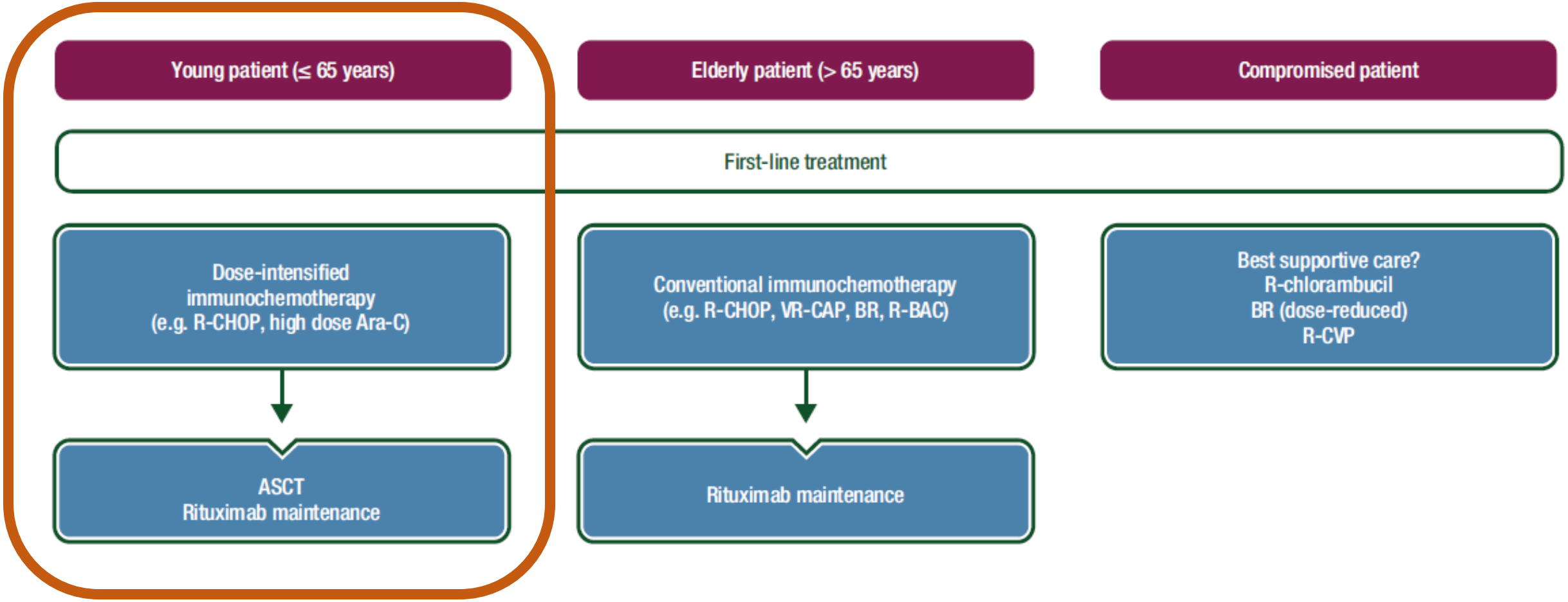
Advances in frontline therapy in mantle cell lymphoma

Mats Jerkeman, Lund, Sweden

ESMO clinical practice guidelines for MCL



* NEWLY DIAGNOSED AND RELAPSED MANTLE CELL LYMPHOMA: ESMO CLINICAL PRACTICE GUIDELINES, Published in 2017 – Ann Oncol (2017) 28 (suppl 4): iv62–iv71

Authors: *M. Dreyling, E. Campo, O. Hermine, M. Jerkeman, S. Le Gouill, S. Rule, O. Shpilberg, J. Walewski and M. Ladetto*

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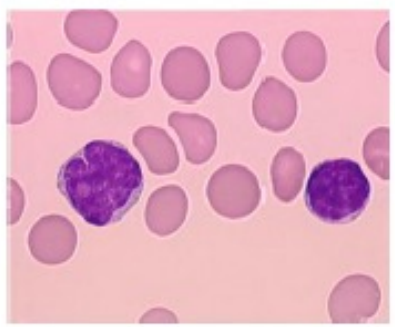
TRIANGLE:

AUTOLOGOUS TRANSPLANTATION AFTER A RITUXIMAB/IBRUTINIB/ARA-C CONTAINING INDUCTION IN GENERALIZED MANTLE CELL LYMPHOMA – A RANDOMIZED EUROPEAN MCL NETWORK TRIAL



M Dreyling, J Doorduijn, E Giné, M Jerkeman, J Walewski, M Hutchings, U Mey, J Riise, M Trneny, V Vergote, M Celli, O Shpilberg, M Gomes da Silva, S Leppa, L Jiang, C Pott, W Klapper, D Gözel, C Schmidt, M Unterhalt, M Ladetto*, E Hoster*

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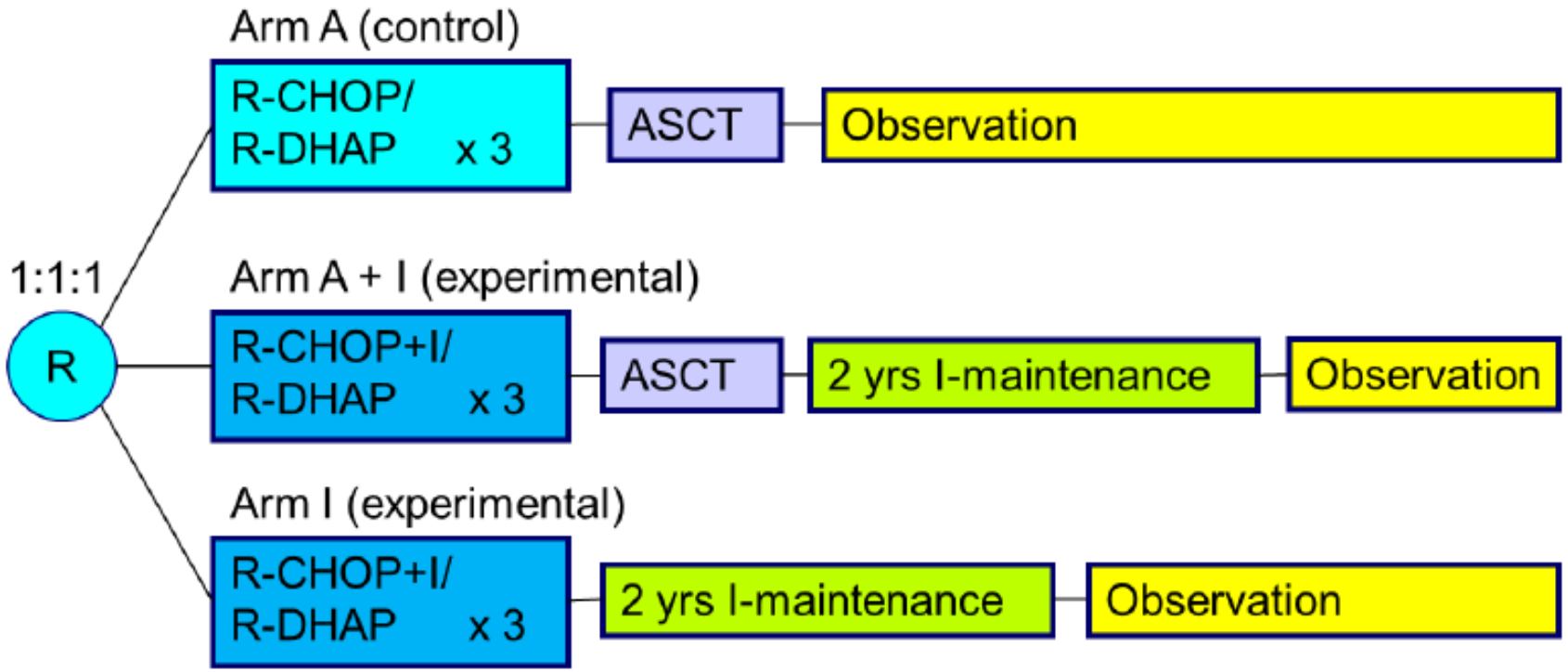
TRIANGLE: Trial Design

- 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.

TRIANGLE: Baseline Characteristics

Characteristic	overall (n=870)	A (n=288)	A+I (n=292)	I (n=290)
Median age, years (range)	57 (27-68)	57 (31-65)	57 (36-68)*	58 (27-65)
Male sex	76%	76%	74%	79%
No MCL	8 (1%)	2 (CLL, FL)	4 (1 NHL NOS, 1 HD, 2 MZL)	2 (HCL, DLBCL)
Ann Arbor Stage (n=864)				
I	0%	0%	0%	0%
II	5%	4%	4%	6%
III	9%	8%	7%	10%
IV	87%	88%	89%	84%
ECOG > 1	1%	2%	1%	2%
MIPI Low	58%	58%	58%	58%
MIPI Intermediate	27%	27%	27%	27%
MIPI High	15%	14%	15%	16%

* 2 patients aged 66/68 randomized

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

TRIANGLE: Response at End of Induction

	Overall	A	A+I/I	A+I	I
ED	2 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	0 (0%)
PD	17 (2%)	11 (4%)	6 (1%)	3 (1%)	3 (1%)
SD	7 (1%)	4 (1%)	3 (0.5%)	1 (0.4%)	2 (0.7%)
PR	458 (55%)	158 (58%)	300 (54%)	152 (54%)	148 (53%)
CR	347 (42%)	98 (36%)	249 (45%)	124 (44%)	125 (45%)
CR+PR	805 (97%)	256 (94%)	549 (98%)	276 (98%)	273 (98%)
Total	831	272	559	281	278
NE	29	11	18	8	10
ND	10	5	5	3	2

