Lymphoma and Transplant

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Disclosures

Clinical trials

- Novartis
- AstraZeneca
- FATE Therapeutics

Consultant/Advisory Board

- Kite (Gilead)
- Intellia Therapeutics
- Via Oncology/Elsevier

This presentation may discuss off-label and investigational therapies

Mantle cell: Background

- R-CHOP/R-DHAP + Auto improves PFS vs R-CHOP + Auto (Hermine, Lancet, 2016)
- BR improves PFS vs R-CHOP (Rummel, Lancet, 2013 & Flinn, JCO, 2019)
- BR-I + IR maintenance improves PFS vs BR + R in older MCL (Wang, NEJM, 2022)

- Auto improves PFS & OS after CHOP like induction (Zoellner, Lancet Haematol, 2021)
  - Benefit reduced if received Rituximab with induction

- R maintenance improves PFS & OS after Auto (Le Gouill, NEJM, 2017)
- Len maintenance improves PFS after Auto but significant toxicity (Ladetto, Lancet Haematol, 2021)

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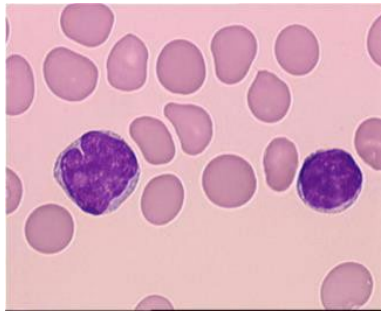
MEDIZINISCHE KLINIK UND POLIKLINIK III
DIREKTOR: PROF. DR. M. VON BERGWELT

TRIANGLE:

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



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*

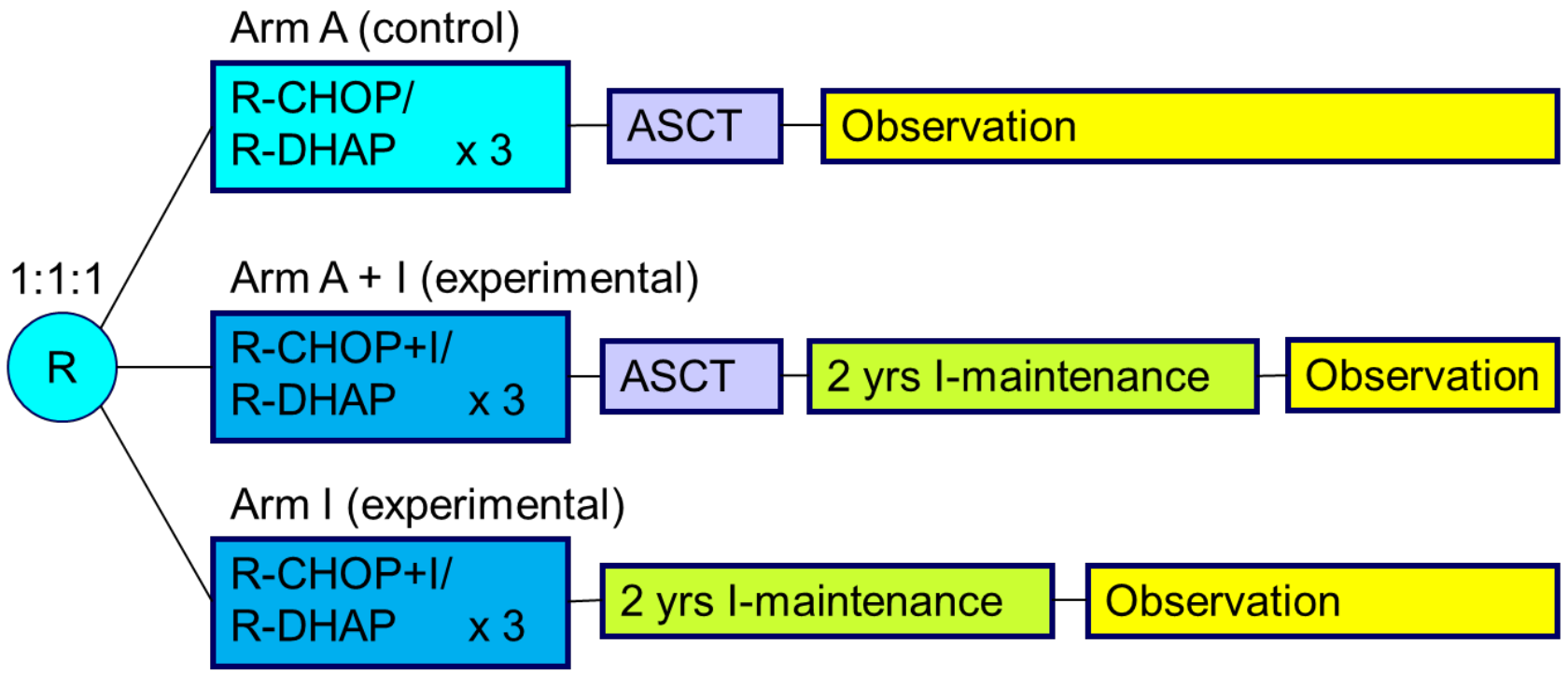
LMU University Hospital Munich, Germany; Erasmus MC Cancer Institute, University Medical Center Rotterdam, Netherlands; Hospital Clinic of Barcelona, Spain; Skane University Hospital and Lund University, Lund, Sweden; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Rigshospitalet, Copenhagen University Hospital, Denmark; Kantonsspital Graubuenden, Chur, Switzerland; Oslo University Hospital, Oslo, Norway; Charles University and General University Hospital, Prague, Czech Republic; University Hospitals Leuven, Belgium; Ospedale degli Infermi di Rimini, Italy; Assuta Ramat Hahayal Medical Center, Tel Aviv, Israel; Instituto Português de Oncologia, Lisboa, Portugal; Helsinki University Hospital Comprehensive Cancer Center, Finland; IBE, LMU University Munich, Germany; University of Schleswig-Holstein, Kiel, Germany; Az Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

