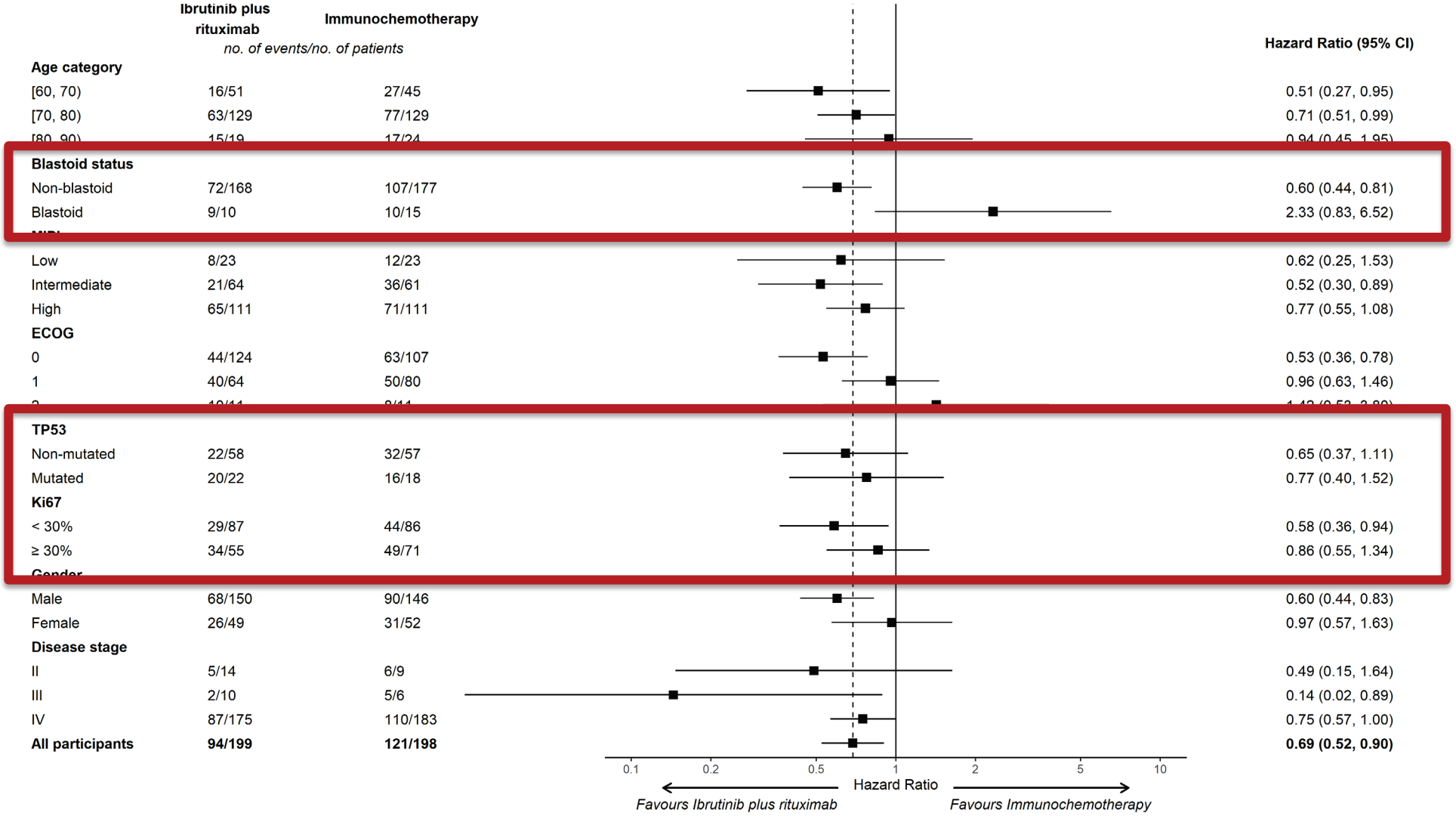
5-year PFS (95% CI)
IR: 52.4% (40.0% to 68.6%)
R-CHOP: 19.2% (10.6% to 35.1%)

PFS for BR choice



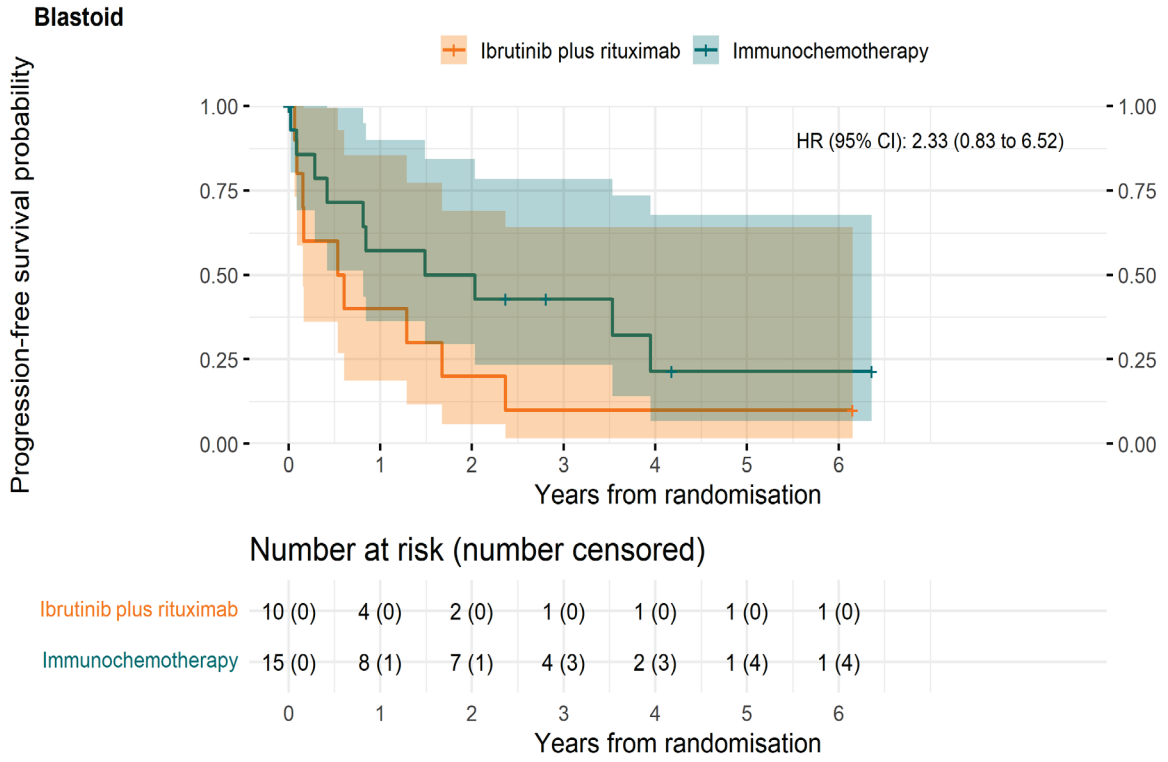
5-year PFS (95% CI)
IR: 50.8% (42.8% to 60.4%)
BR: 47.4% (39.5% to 56.9%)