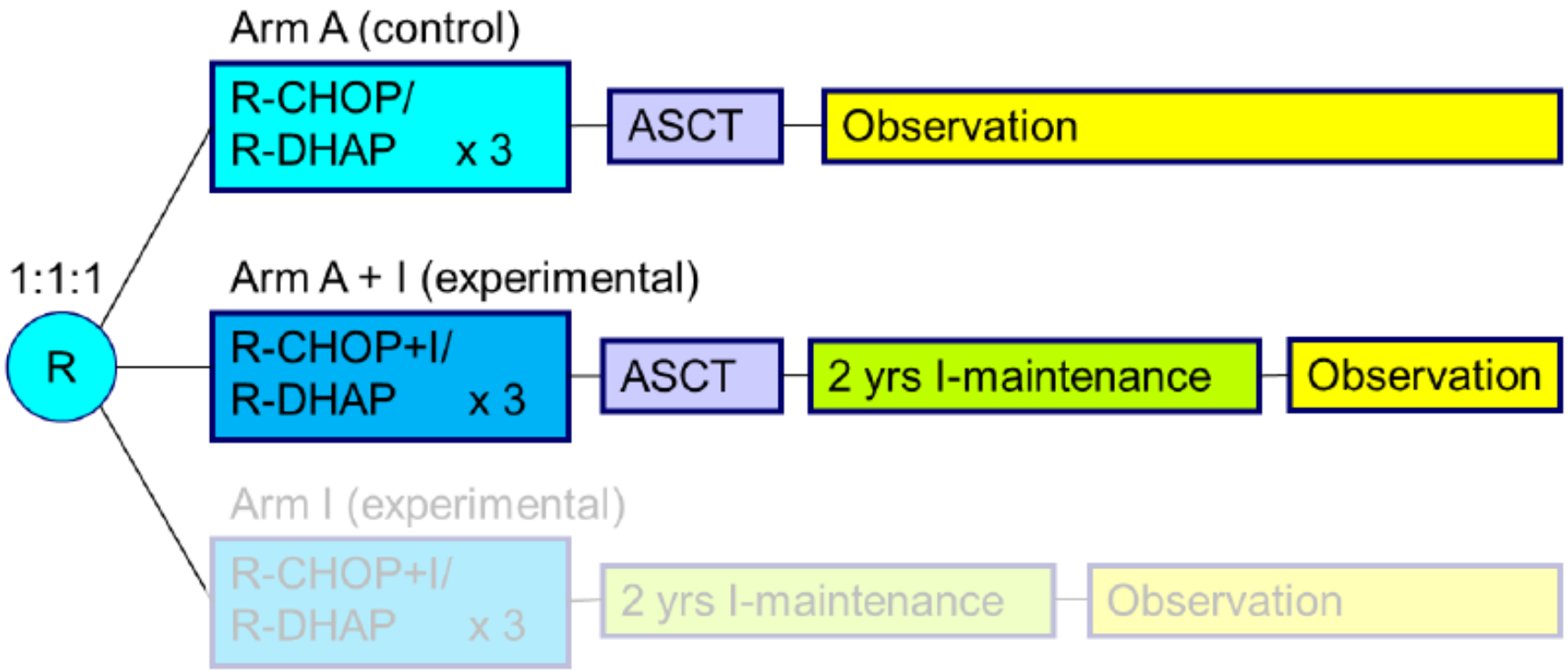
- CR- and OR-Rates significantly higher in the combined I induction (A+I/I) versus control (A) (CR: p=0.0203, OR: p=0.0025)
- MCL Younger R-CHOP/R-DHAP group: 38% (CR), 94% (OR)

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

TRIANGLE: Evaluation of primary endpoint FFS

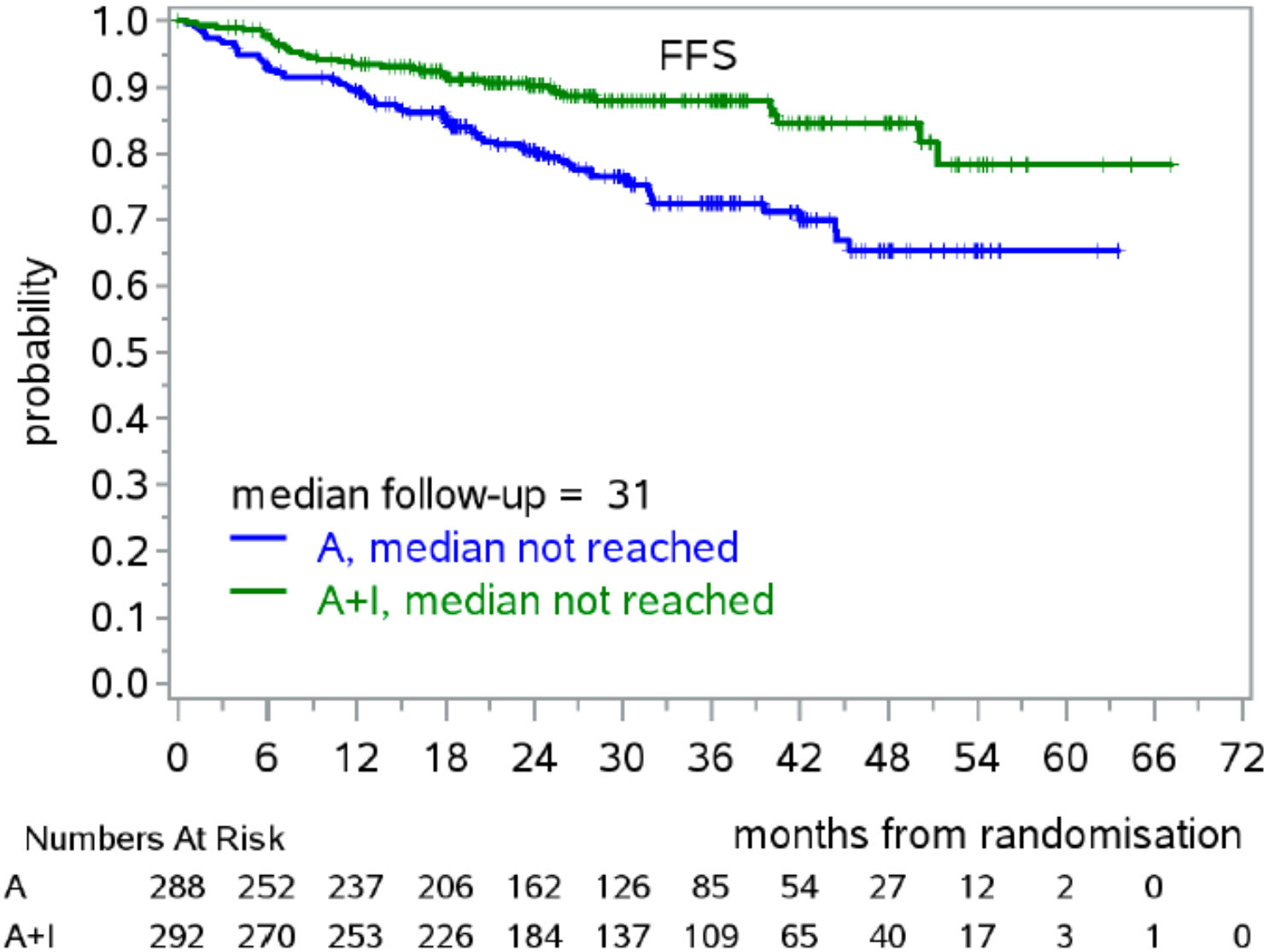
Test 1: FFS Superiority of A+I vs. A

- 90% power to detect HR of 0.60
- one-sided alpha 0.016665



All three hypotheses were monitored with regular sequential analyses to allow for early stop for efficacy or futility (truncated sequential probability ratio test, *Whitehead, 1985*)

TRIANGLE: FFS Superiority of A+I vs. A

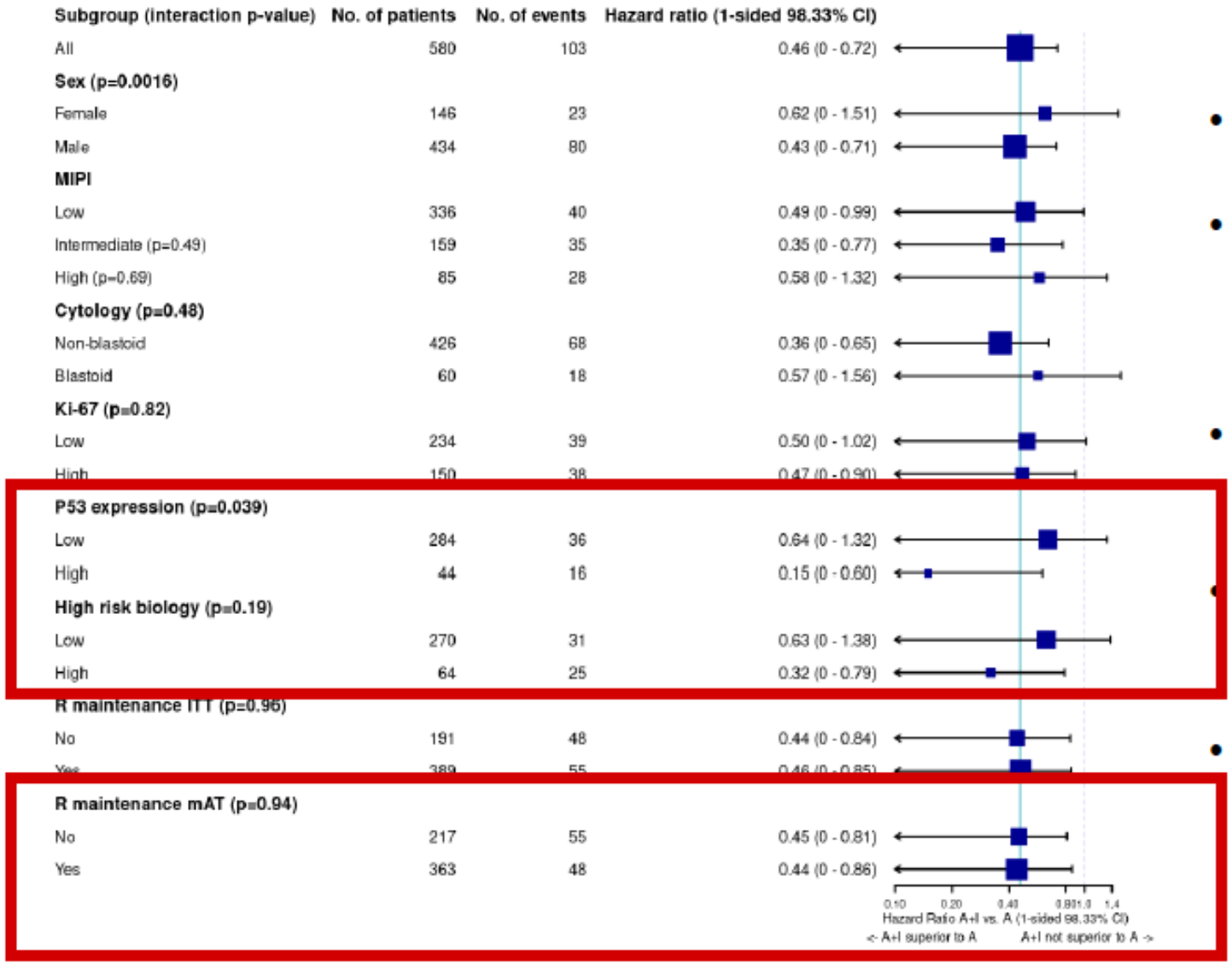


Numbers At Risk													
A	288	252	237	206	162	126	85	54	27	12	2	0	
A+I	292	270	253	226	184	137	109	65	40	17	3	1	0

- Superiority of A+I vs. A (FFS) is confirmed
- Kaplan-Meier plots:
  - 3-year FFS A+I: 88%
  - 3-year FFS A: 72%
- p-value (corrected for sequential design) p=0.0008
- HR (A+I vs. A): HR=0.52