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

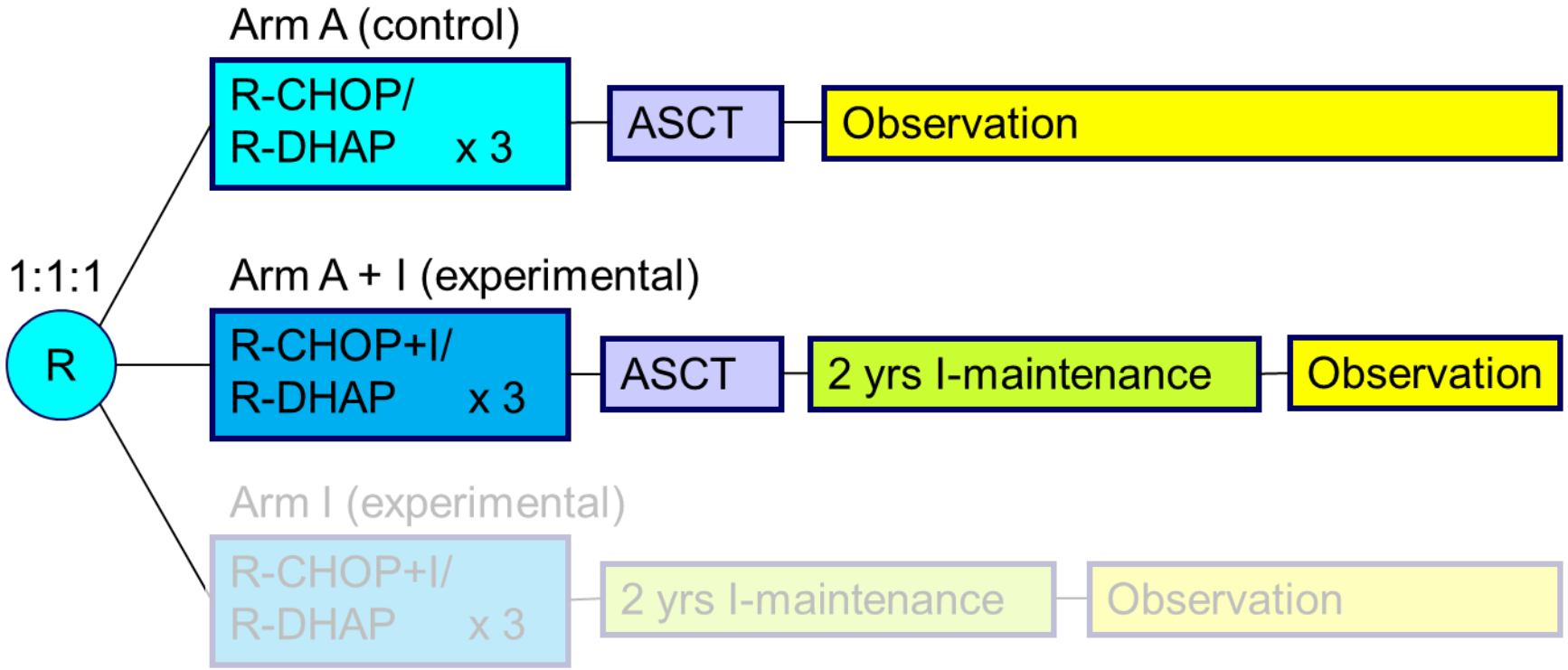
- CR- and OR-Rates significantly higher in the combined I induction (A+I/I) versus control (A) (CR: p=0.0203, OR: p=0.0025)
- MCL Younger R-CHOP/R-DHAP group: 38% (CR), 94% (OR)