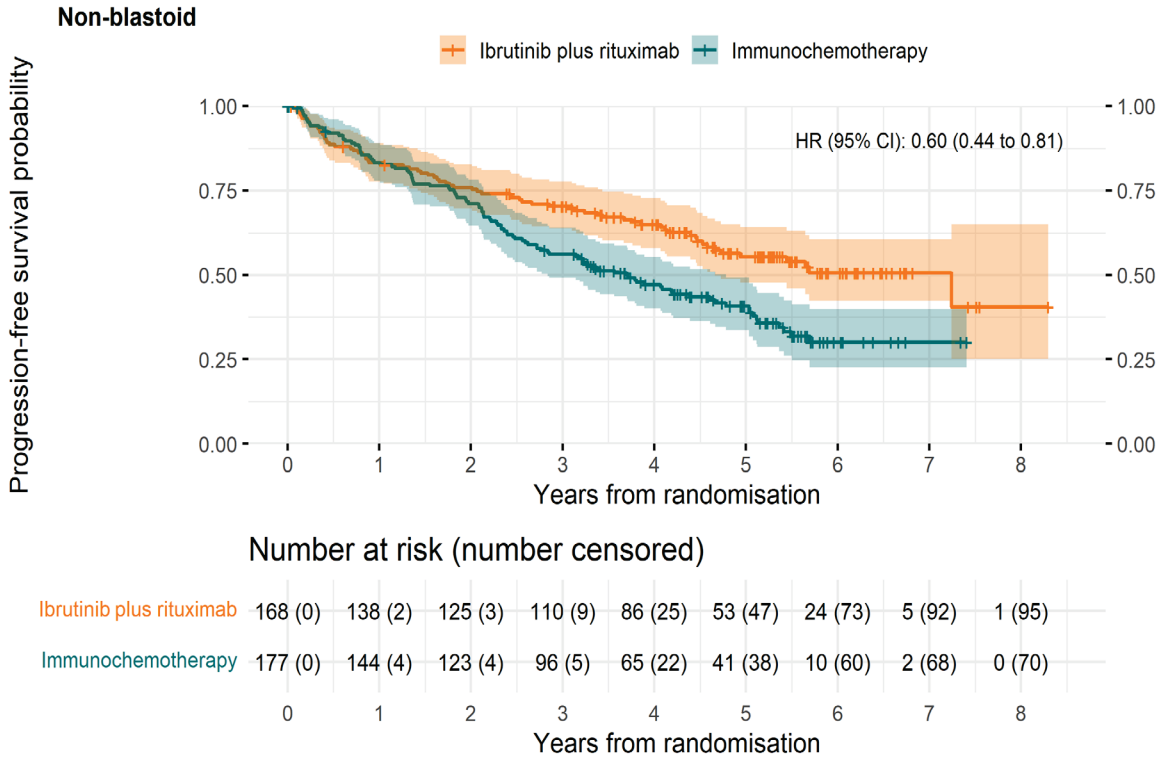
Progression-free survival subgroups



Blastoid disease

Suggestion of inferior PFS for blastoid disease for those randomised to IR

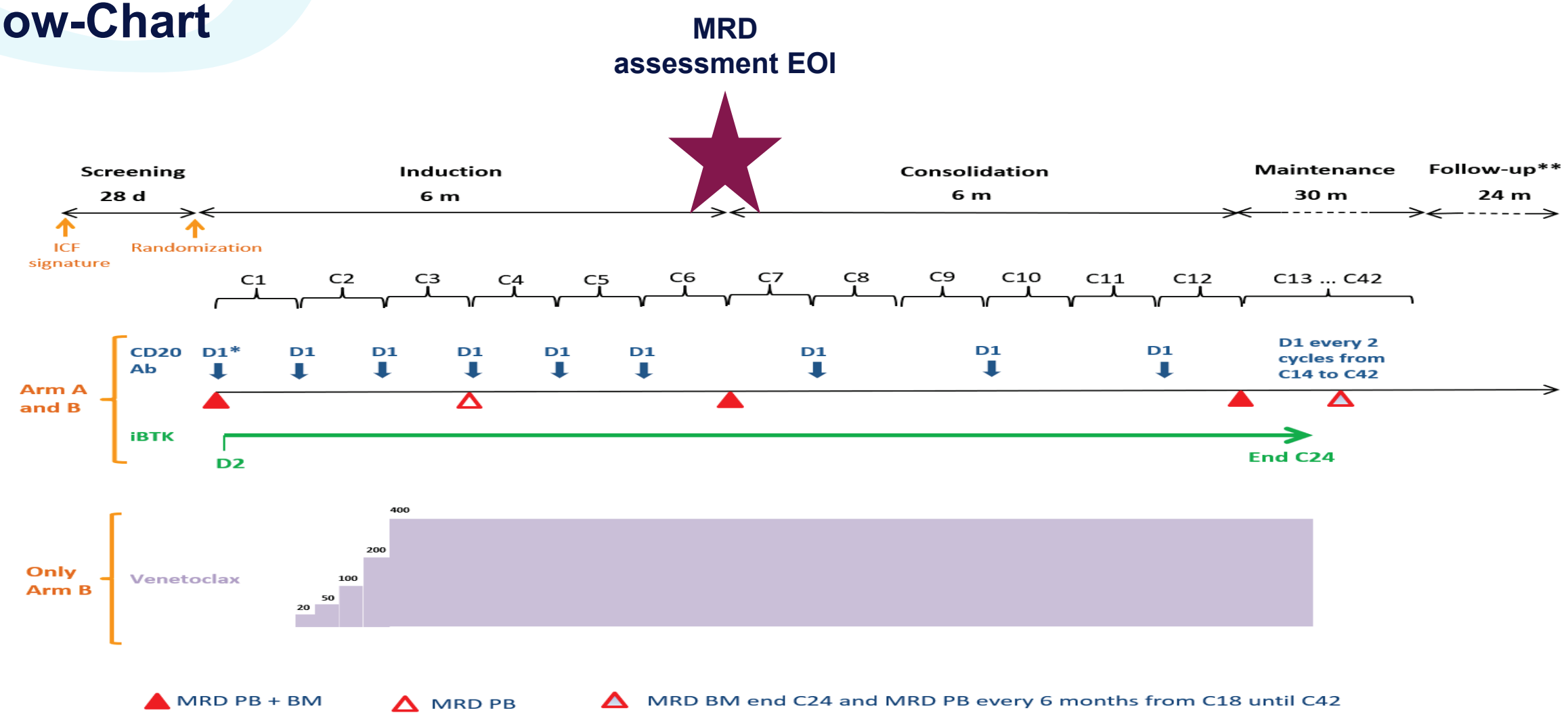




Blastoid subgroup (n=25) PFS 6.9 (95% CI 1.9 to NE) months for IR vs 21.1 (95% CI 9.8 to NE) months for immunochemotherapy)