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

TRIANGLE: FFS Superiority of A+I vs. A



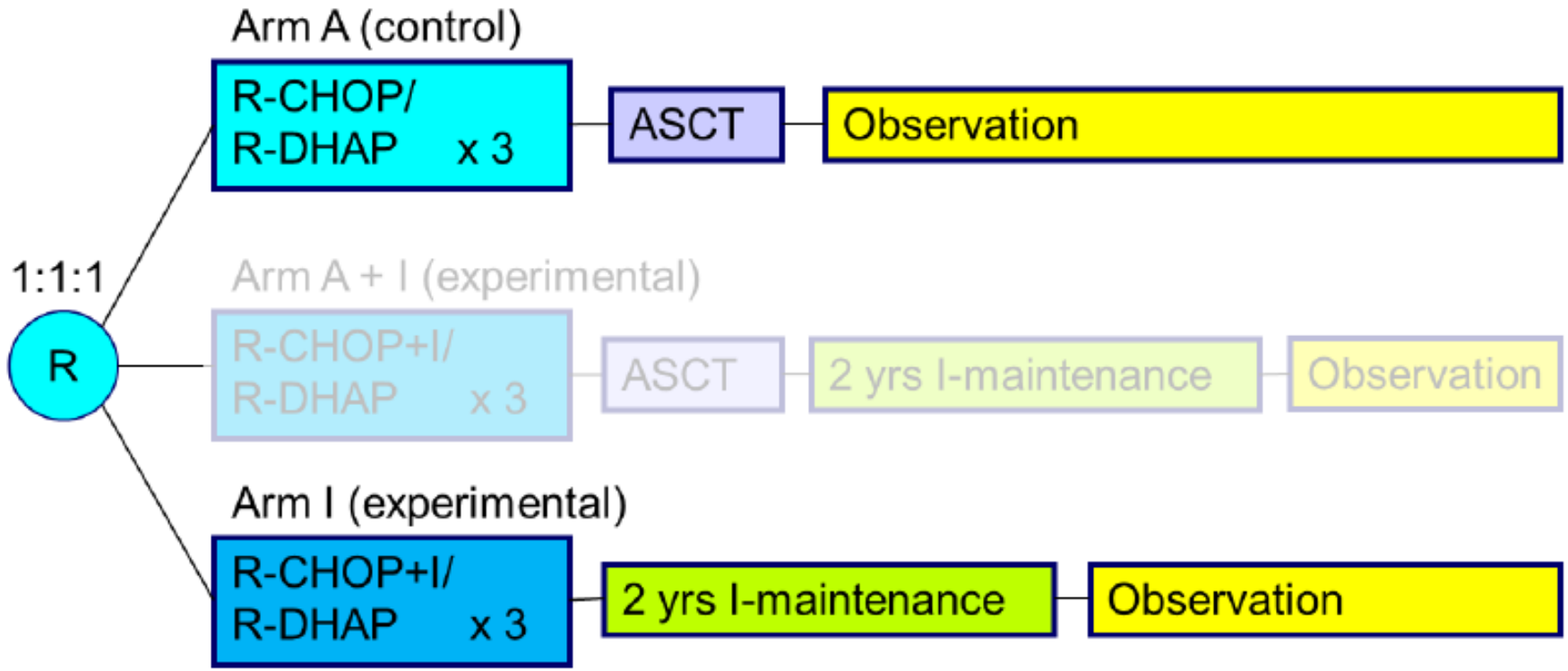
- similar in all MIPI groups
- No differential efficacy according to cytology and Ki-67
- More effective in high p53 expressors
- Trend toward higher efficacy in high risk biology
- No differential efficacy by rituximab maintenance

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

TRIANGLE: Evaluation of primary endpoint FFS

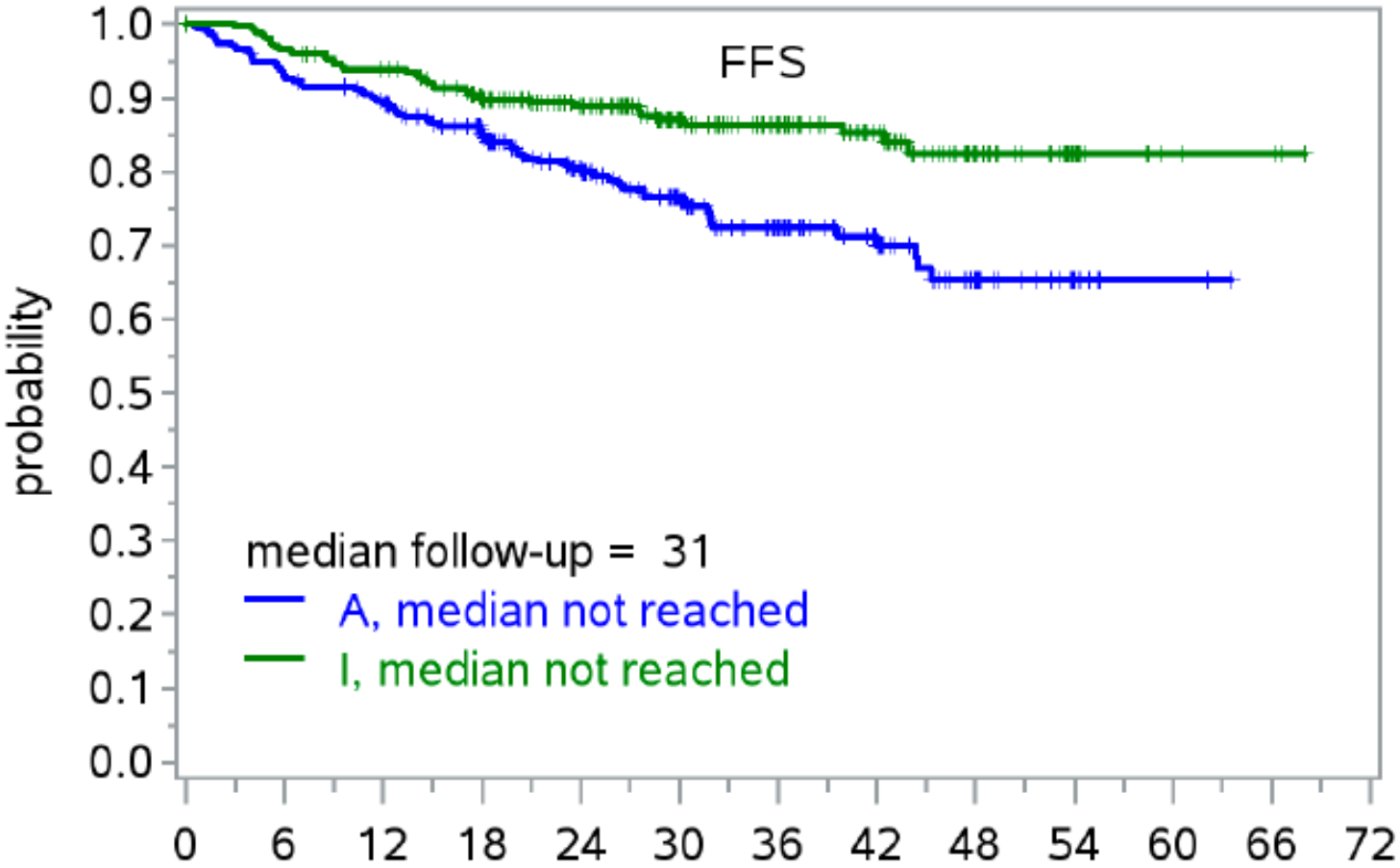
Test 2: FFS Superiority of A vs. I

- 95% power to detect HR of 0.60
- one-sided alpha 0.016665



All three hypotheses were monitored with regular sequential analyses to allow for early stop for efficacy or futility (truncated sequential probability ratio test, *Whitehead, 1985*)

TRIANGLE: No FFS Superiority of A vs. I



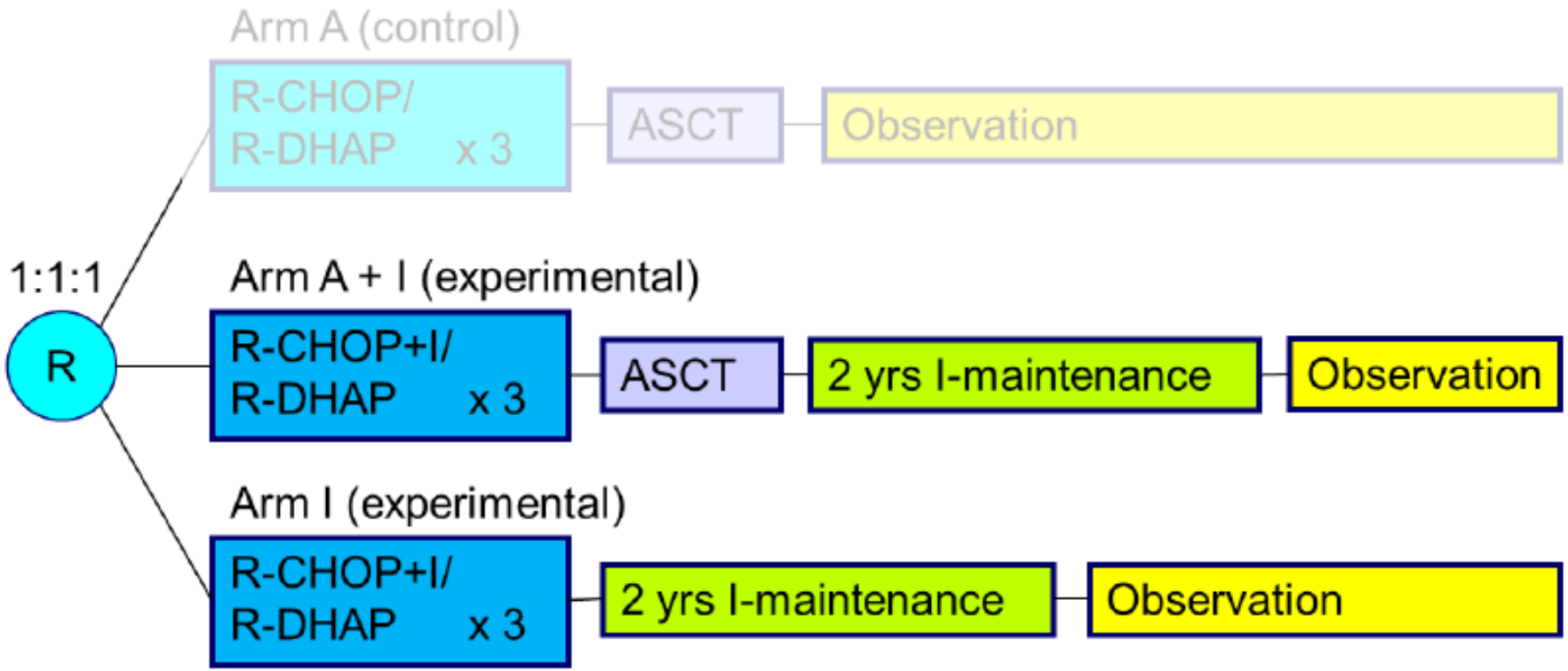
Numbers At Risk

A	288	252	237	206	162	126	85	54	27	12	2	0
I	290	269	257	229	180	133	100	68	34	16	4	3	0

- Superiority of A vs. I (FFS) was rejected
- Kaplan-Meier plots:
  - 3-year FFS A: 72% (MCL Younger: 75%)
  - 3-year FFS I: 86%
- p-value corrected for sequential design: p=0.9979
- HR (A vs. I): HR=1.77