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

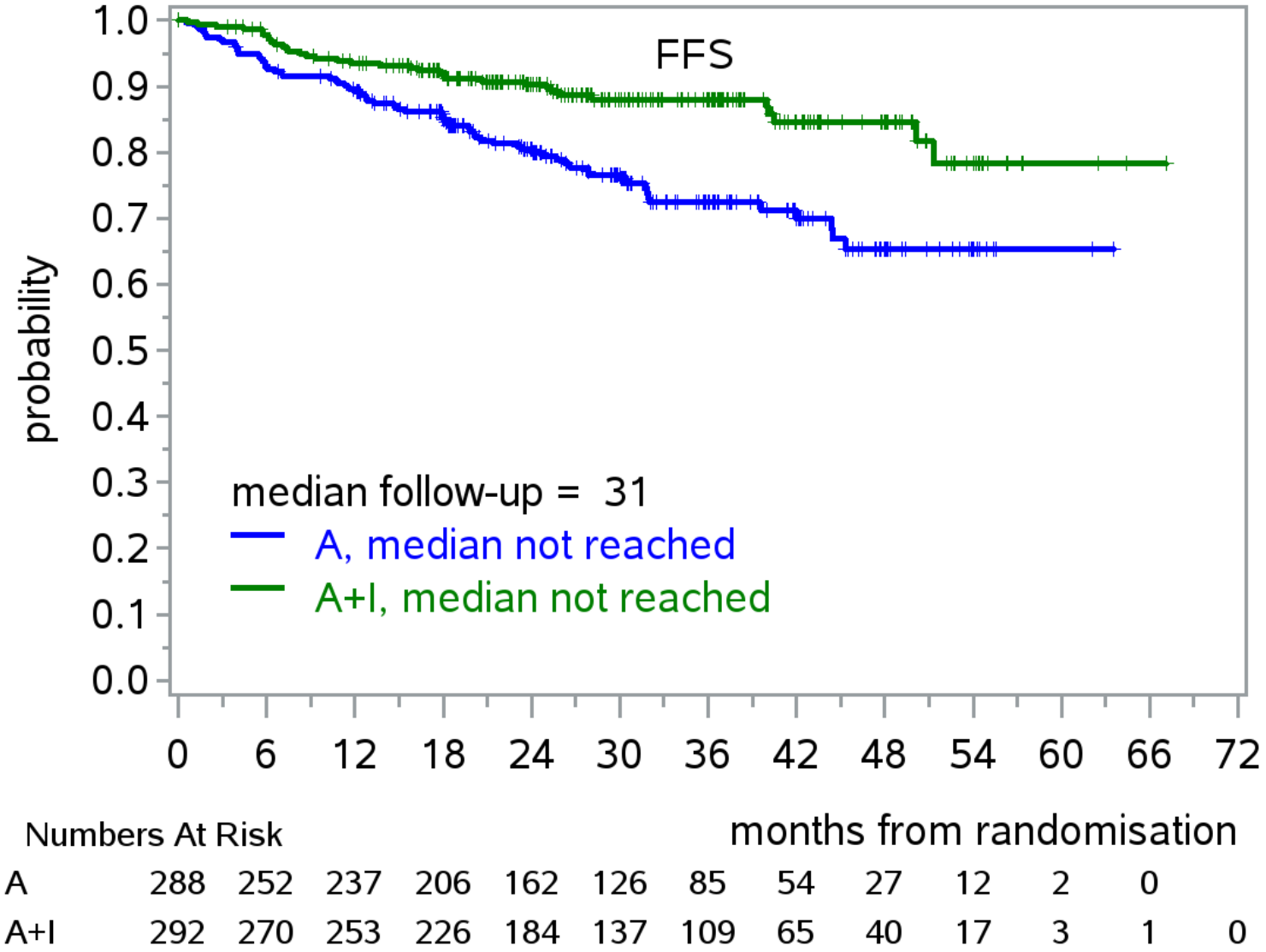
Test 1: FFS Superiority of A+I vs. A

- 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

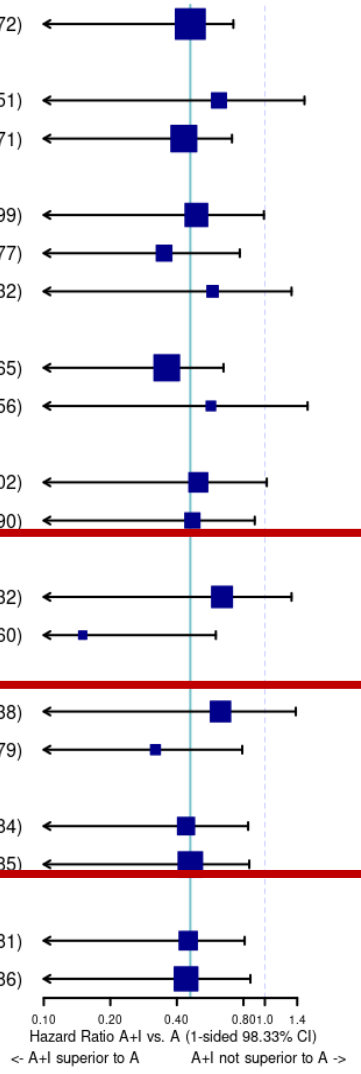


- Superiority of A+I vs. A (FFS) is confirmed
- Kaplan-Meier plots:
  - 3-year FFS A+I: 88%
  - 3-year FFS A: 72%
- p-value (corrected for sequential design) p=0.0008
- HR (A+I vs. A): HR=0.52

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

TRIANGLE: FFS Superiority of A+I vs. A

Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% CI)
All	580	103	0.46 (0 - 0.72)
Sex (p=0.0016)			
Female	146	23	0.62 (0 - 1.51)
Male	434	80	0.43 (0 - 0.71)
MIPI			
Low	336	40	0.49 (0 - 0.99)
Intermediate (p=0.49)	159	35	0.35 (0 - 0.77)
High (p=0.69)	85	28	0.58 (0 - 1.32)
Cytology (p=0.48)			
Non-blastoid	426	68	0.36 (0 - 0.65)
Blastoid	60	18	0.57 (0 - 1.56)
Ki-67 (p=0.82)			
Low	234	39	0.50 (0 - 1.02)
High	150	38	0.47 (0 - 0.90)
P53 expression (p=0.039)			
Low	284	36	0.64 (0 - 1.32)
High	44	16	0.15 (0 - 0.60)
High risk biology (p=0.19)			
Low	270	31	0.63 (0 - 1.38)
High	64	25	0.32 (0 - 0.79)
R maintenance ITT (p=0.96)			
No	191	48	0.44 (0 - 0.84)
Yes	389	55	0.46 (0 - 0.85)
R maintenance mAT (p=0.94)			
No	217	55	0.45 (0 - 0.81)
Yes	363	48	0.44 (0 - 0.86)



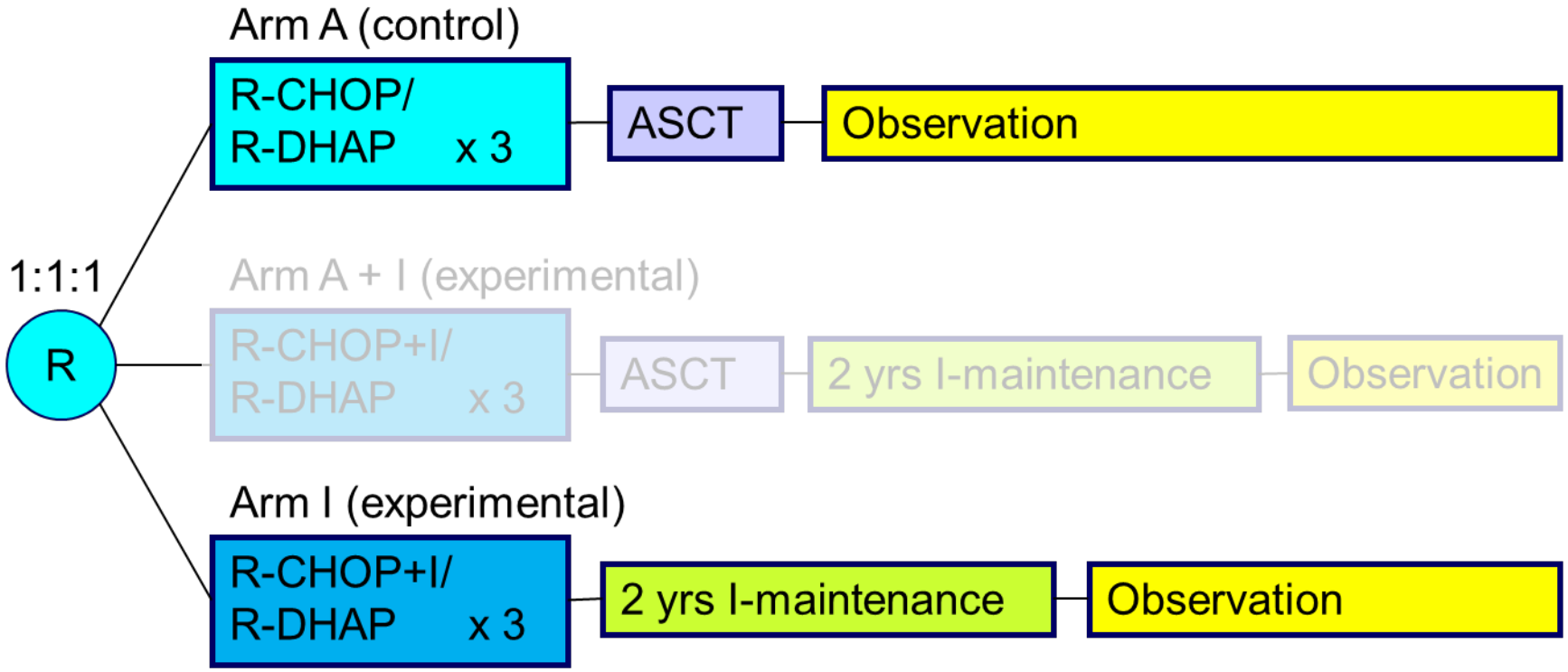
- similar in all MIPI groups
- No differential efficacy according to cytology and Ki-67
- More effective in high p53 expressors
- Trend toward higher efficacy in high risk biology
- No differential efficacy by rituximab maintenance