HR 2.33, 95% CI 0.83 to 6.52

Flow-Chart



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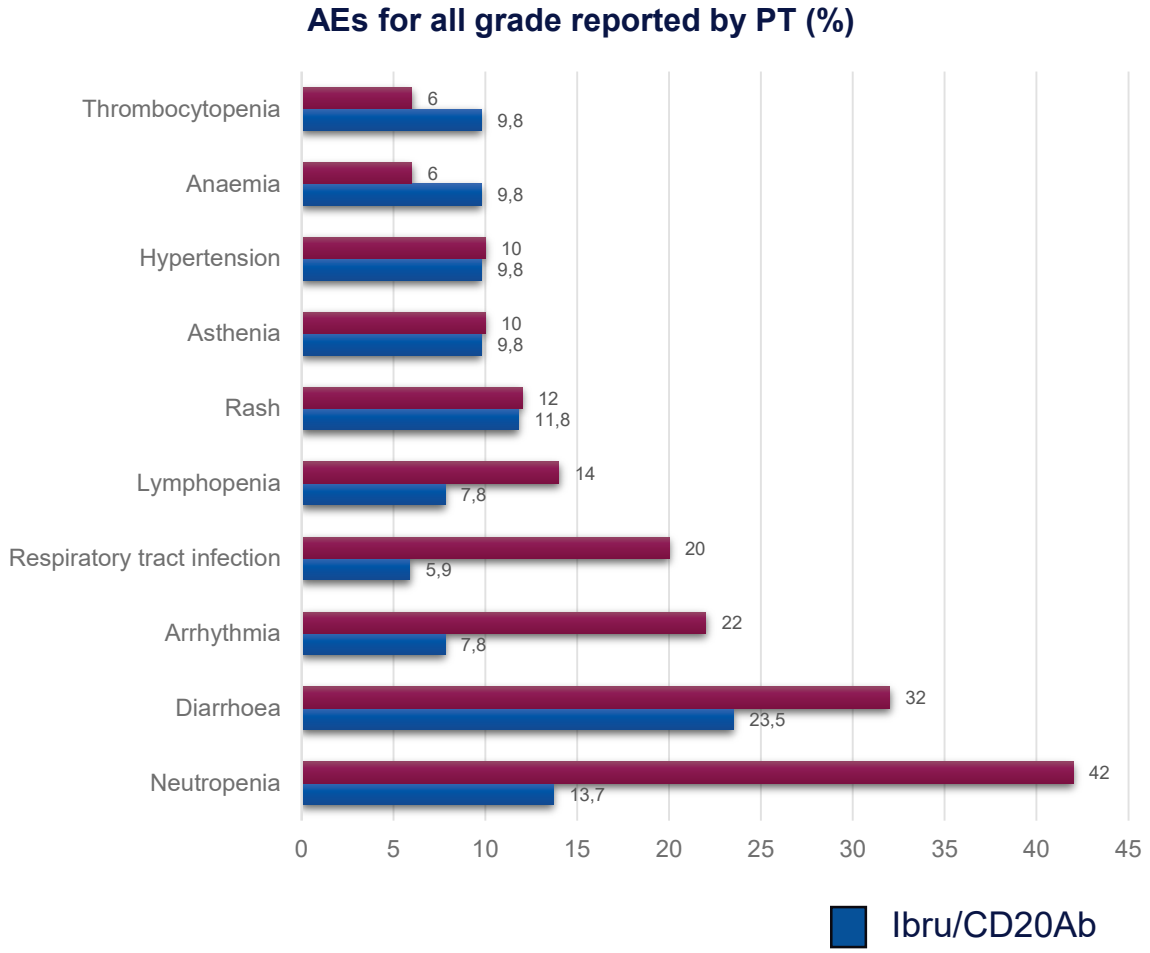
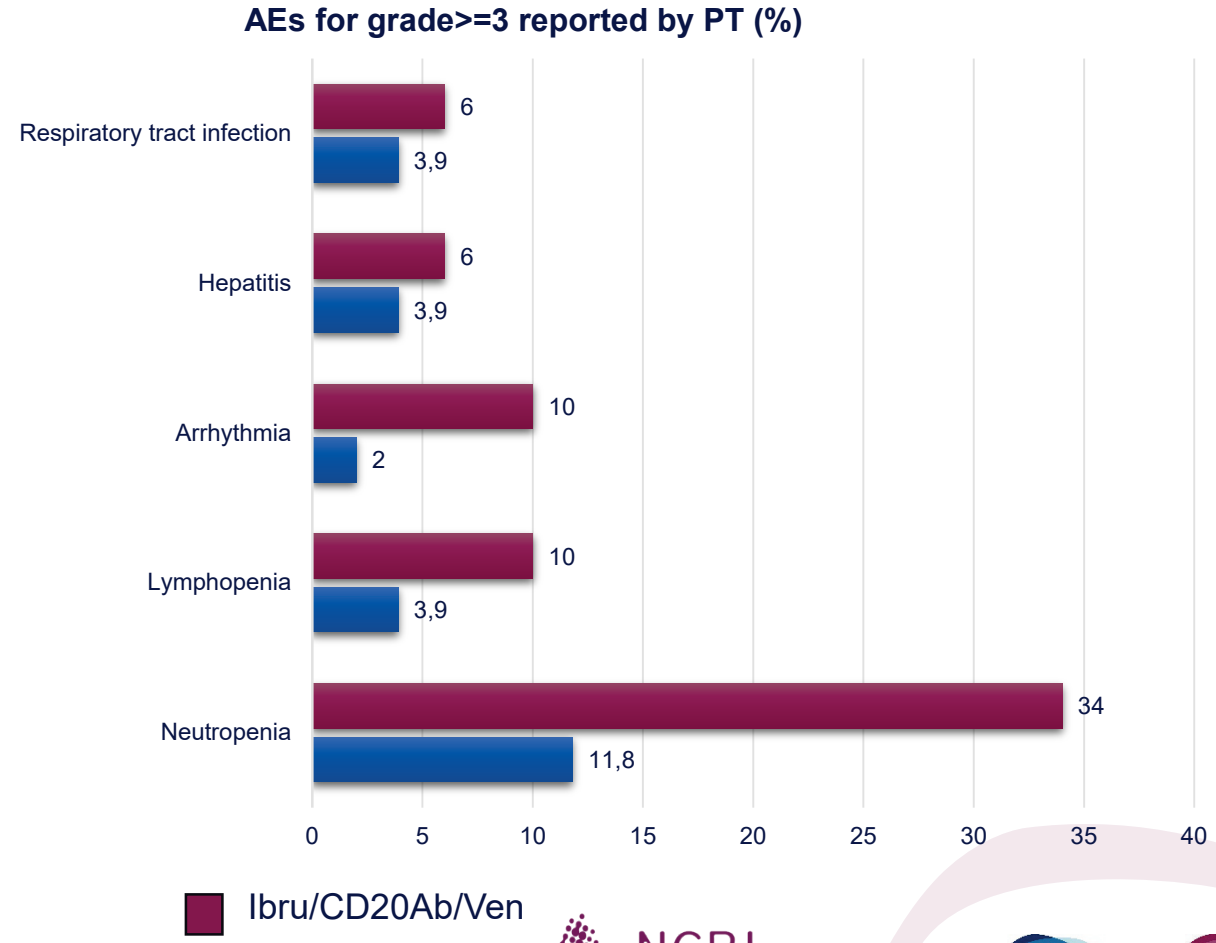
Safety evaluation – Most frequent AE (n=101)