A arm: R-CHOP/R-DHAP+ASCT; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

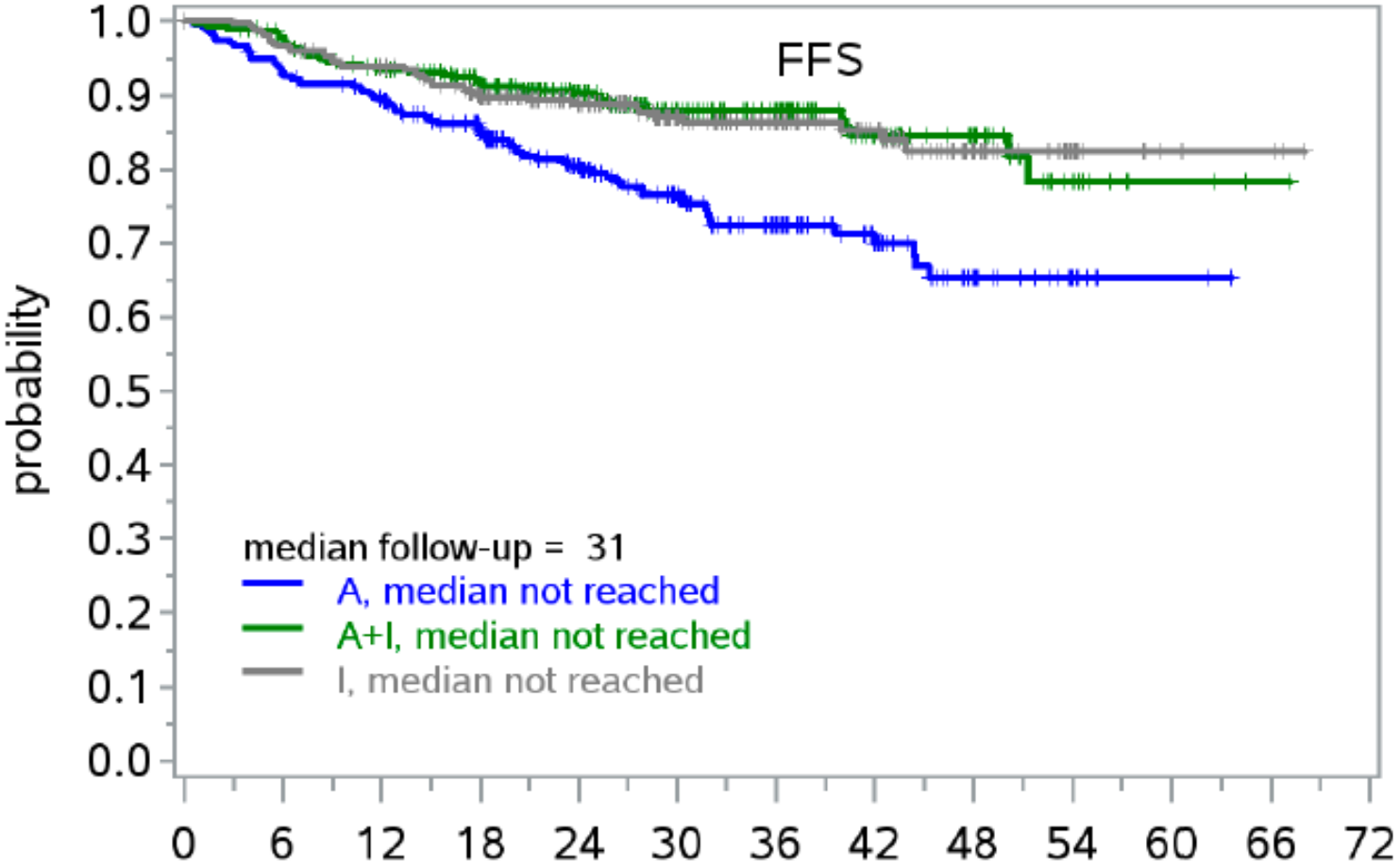
TRIANGLE: Evaluation of primary endpoint FFS



- Test 3: FFS Superiority of A+I vs. I
  - 90% power to detect HR of 0.60
  - one-sided alpha 0.016665

- All three hypotheses were monitored with regular sequential analyses to allow for early stop for efficacy or futility (truncated sequential probability ratio test, *Whitehead, 1985*)

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



Numbers At Risk

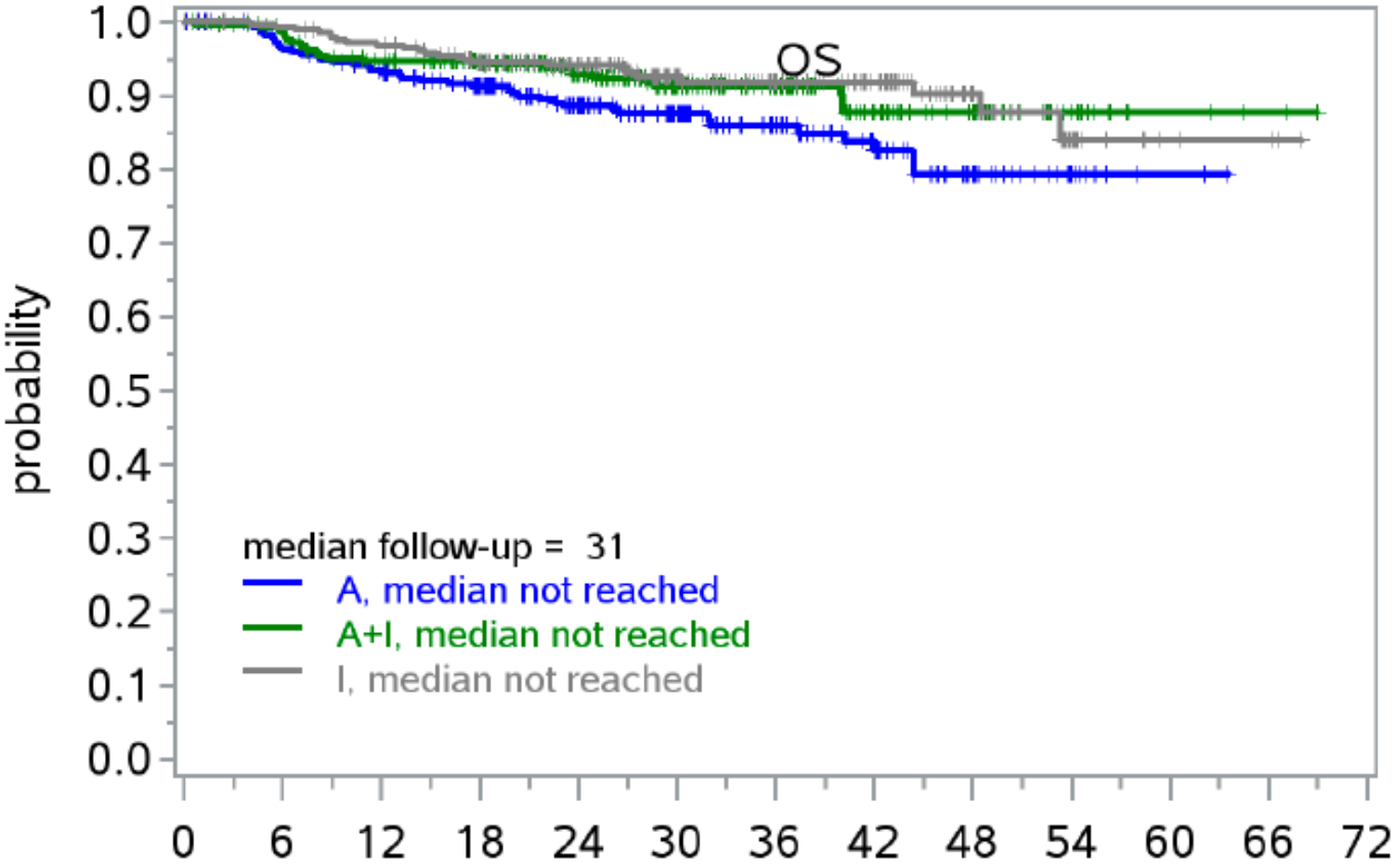
A	288	252	237	206	162	126	85	54	27	12	2	0
A+I	292	270	253	226	184	137	109	65	40	17	3	1
I	290	269	257	229	180	133	100	68	34	16	4	3

- Test A+I vs. I ongoing, no decision yet

Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	

A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

TRIANGLE: Overall survival



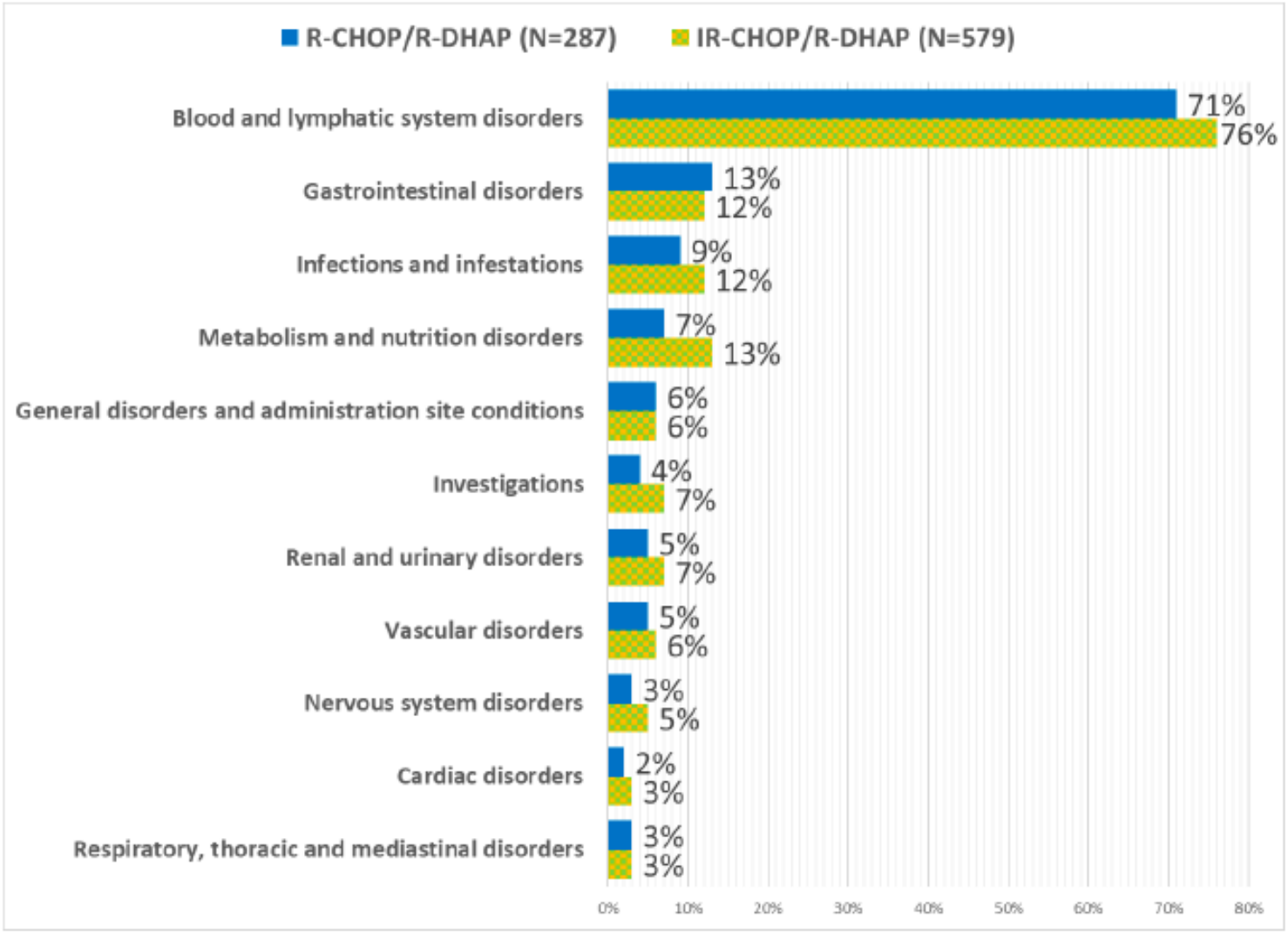
Numbers At Risk

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% (MCL Younger exp.: 84%)
  - A+I: 91%
  - I: 92%
- Too early to evaluate statistical significance