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

TRIANGLE: Evaluation of primary endpoint FFS

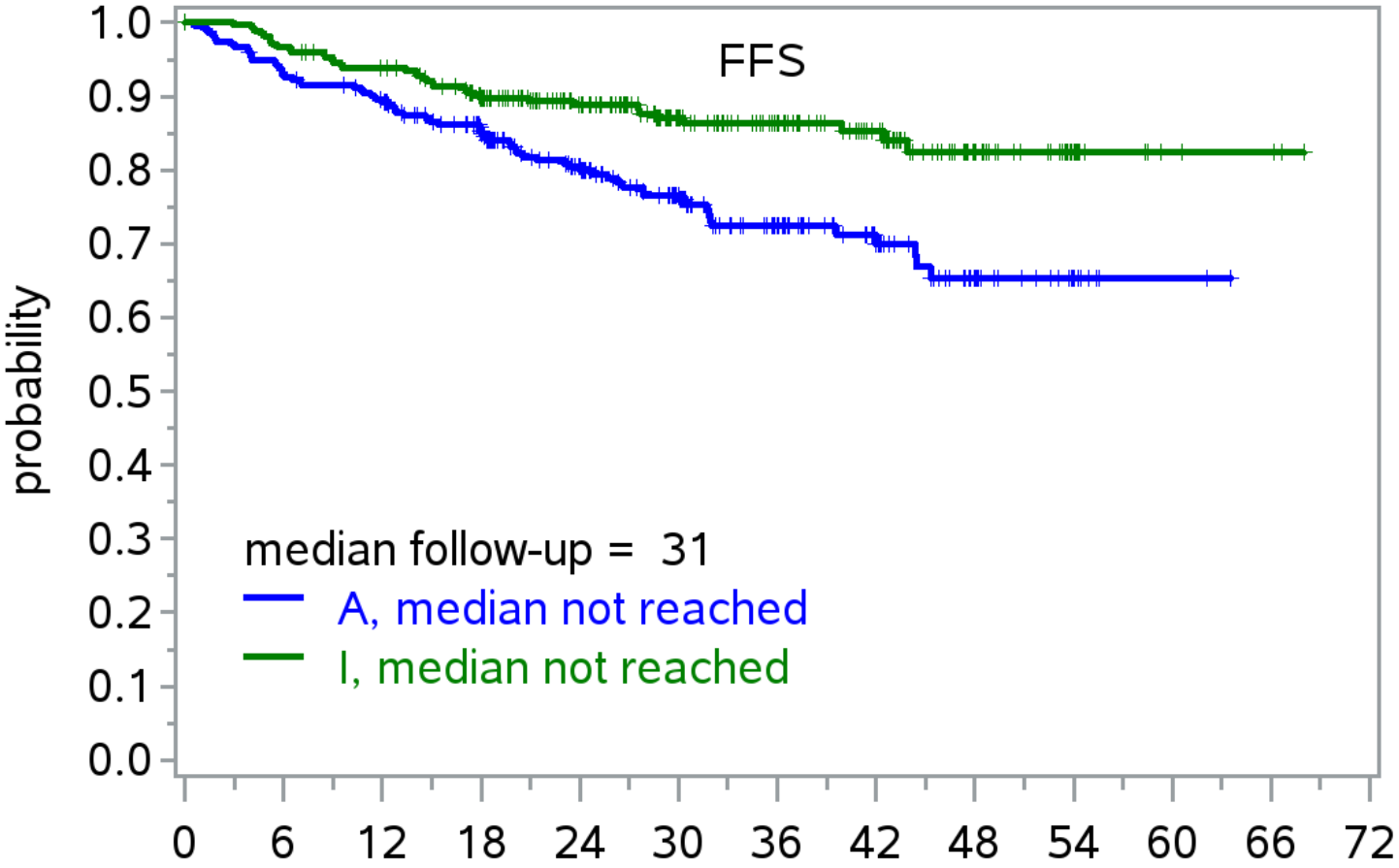
Test 2: FFS Superiority of A vs. I

- 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