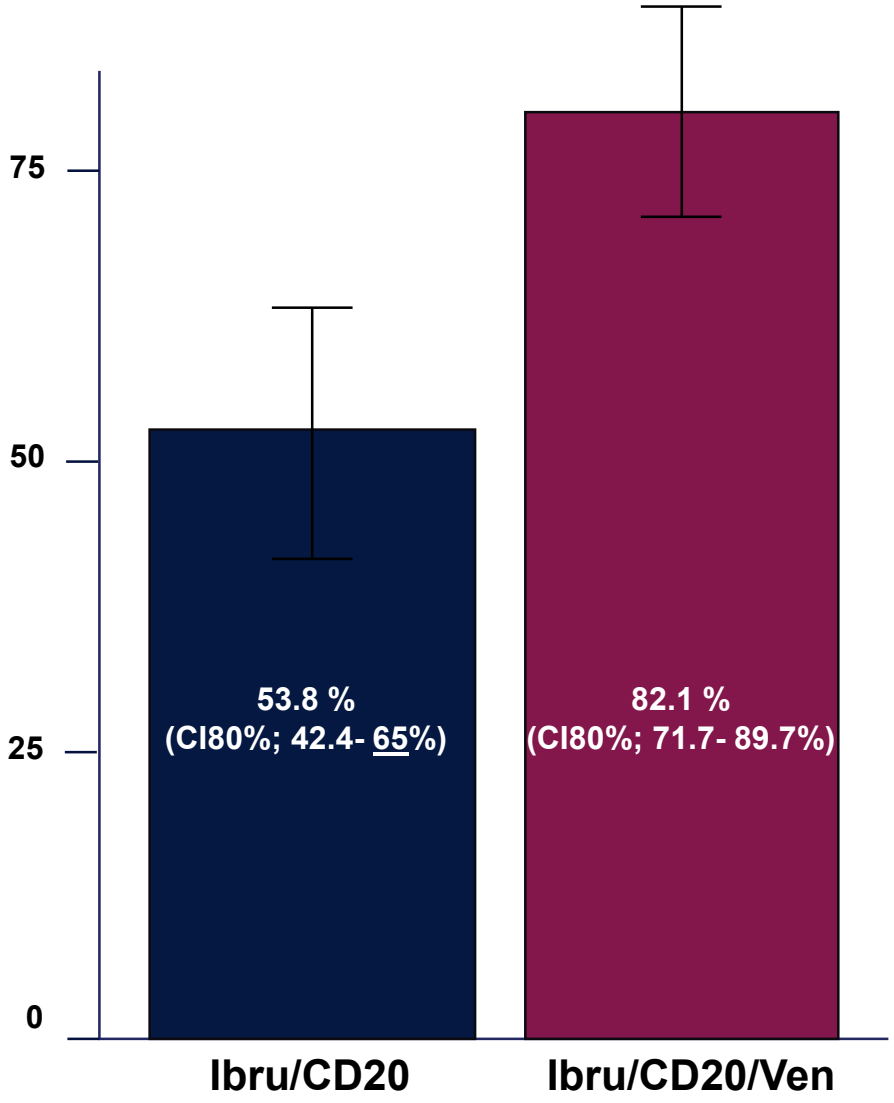
NCRI National Cancer Research Institute

Lysa Lysarc

Le Gouill et al abstract #745 , San-Diego, ASH 2024

MRD Negativity at End of Induction (Primary Efficacy Endpoint) (n=39)

- MRD negativity rate assessed by ddPCR at the end of induction (after C6)
- N=39 in each arms



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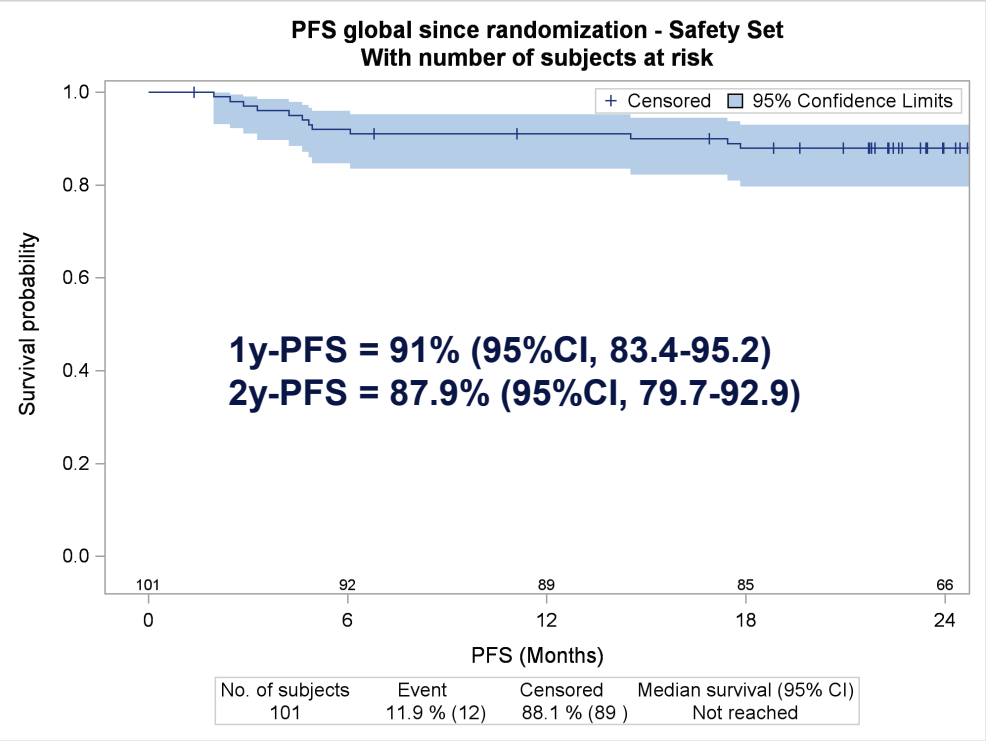
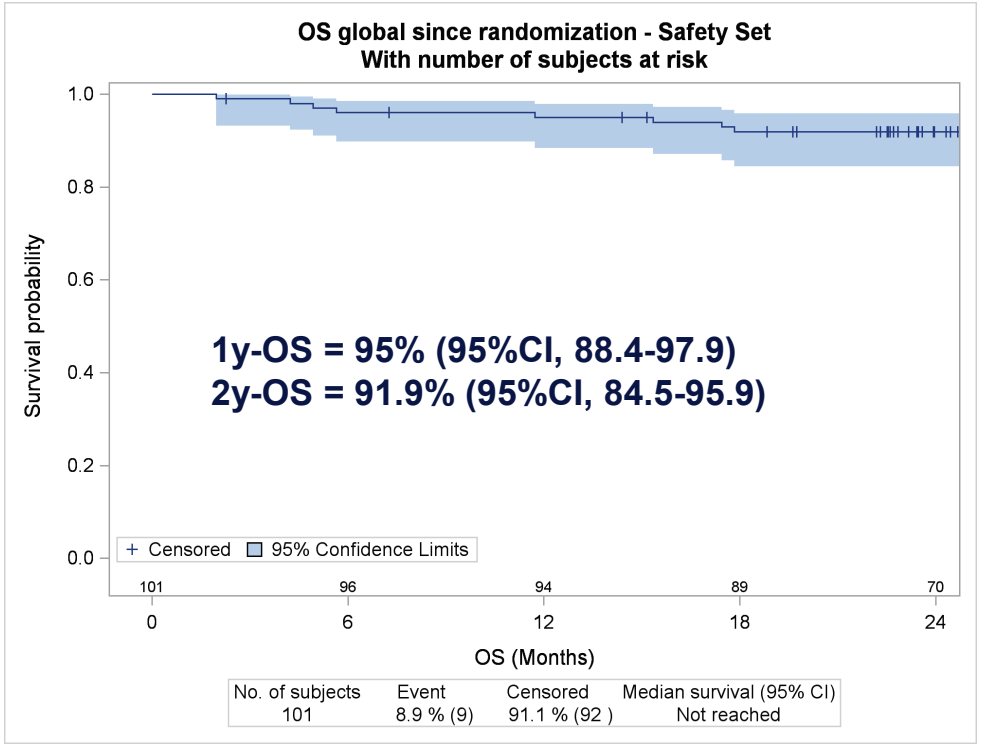
Secondary Efficacy Endpoints (PFS, OS) (n=101)