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

TRIANGLE: Grade 3-5 AEs (induction period; >2%)



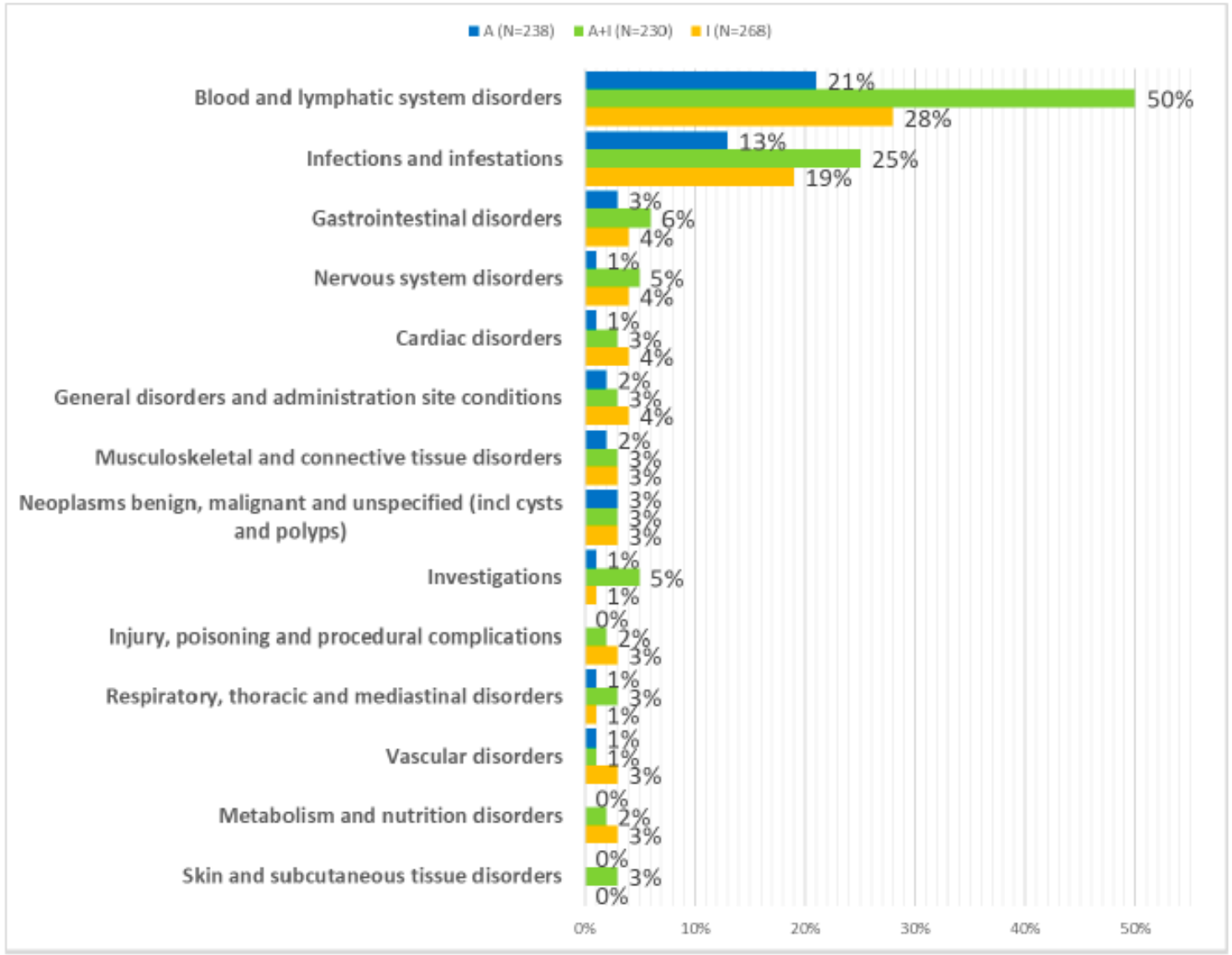
Grade 3-5

Adverse Events by Preferred Term	R-CHOP/R-DHAP (N=287)		IR-CHOP/R-DHAP (N=579)	
Thrombocytopenia	169	59%	351	61%
Neutropenia	134	47%	283	49%
Anaemia	62	22%	140	24%
Leukopenia	44	15%	88	15%
Febrile neutropenia	25	9%	70	12%
Lymphopenia	15	5%	38	7%

Grade 5

Adverse Events by System Organ Class	R-CHOP/R-DHAP (N=287)		IR-CHOP/R-DHAP (N=579)	
Gastrointestinal disorders	2	1%	0	0%
Infections and infestations	1	0%	1	0%
Psychiatric disorders	0	0%	1	0%

TRIANGLE: Grade 3-5 AEs (maintenance/follow-up, >2%)



Grade 3-5

Adverse Events by Preferred Term	A (N=238)		A+I (N=230)		I (N=268)	
Neutropenia	40	17%	101	44%	62	23%
Febrile neutropenia	6	3%	14	6%	7	3%
Thrombocytopenia	5	2%	13	6%	8	3%
Leukopenia	4	2%	10	4%	6	2%
Anaemia	4	2%	6	3%	4	1%
Lymphopenia	3	1%	1	0%	5	2%

Grade 5

Patients with at least one grade 5 AE by SOC

Adverse Events by System Organ Class	A (N=238)		A+I (N=230)		I (N=268)	
Infections and infestations	3	1%	2	1%	2	1%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0%	1	0%	0	0%
Cardiac disorders	0	0%	0	0%	1	0%
Respiratory, thoracic and mediastinal disorders	0	0%	1	0%	0	0%
Vascular disorders	1	0%	0	0%	0	0%

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Conclusions: current Triangle results

Based on FFS (primary endpoint):

- **A+I (auto SCT + ibrutinib) is superior to A (auto SCT only)**
- **A (auto SCT) is not superior to I (ibrutinib without auto SCT)**
- **currently, no decision whether autologous SCT adds to I (ibrutinib) but toxicity favors Ibru only**

numerical overall survival benefit in the ibrutinib arms (I, A+I)

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

What will come next?

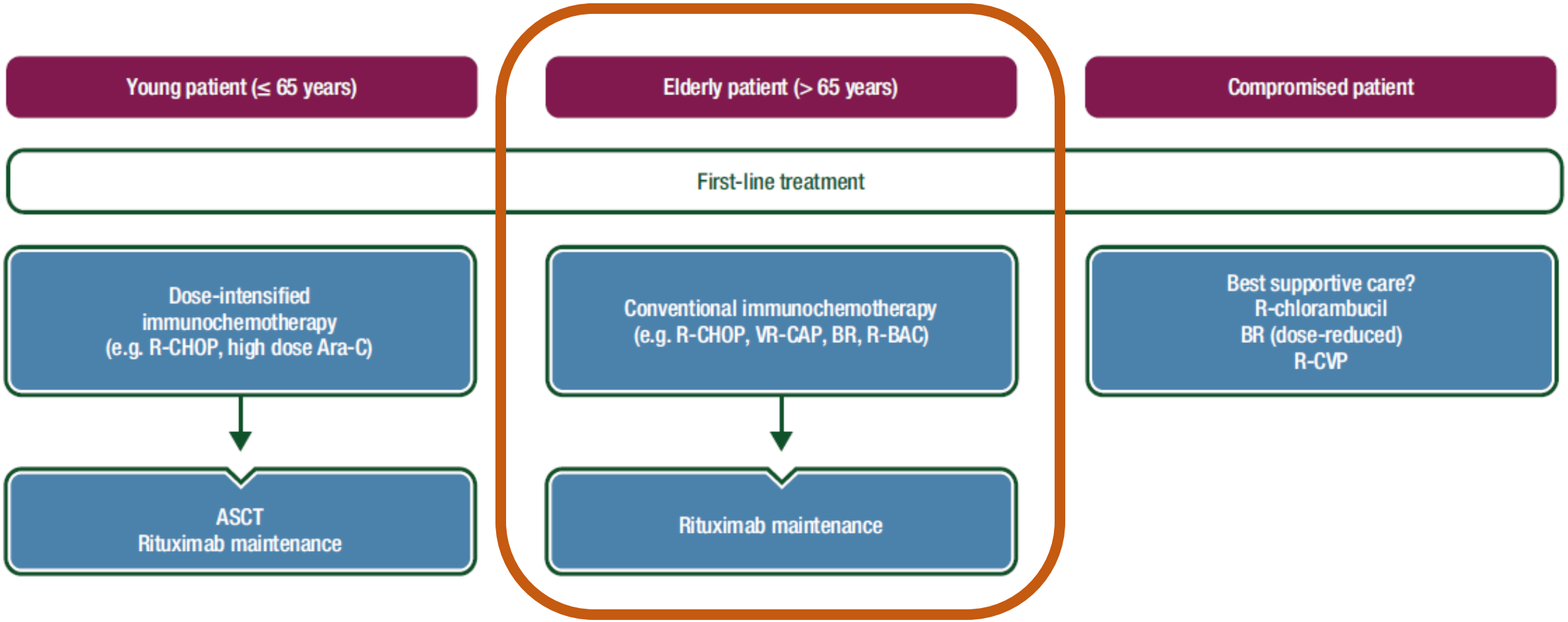
TRIANGLE - comparison Arm I vs A+I

Good bye to ‘transplant-eligible´?