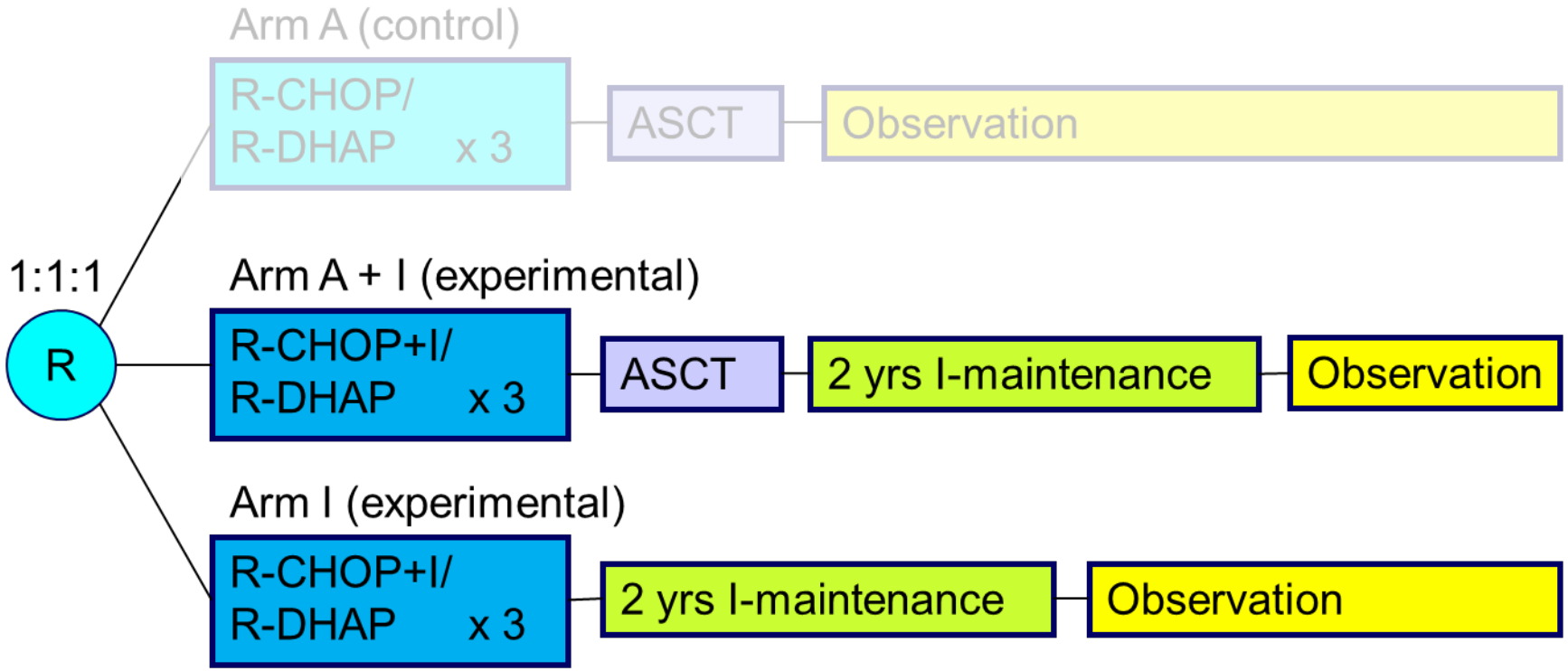
Numbers At Risk

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

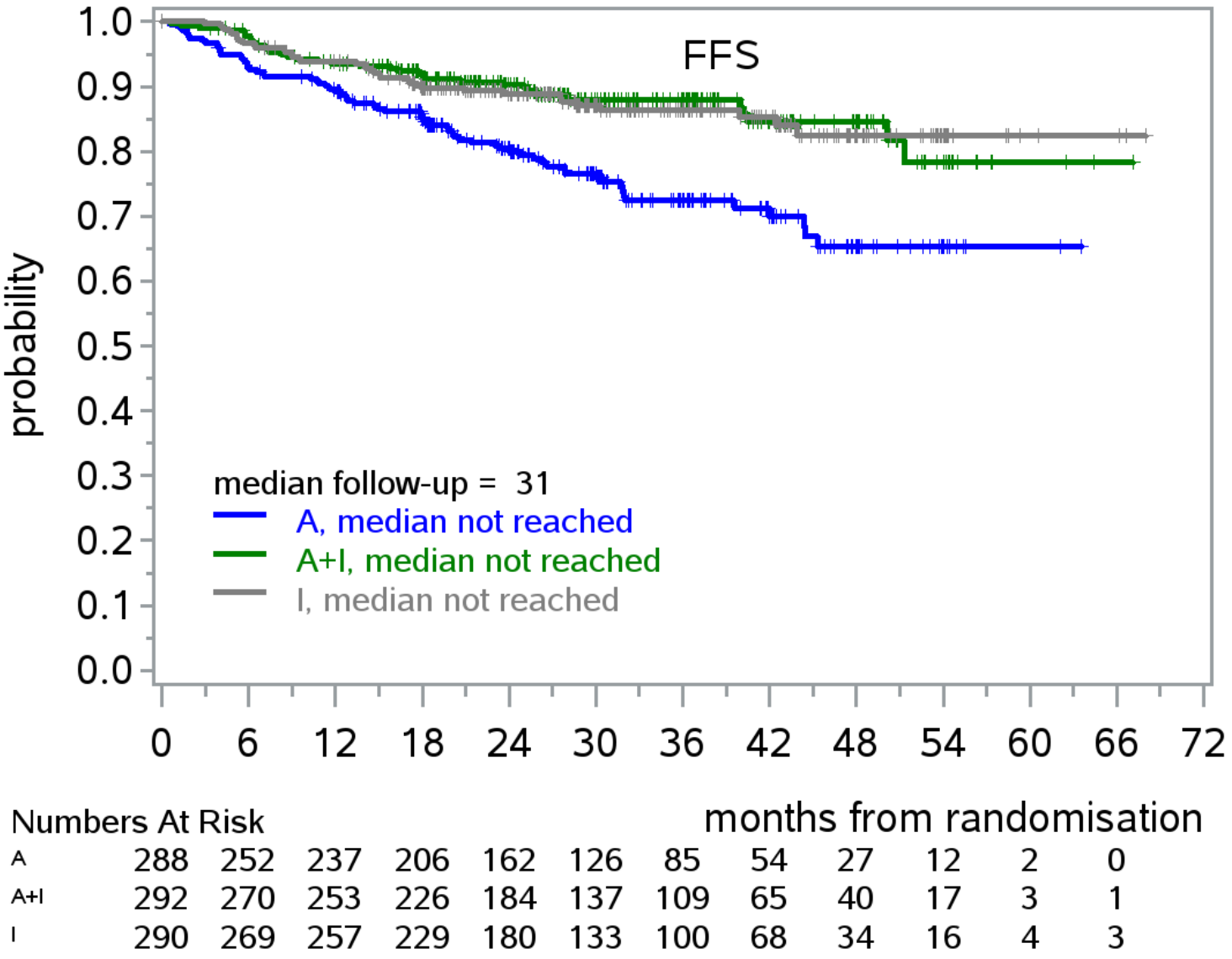
TRIANGLE: Evaluation of primary endpoint FFS



- 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 ?