Follow-up duration:

- Export date: 10NOV23: 13.5m (95%CI, 12.6 - 14.4)
- Export date: 21OCT24: 27m (95%CI, 25.6 - 27.7)

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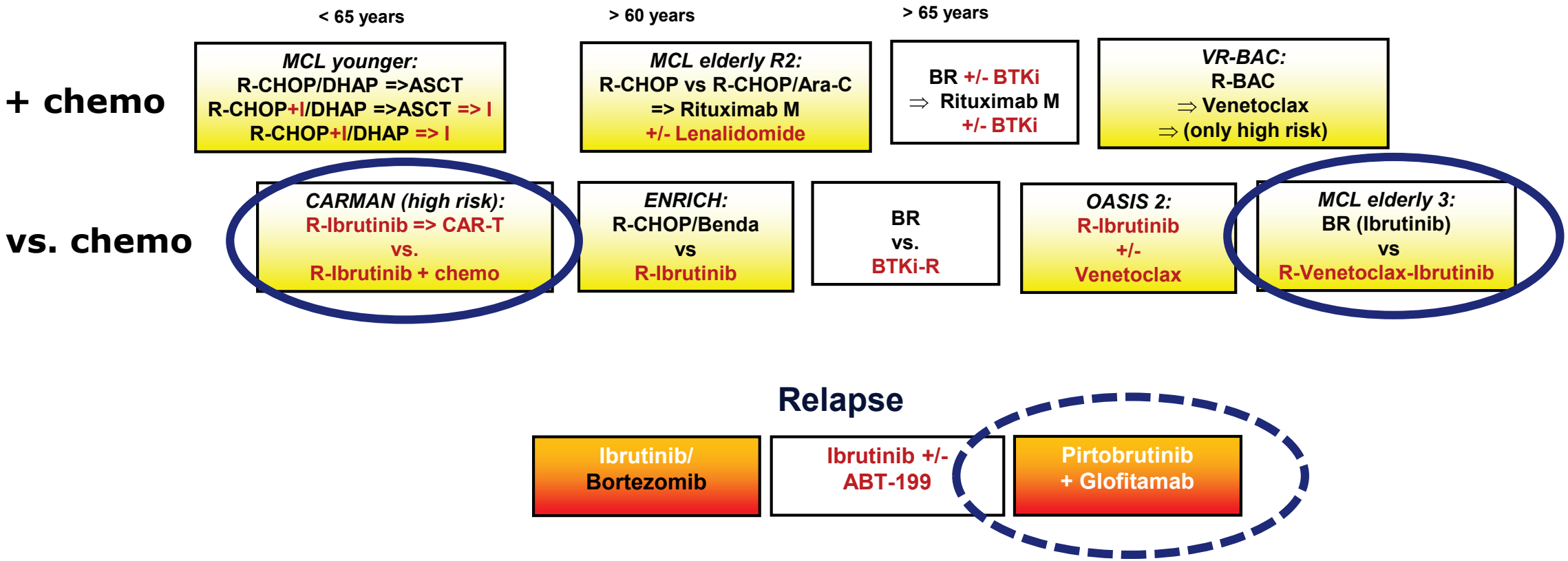
European MCL Network
Study generation 2024



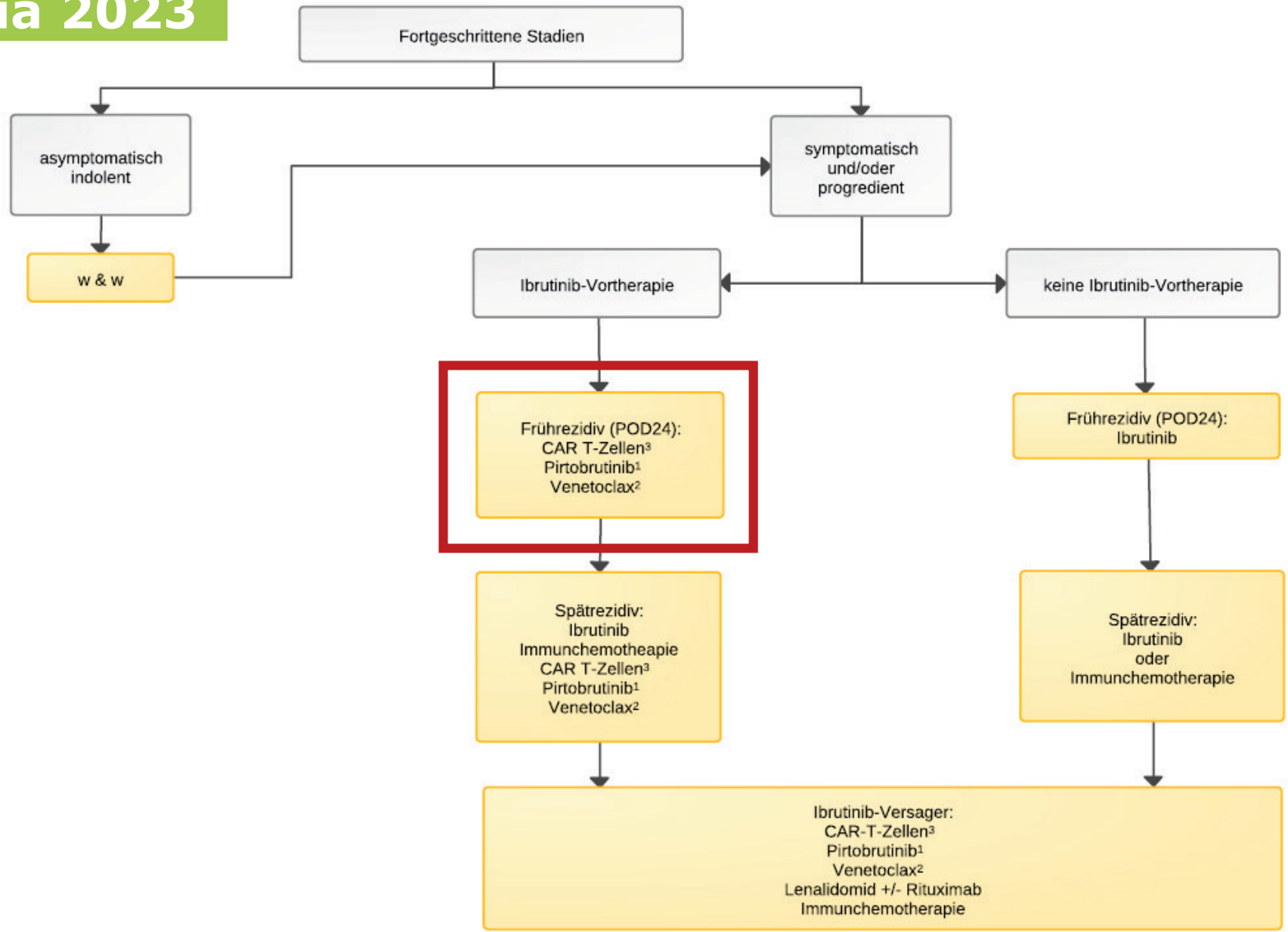
Kapitel 2

Rezidiertes Mantelzell-Lymphom:

Targeted Therapie

Relapsed Mantle cell Lymphoma

Onkopedia 2023



Primary Analysis of ZUMA-2 Cohort 3: Brexucabtagene Autoleucel in Patients With Relapsed/Refractory Mantle Cell Lymphoma Who Are Naive to Bruton Tyrosine Kinase Inhibitors

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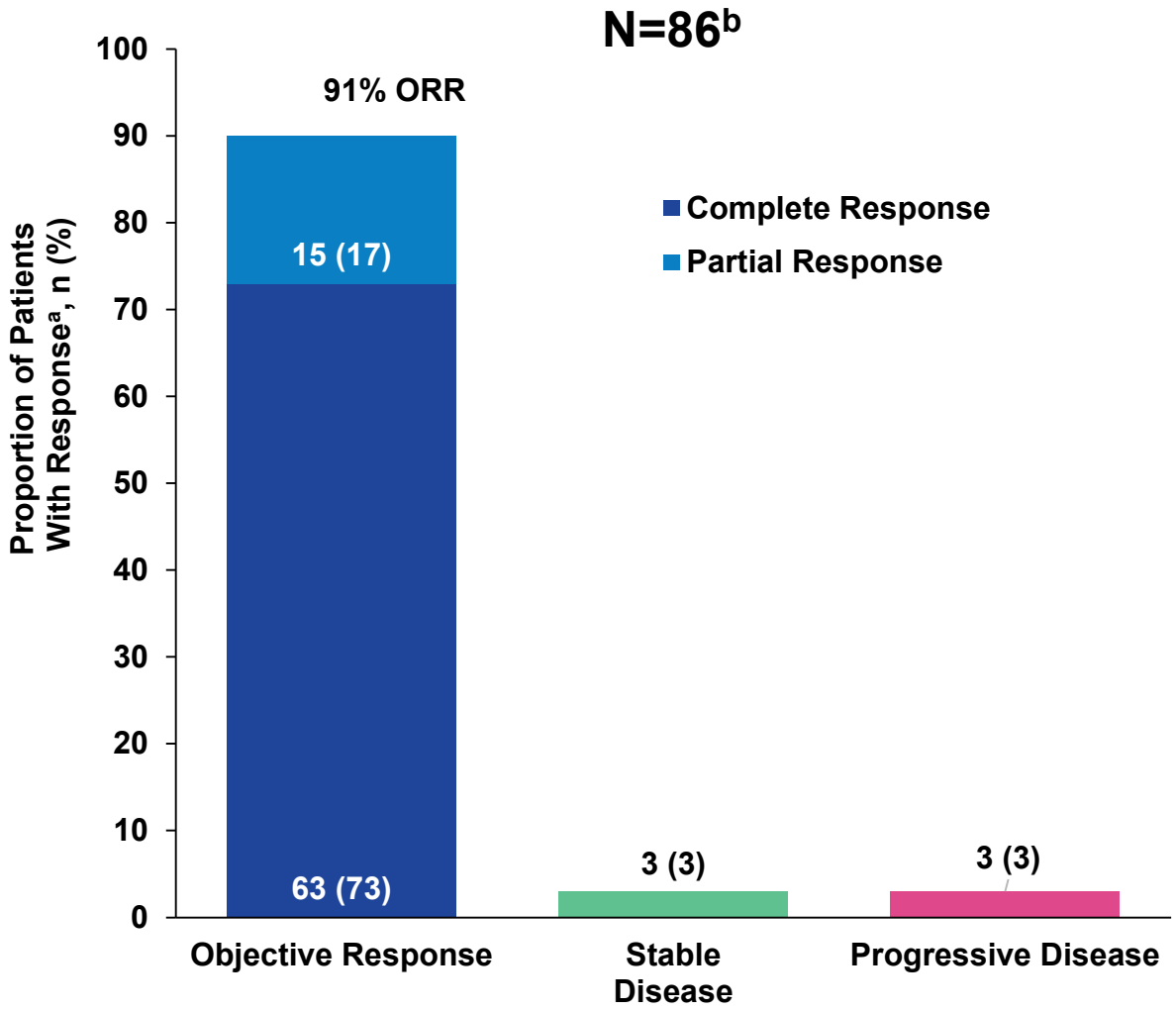
Best Objective Response

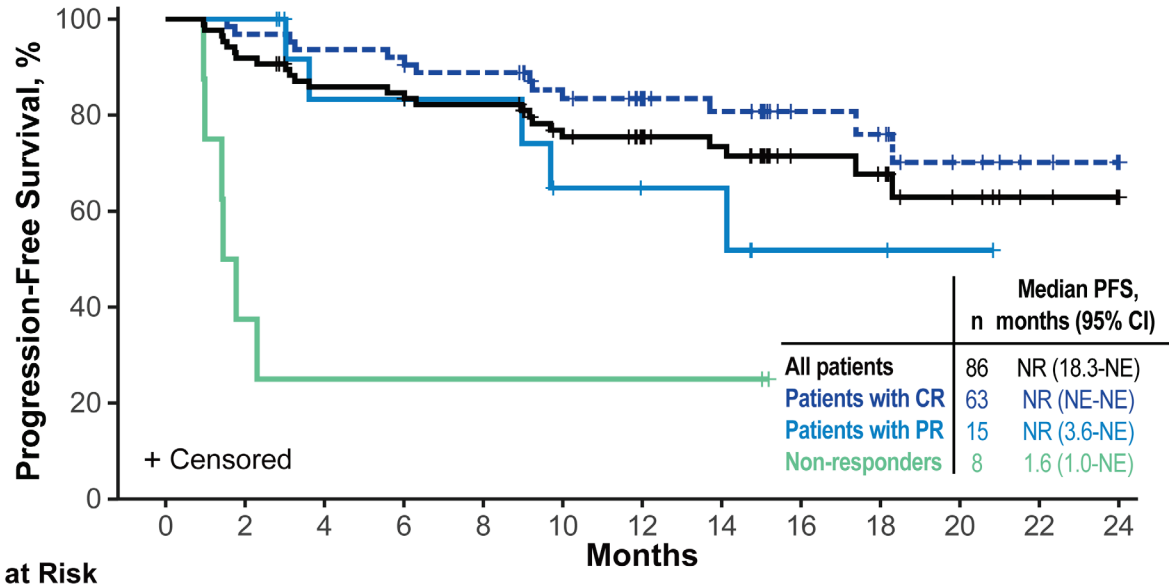


- The primary endpoint was met with an ORR of 91% (95% CI, 83-96), including a 73% CR rate
- High ORRs were observed across key subgroups of interest including:
  - 100% of patients with confirmed *TP53* mutations (n=15)
  - 97% of patients with ≥ the median tumor burden at baseline (38/39)
  - 94% of patients with Ki-67 scores of ≥50% (17/18)
  - 89% of patients with intermediate or high-risk sMIPI scores (56/63)
  - 83% of patients with prior bendamustine treatment (19/23)

[a] Per IRRC assessment. [b] Two patients were not assessable but included in N.
CR, complete response; IRRC, independent radiology review committee; ORR, objective response rate; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; TP53, tumor protein 53.