Response adaption - ECOG-ACRIN 4151 – MRD-neg rand to ASCT +R vs R

Risk adaption - CARMAN – CAR-T based frontline therapy in high risk MCL

ESMO clinical practice guidelines for MCL



*** NEWLY DIAGNOSED AND RELAPSED MANTLE CELL LYMPHOMA: ESMO CLINICAL PRACTICE GUIDELINES, Published in 2017** – Ann Oncol (2017) 28 (suppl 4): iv62–iv71

Authors: *M. Dreyling, E. Campo, O. Hermine, M. Jerkeman, S. Le Gouill, S. Rule, O. Shpilberg, J. Walewski and M. Ladetto*

SHINE: A Randomized Phase 3 Study- BR vs BRi

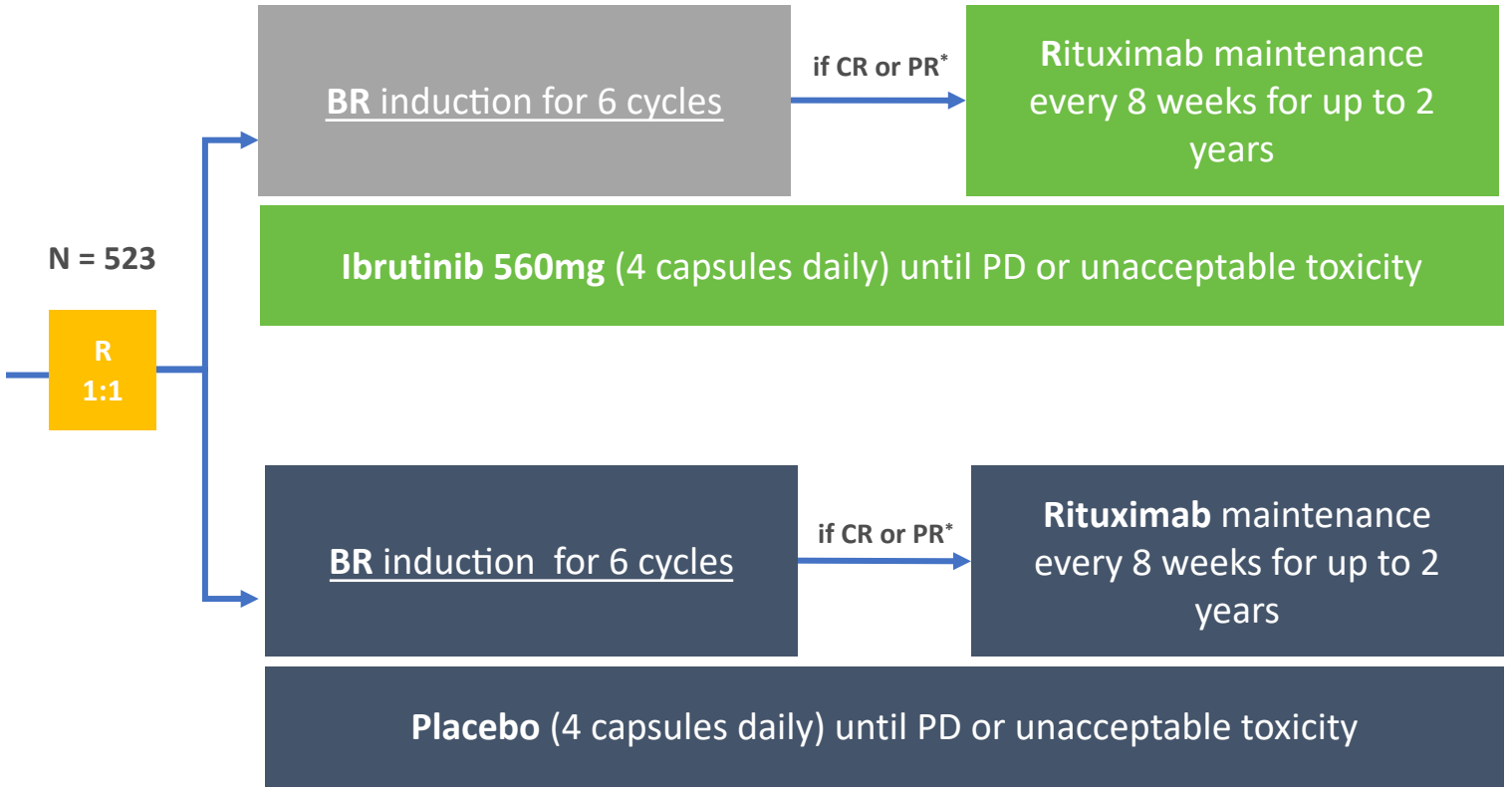
Patients

- Previously untreated MCL
- ≥ 65 years of age
- Stage II-IV disease
- No stem cell transplant

Stratification factor

- Simplified MIPI score (low vs intermediate vs high)

Enrolled between May 2013 and November 2014 in 29 countries and 183 sites



Primary endpoint:

- PFS (investigator-assessed)

Key Secondary endpoints:

- Complete response rate and overall response rate
- Time to next treatment
- Overall survival
- Safety

Data cutoff for the primary analysis: June 30, 2021

Median follow-up: 84.7 months

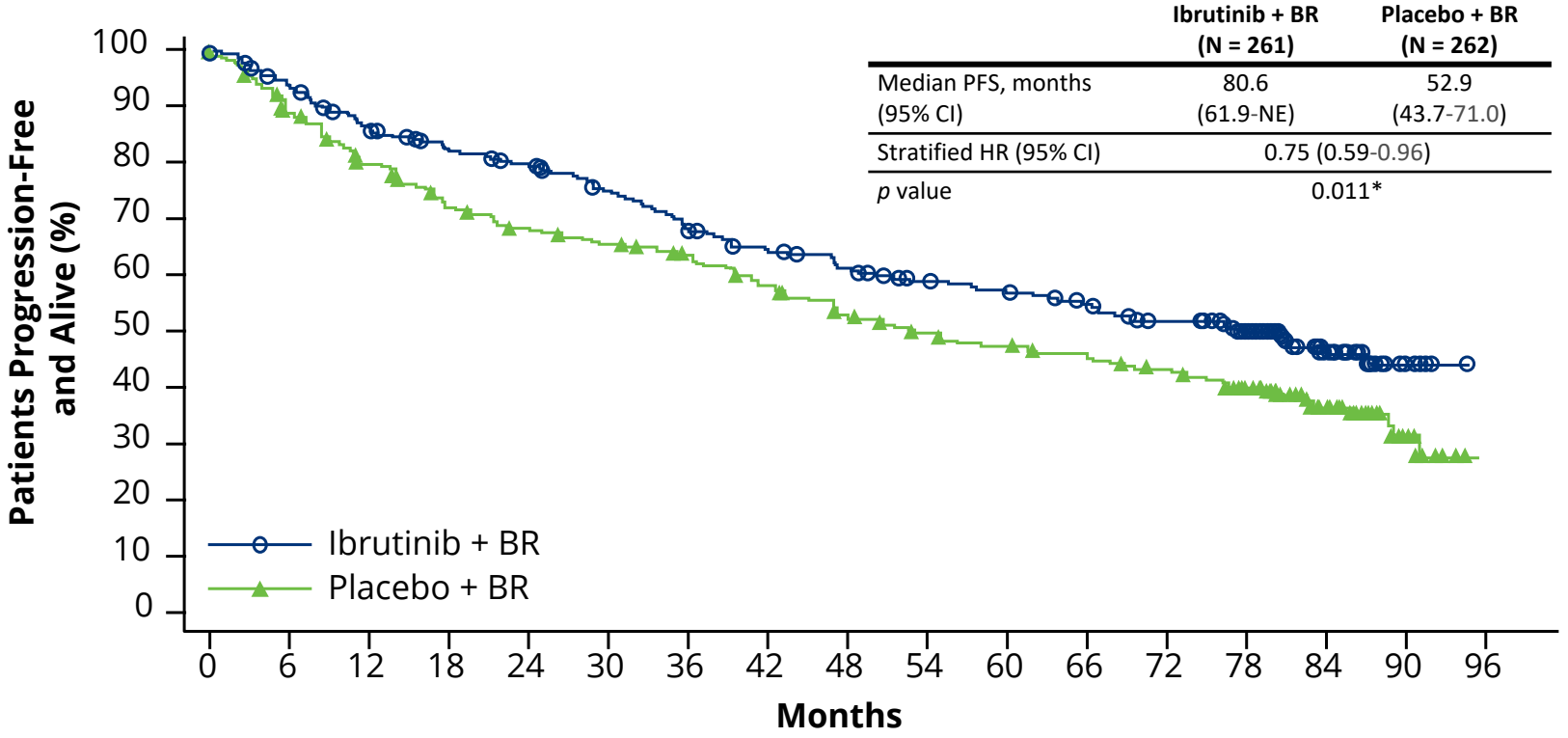
Bendamustine 90 mg/m^2 Days 1 and 2, **R**ituximab 375 mg/m^2 Day 1, Q4W for 6 cycles. A cycle is defined as 28 days.

Baseline Characteristics

		Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median age (range) — years		71 (65–86)	71 (65–87)
Age, ≥ 75 years — no. (%)		74 (28.4)	82 (31.3)
Sex, male — no. (%)		178 (68.2)	186 (71.0)
ECOG PS 1 or 2 — no. (%)		127 (48.7)	121 (46.2)
Simplified MIPI score — no. (%)	Low risk	44 (16.9)	46 (17.6)
	Intermediate risk	124 (47.5)	129 (49.2)
	High risk	93 (35.6)	87 (33.2)
Bone marrow involvement at study entry — no. (%)		198 (75.9)	200 (76.3)
Blastoid/pleomorphic histology — no. (%)		19 (7.3)	26 (9.9)
Extranodal disease — no. (%)		234 (89.7)	226 (86.3)
Bulky disease (≥ 5 cm) — no. (%)		95 (36.4)	98 (37.4)
TP53 mutated — no. (%)		26 (10.0)	24 (9.2)
TP53 mutation status unknown — no. (%)		121 (46.4)	133 (50.8)

Primary Endpoint: PFS (ITT Population)

Addition of Ibrutinib to BR and R maintenance significantly improved PFS



	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median PFS, months (95% CI)	80.6 (61.9-NE)	52.9 (43.7-71.0)
Stratified HR (95% CI)	0.75 (0.59-0.96)	
p value	0.011*	

Patients at Risk

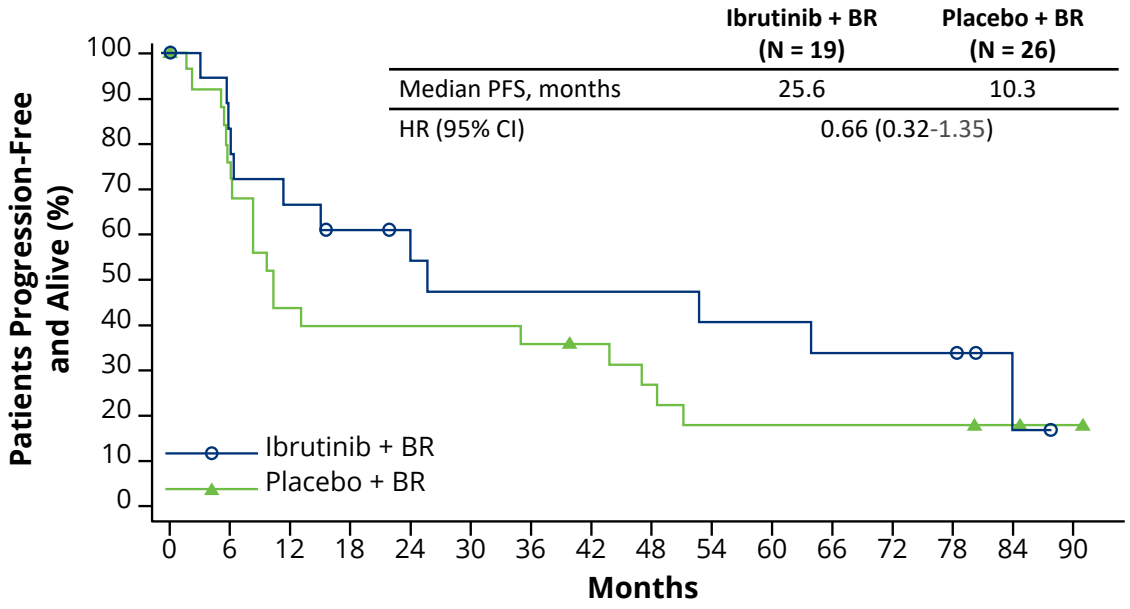
Ibrutinib + BR	261	228	207	191	182	167	152	139	130	120	115	106	95	78	39	11	0
Placebo + BR	262	226	199	177	166	158	148	135	119	109	103	98	90	78	41	11	0

- Ibrutinib combined with BR and R maintenance demonstrated **a 25% reduction in the relative risk of disease progression or death** versus BR and R maintenance
- **Significant improvement in median PFS:** 80.6 month (6.7 years) versus 52.9 months (4.4 years) **(Δ=2.3 years)**

NE, not evaluable.
*Significance boundary for superiority was $p<0.023$.