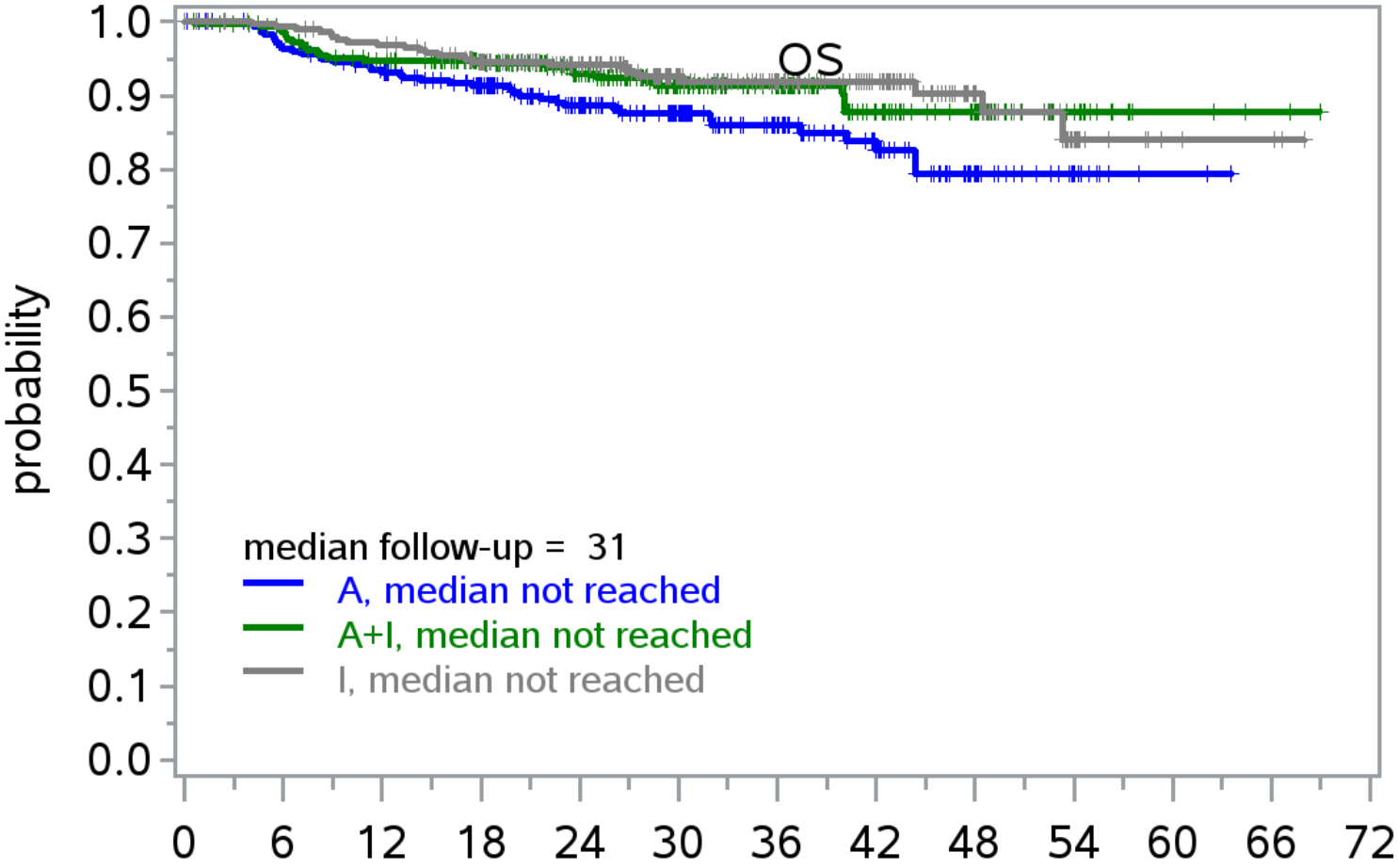


- Test A+I vs. I ongoing, no decision yet

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

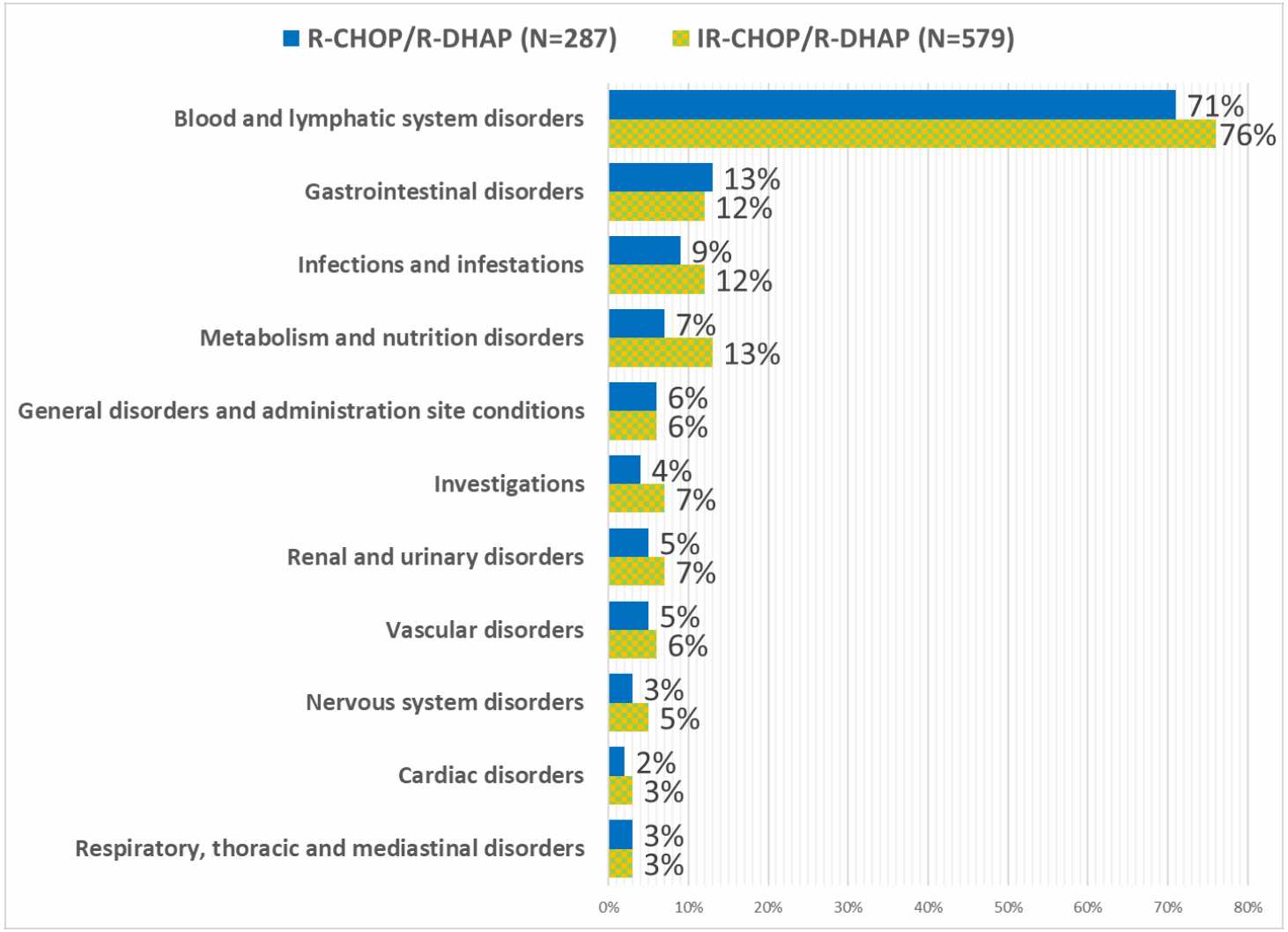


Numbers At Risk												
A	288	270	256	230	181	145	97	63	32	15	2	0