Progression-Free Survival and Overall Survival

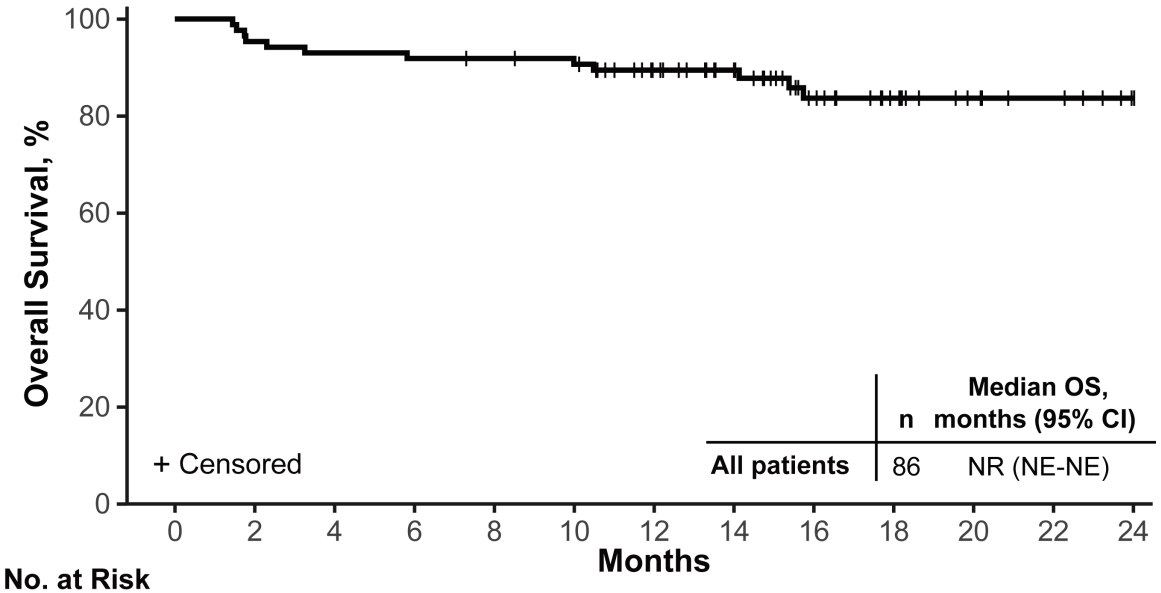
Progression-Free Survival[a]



No. at Risk

All patients	86	79	71	70	66	54	42	37	19	17	11	6	2
Pts. with CR	63	61	59	58	55	46	35	30	17	15	10	6	2
Pts. with PR	15	15	10	10	9	6	5	5	2	2	1	0	0
Non-responders	8	3	2	2	2	2	2	2	0	0	0	0	0

Overall Survival



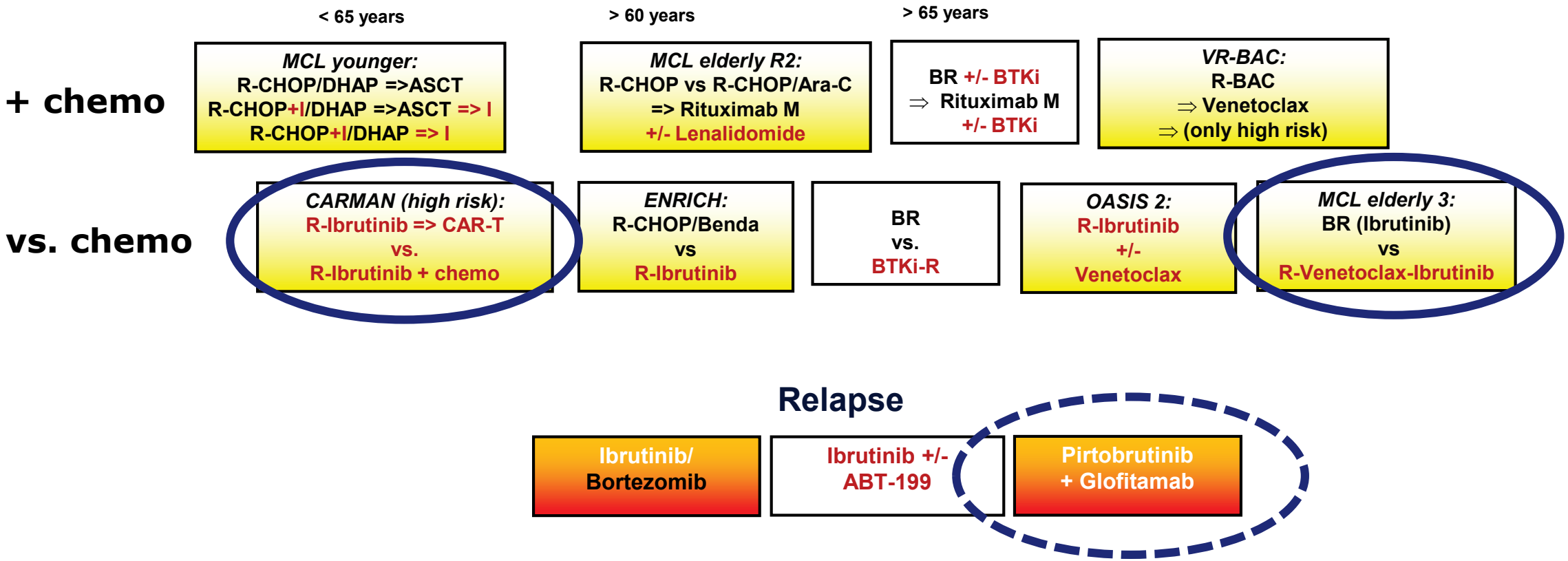
No. at Risk

All patients	86	82	80	79	78	76	64	54	37	25	16	13	6

- The 12-month PFS rates were 75% for all patients (N=86), 84% for those with CR (n=63), and 65% for those with PR (n=15)
- The 12-month OS rate was 90%, with 85% of patients (73/86) still alive at data cutoff

[a] Per IRRC assessment.
CR, complete response; IRRC, independent radiology review committee; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response; pts, patients.