PFS in Biological High Risk Subgroups

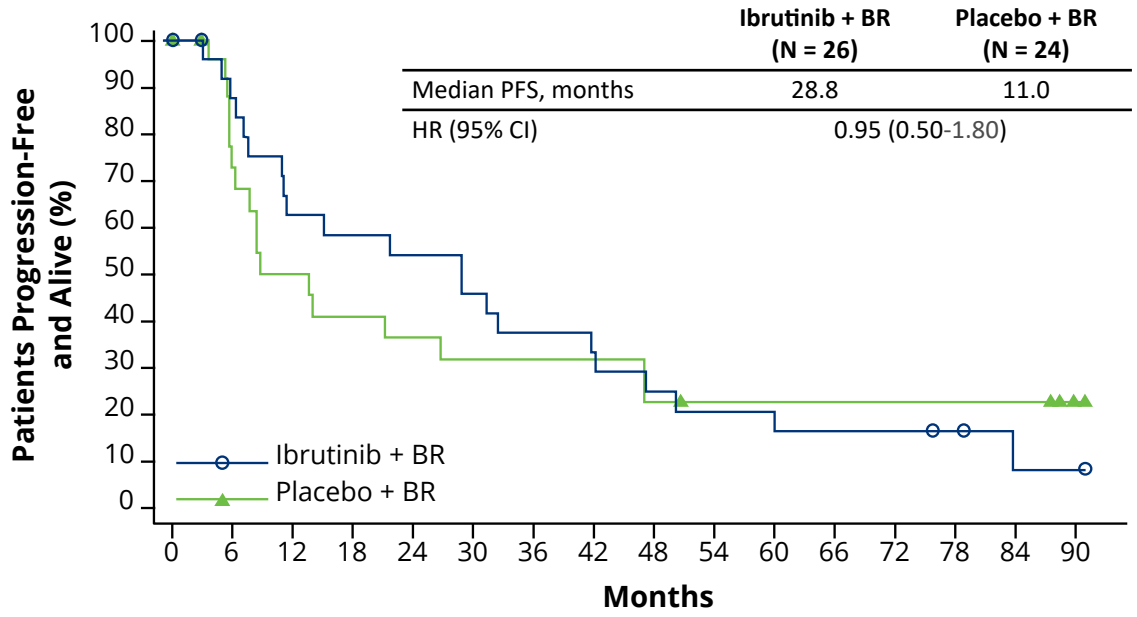
Patients with blastoid/pleomorphic histology



Patients at Risk

Ibrutinib + BR	19	14	12	10	8	7	7	7	7	6	6	5	5	5	1	0
Placebo + BR	26	19	11	10	10	10	9	8	6	4	4	4	4	4	3	1

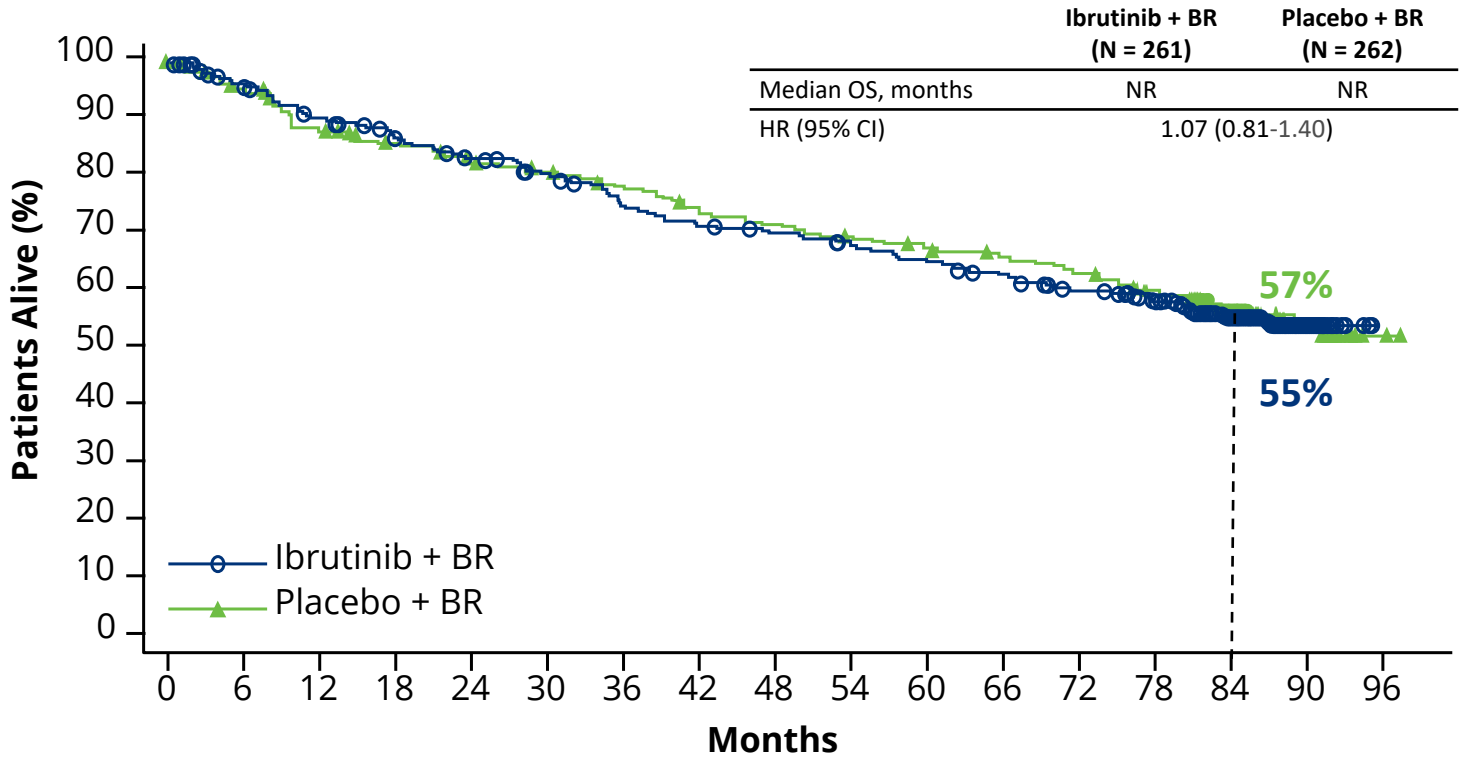
Patients with a *TP53* mutation



Patients at Risk

Ibrutinib + BR	26	21	15	14	13	11	9	7	6	5	4	4	4	3	1	1
Placebo + BR	24	16	11	9	8	7	7	7	5	4	4	4	4	4	4	1

Overall Survival Similar in Both Arms



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

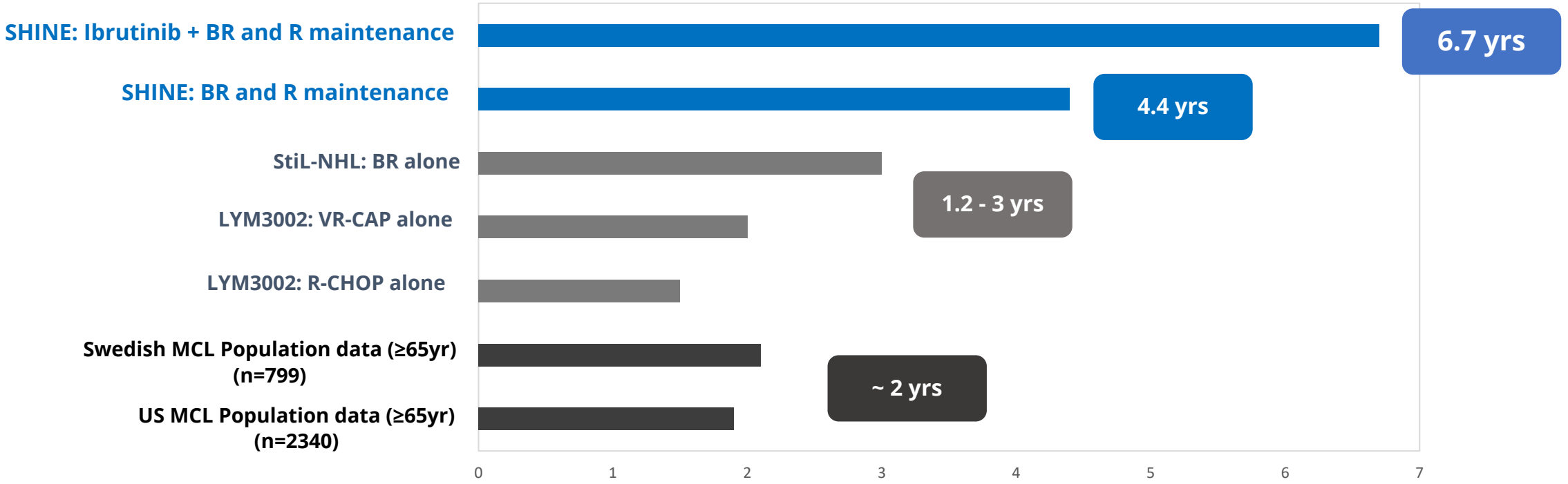
Cause of death	Ibrutinib+BR (N=261)	Placebo+BR (N=262)
Death due to PD	30 (11.5%)	54 (20.6%)
Death due to TEAEs*	28 (10.7%)	16 (6.1%)
Death during post-treatment follow-up period excluding PD	46 (17.6%)	37 (14.1%)
Total deaths	**104 (39.8%)**	**107 (40.8%)**

*The most common Grade 5 TEAE was infections in the ibrutinib and placebo arms: 9 vs 5 patients. Grade 5 TEAE of cardiac disorders in 3 vs 5 patients, respectively.

NR, not reached.