A+I	292	280	262	238	195	142	113	67	42	19	4	2
I	290	281	272	248	197	145	109	77	38	16	4	3

- 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%)



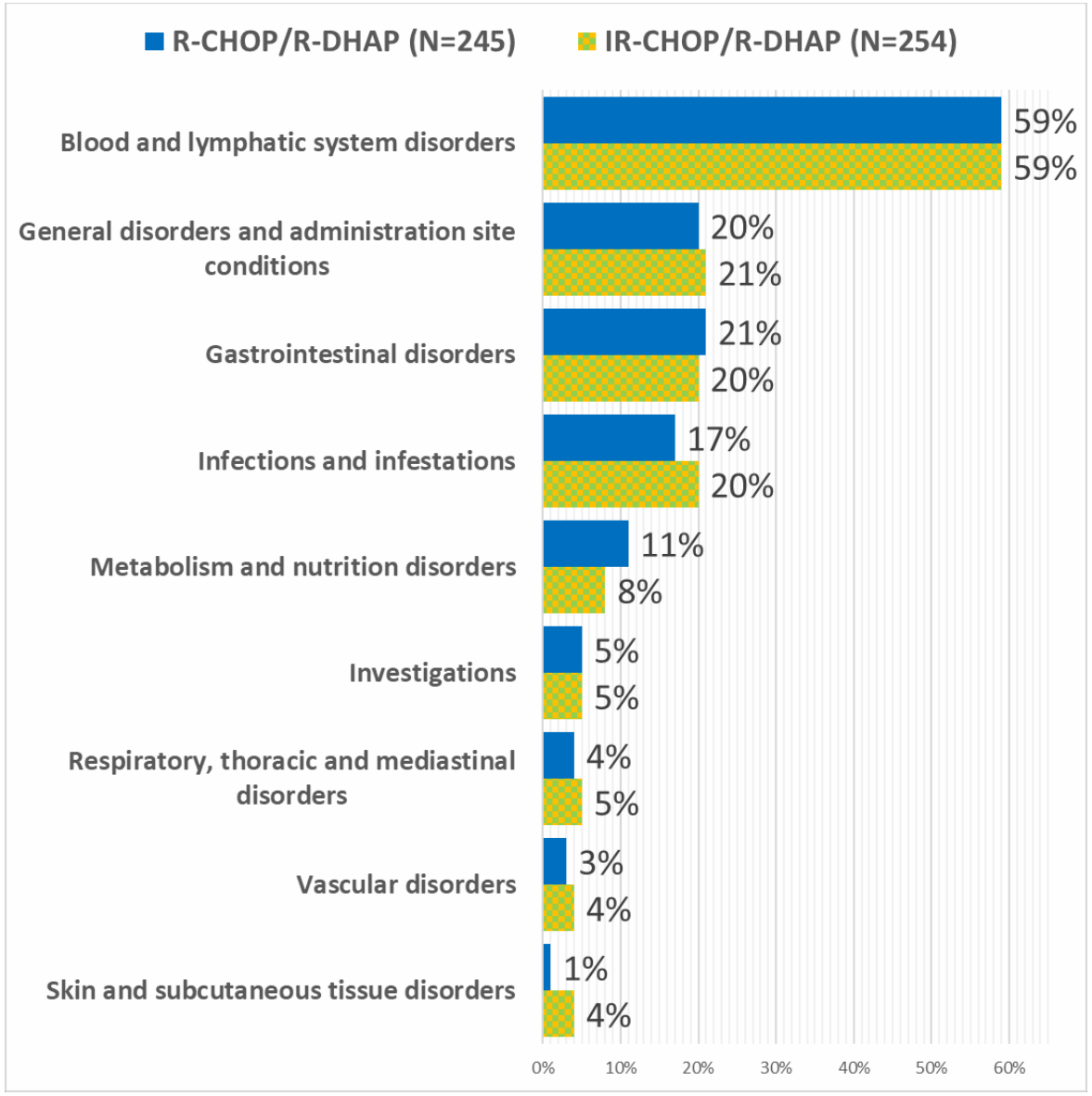
Grade 3-5

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 (ASCT; >2% frequency)