European MCL Network
Study generation 2024



TRIALS IN PROGRESS: CARMAN - AN INTERNATIONAL, RANDOMIZED PHASE II STUDY EVALUATING EARLY TREATMENT INTENSIFICATION IN PATIENTS WITH HIGH RISK MANTLE CELL LYMPHOMA USING CAR-T-CELL TREATMENT AFTER AN ABBREVIATED INDUCTION THERAPY WITH RITUXIMAB AND IBRUTINIB AND 6 MONTHS IBRUTINIB MAINTENANCE (ARM A) AS COMPARED TO STANDARD OF CARE INDUCTION AND MAINTENANCE (ARM B)

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BACKGROUND

Mantle cell lymphoma (MCL) is a rare lymphoma subtype accounting for 8% of Non-Hodgkin lymphomas and is still considered incurable. Prognostic parameters such as TP53 alterations, high Ki-67 proliferation index, blastoid or pleomorphic morphologic characteristics and/or high-risk combined MCL International Prognostic Index (MIPI-c) are associated with poor outcome.

Chemoimmunotherapy and targeted therapies such as Bruton's tyrosine kinase inhibitors (BTKi) may induce remission in such high-risk patients, but early relapses frequently occur and actually there is an unmet need for improved treatment.

The anti-CD19 chimeric antigen receptor T-cell (CAR-T) product brexucabtagene autoleucel has demonstrated encouraging efficacy in relapsed or refractory aggressive MCL, failing to previous BTKi therapy after up to 5 prior regimens. However, restricting CAR-T cell therapy to subsequent treatment lines increases the risk of disease evolution causing potentially limited treatment efficacy.

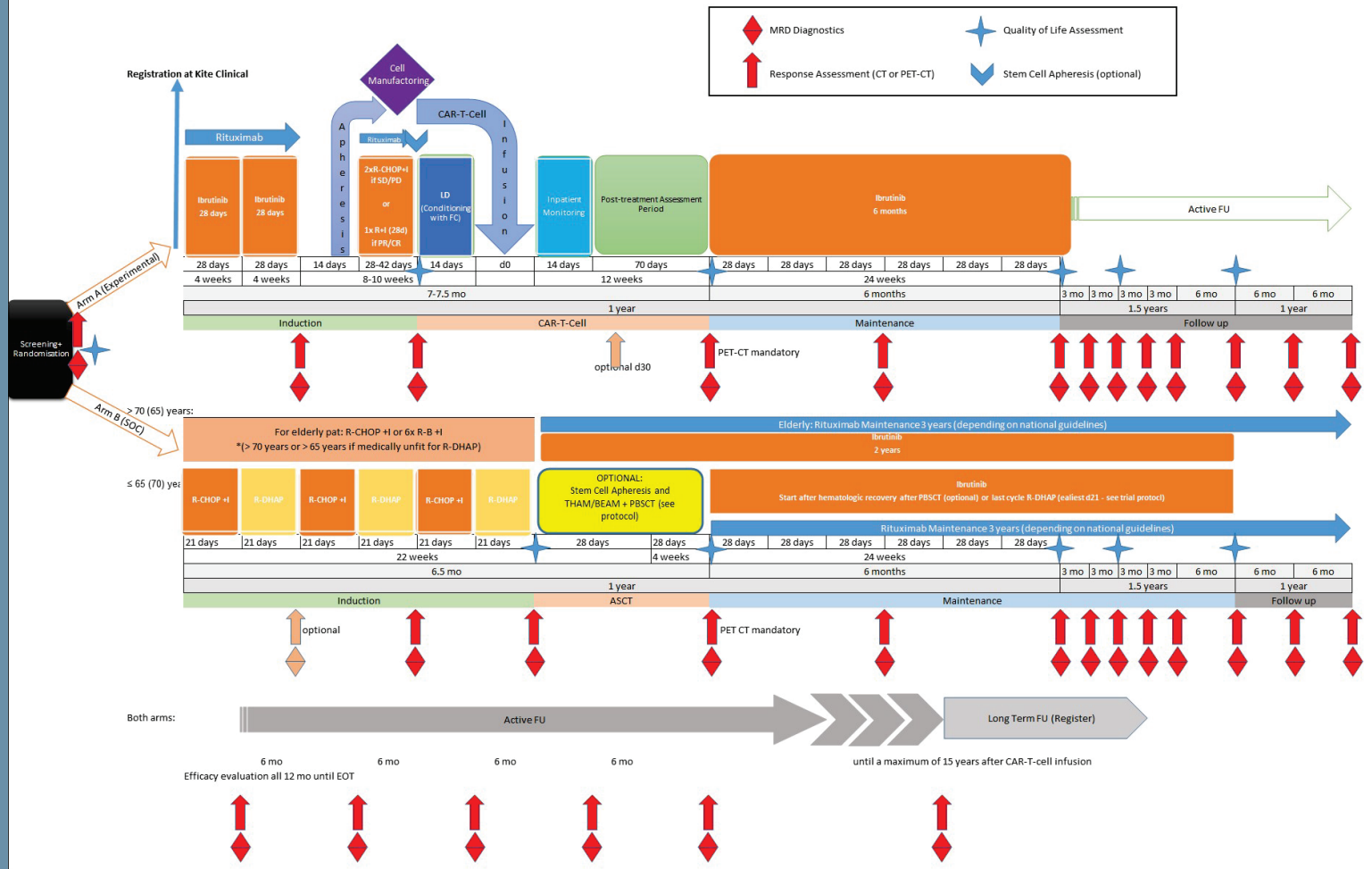
Thus, applying CAR T cells in first line, targeting more susceptible malignant cells, seems reasonable. The combination with Ibrutinib is likely to induce synergistic effects with CAR-T-cells by increasing the viability and expansion of T-cells while inhibiting T-cell exhaustion.

STUDY DESIGN

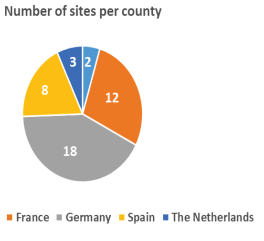
This is a **randomized controlled, international, multicenter, open-label phase II trial** of the European Mantle Cell Lymphoma (EMCL) Network.

CARMAN explores early treatment intensification through the integration of brexucabategene autoleucel into the **first line treatment** of **high-risk**

TREATMENT REGIMEN



- **Arm A:** abbreviated induction (3 cycles of Ibrutinib + Rituximab (IR) and 2 cycles of Ibrutinib + R-CHOP in patients not achieving at least a PR to IR), and 6 months Ibrutinib maintenance starting 3 months post CAR-T-treatment
- **Arm B**: Patients **≤ 65y** will receive 3 cycles R-CHOP+Ibrutinib/ 3 cycles R-DHAP alternating, optionally followed by ASCT if appropriate and Ibrutinib/Rituximab maintenance.
- Patients **≥65y** will receive 6 cycles of Bendamustine and Rituximab + Ibrutinib or R-CHOP + Ibrutinib without ASCT) and 2 years maintenance with Ibrutinib with or without Rituximab maintenance, according to national guidelines
- The maximum duration of the study will be 7 years, with up to 2 years recruitment, 2.5 years of treatment (Arm B) and up to 2.5 years additional follow-up.
- Primary endpoint: FFS from randomization to stable disease or progressive disease after end of induction, or death from any cause.
- **150 patients** in about **40 sites** in **5 countries** are planned, see below:



Studientreffen 2024, München

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2024

Für den Inhalt verantwortlich:

Prof. Dr. med. Martin Dreyling

Klinikum der Universität München

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