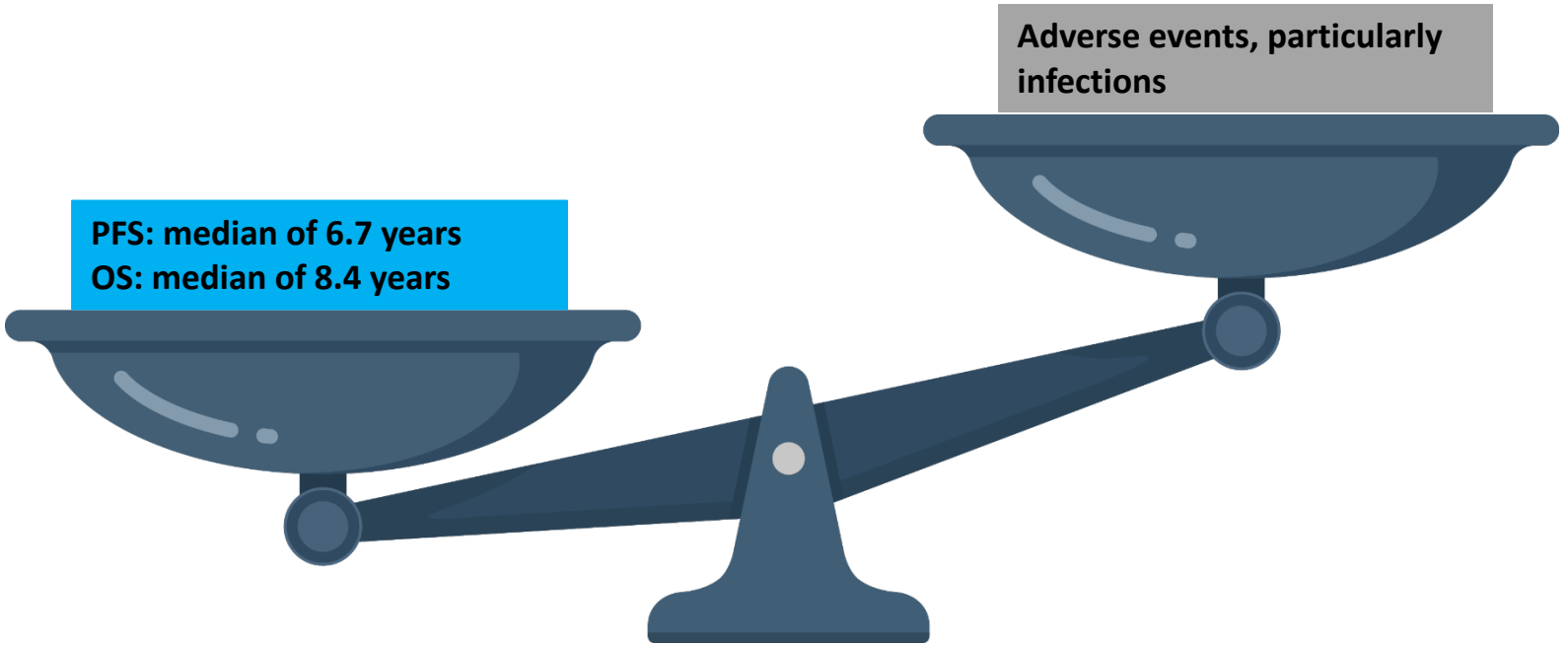
Median PFS cross comparison

Median PFS with ibrutinib combination is unprecedented in the context of other available randomized clinical trial and population-based data in older patients with MCL



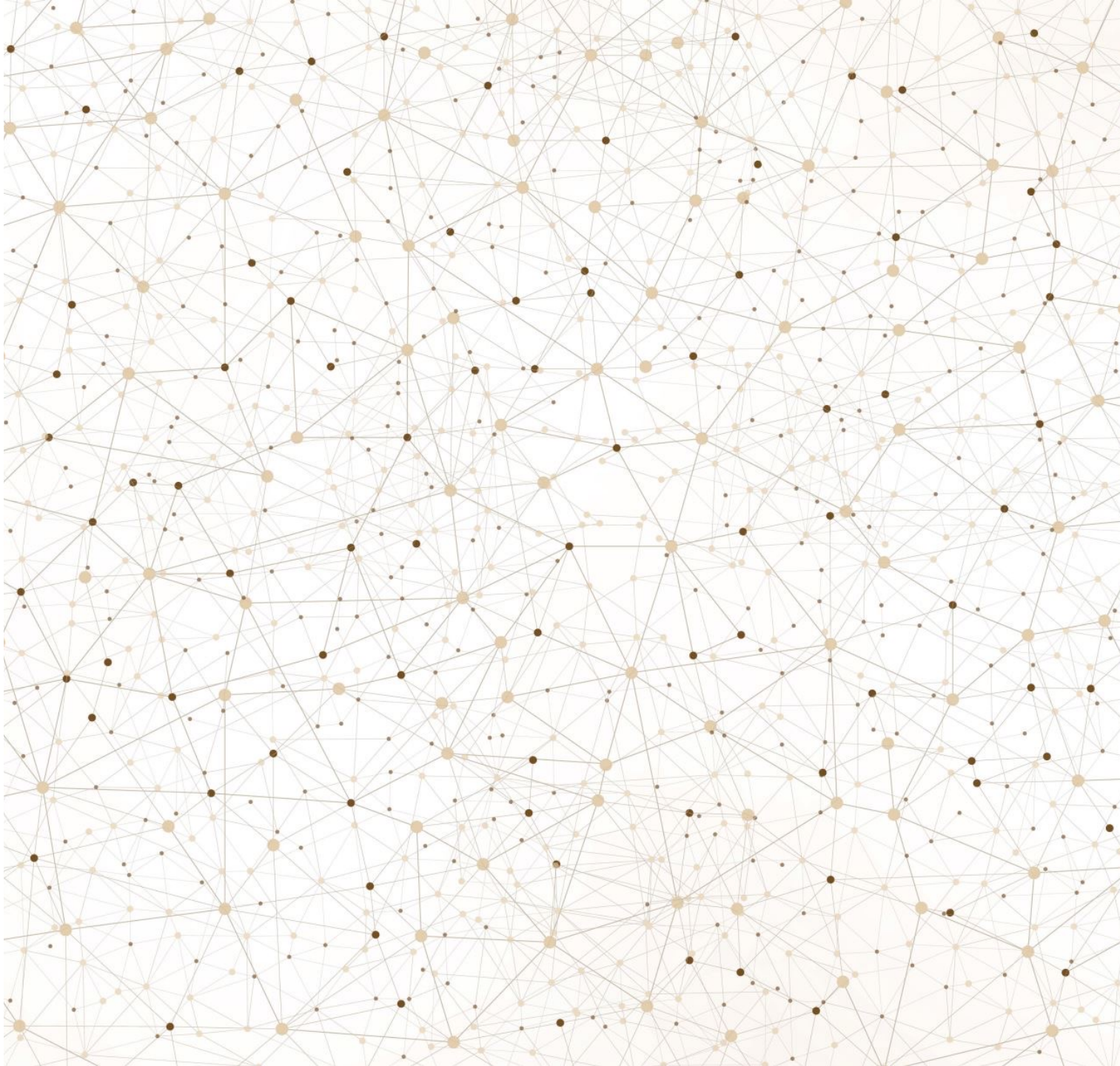
Reference: 1) Wang ML et al. N Engl J Med 2022 Jun 30;386(26):2482-2494.; 2) Robak T et al. Lancet Oncol 2018; 19: 1449–58. 3) Martin P et al. J Clin Oncol. 2022 Jun 28;JCO2102698. 4) Rummel MJ et al. Lancet 2013 Apr 6;381(9873):1203-10. 5) Unpublished Swedish Population data.

Clinicians' Perspectives on Ibrutinib + BR Combination in Data from SHINE



SHINE vs TRIANGLE

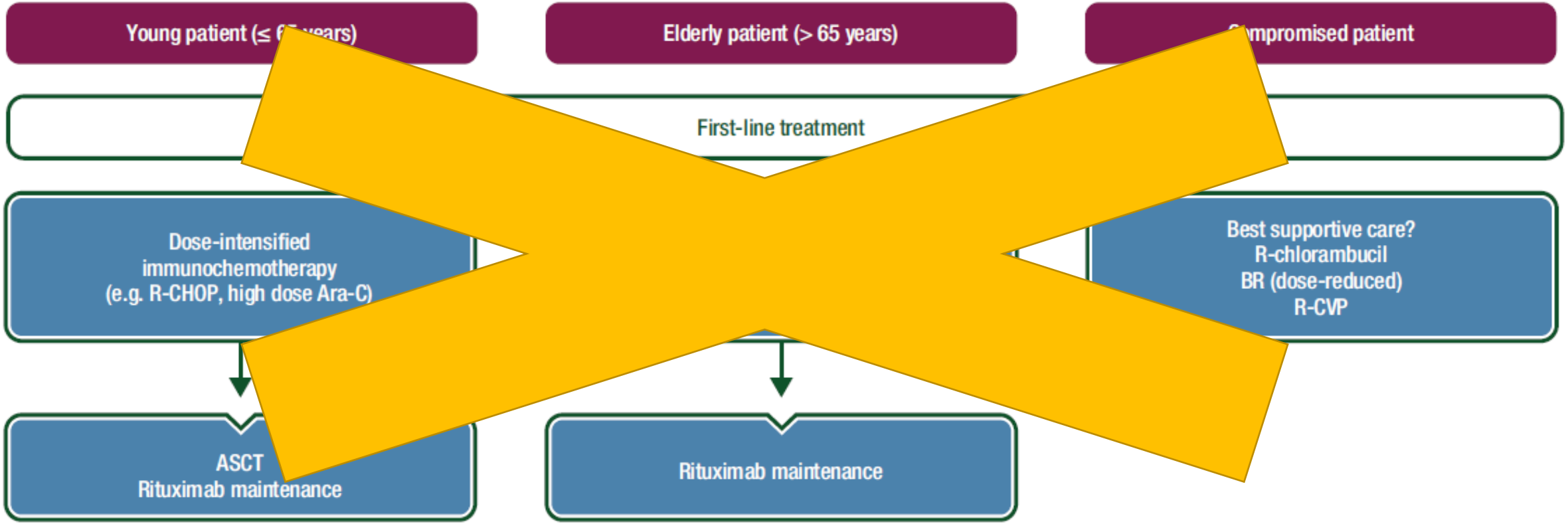
- Ibrutinib
  - Induction – continuous vs intermittent
  - Maintenance – until progression vs time limited
- Chemotherapy backbone



What will come next - in elderly pts?

- **ECHO**
  - Like SHINE, but with acalabrutinib – *late 2023?*
- **ENRICH**
  - IR *vs* BR or R-CHOP – *2024!*
- **MANGROVE**
  - ZR *vs* BR – *2024?*
- **OASIS-II**
  - IR vs IVR – *2025?*

New ESMO guidelines for MCL 2023



* NEWLY DIAGNOSED AND RELAPSED MANTLE CELL LYMPHOMA: ESMO CLINICAL PRACTICE GUIDELINES, Published in 2017 – Ann Oncol (2017) 28 (suppl 4): iv62–iv71

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