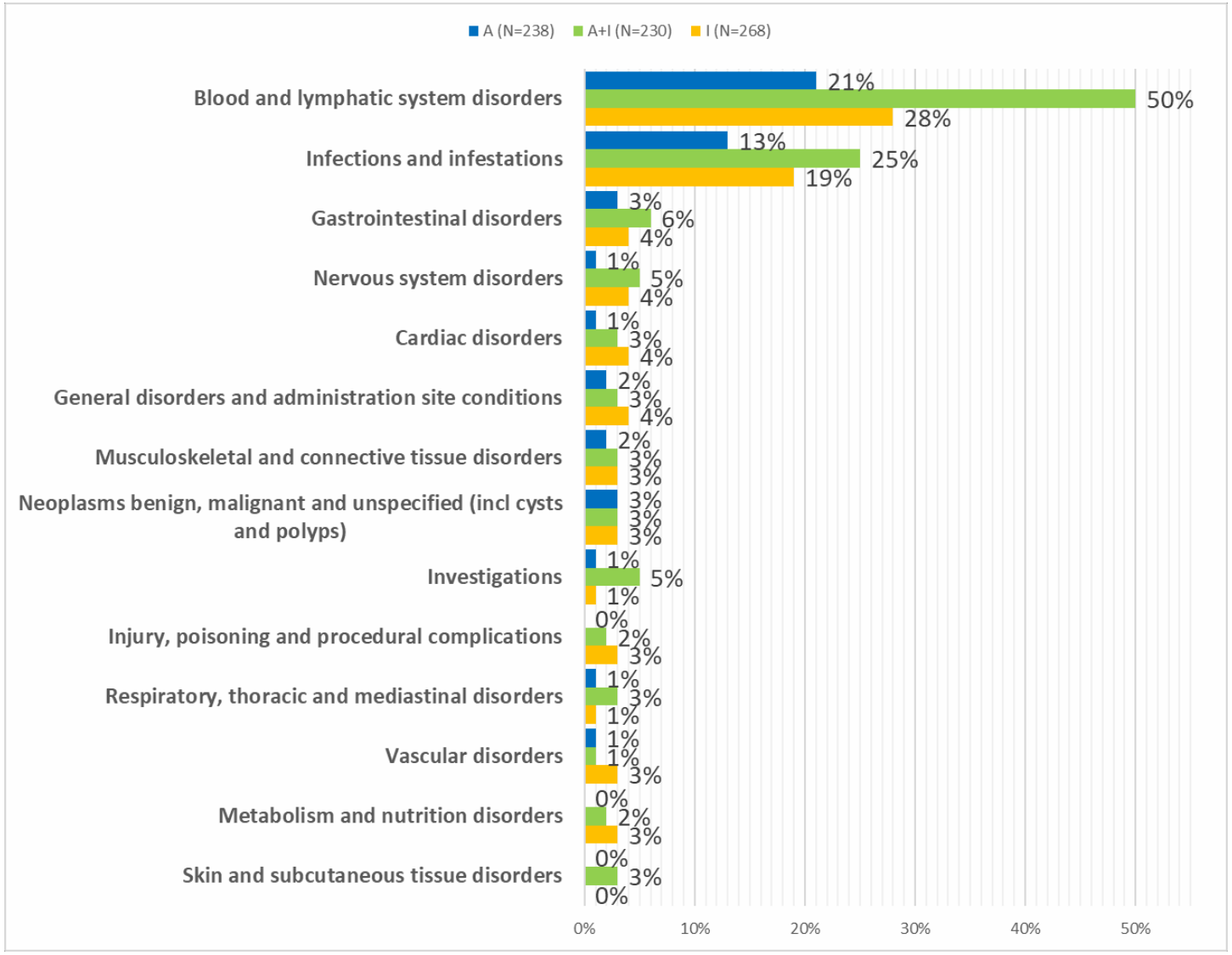
Grade 3-5

Adverse Events by Preferred Term	R-CHOP/R-DHAP (N=245)		IR-CHOP/R-DHAP (N=254)	
Thrombocytopenia	119	49%	111	44%
Neutropenia	88	36%	83	33%
Anaemia	50	20%	56	22%
Febrile neutropenia	49	20%	56	22%
Leukopenia	42	17%	42	17%
Lymphopenia	9	4%	7	3%

Grade 5

Adverse Events by System Organ Class	R-CHOP/R-DHAP (N=245)		IR-CHOP/R-DHAP (N=254)	
Infections and infestations	4	2%	5	2%
Gastrointestinal disorders	1	0%	1	0%
Respiratory, thoracic and mediastinal disorders	1	0%	1	0%
Blood and lymphatic system disorders	0	0%	1	0%
Congenital, familial and genetic disorders	1	0%	0	0%
General disorders and administration site conditions	1	0%	0	0%
Nervous system disorders	1	0%	0	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

Mantle cell: Triangle study

- Ibrutinib arms (A+I and I) superior in FFS to Auto alone
- Need longer f/u to see if OS benefit from Ibrutinib

- Comparison to Bendamustine based induction (eg BR-I)
- Effect of Rituximab maintenance

- Does Auto add to Ibrutinib (A+I vs I)?

- Frontline indication & coverage for Ibrutinib?

Primary CNS Lymphoma: Background

Methotrexate based induction

- MT-R
- R-MPV
- MATRix

Consolidation options

- Non-myeloablative chemotherapy (eg EA or A)
- Radiation – standard vs low dose
- AutoSCT - thiotepa

Primary CNS Lymphoma: Radiation

- IELSG32: random Ph2 Auto vs WBRT - No difference in 7 yr PFS but increased cognitive toxicity with WBRT (Ferreri, Leukemia, 2022)

- PRECIS: random Ph2 Auto vs WBRT – Trend toward AutoSCT in 2 yr PFS plus increased cognitive impairment in WBRT arm (Houillier, JCO, 2019)

- RTOG: random Ph2 R-MPV -> low dose WBRT (23.4 Gy) vs Cytarabine consolidation

  LD-WBRT improves 2 yr PFS with no significant neurotoxicity (Omuro, ASCO, 2020)

Primary CNS Lymphoma: AutoSCT

- CALGB 51101: random Ph2 MT-R -> AutoSCT vs EA consolidation (Batchelor, ASCO, 2021)
  - PFS in higher in auto arm (median 6 vs 2.4 yrs) but more Pts in EA arm progressed or died during induction prior to consolidation (arms unbalanced)
  - No significant difference in OS
  - Cognitive function not reported

ASH, New Orleans, December 2022

Effects on Survival of Non-Myeloablative Chemoimmunotherapy Compared to High-Dose Chemotherapy Followed By Autologous Stem Cell Transplantation As Consolidation Therapy in Patients with Primary CNS Lymphoma – Results of an International Randomized Phase III Trial (MATRix/IELSG43)

Gerald Illerhaus, A.J.M. Ferreri, M. Binder, P. Borchmann, J. Hasenkamp, S. Stilgenbauer, A. Roeth, T. Weber, G. Egerer, T. Ernst, B. Hertenstein, G. Lenz, G. Kobbe, U. Brunnberg, C. Schmidt, M. Kneba, M. Dreyling, R. Möhle, J. Panse, T. Heinicke, S. Schroll, T.S. Larsen, H. Salwender, R. Naumann, G. Hess, L. Thurner, T. Pukrop, U. Keller, A.K. Blystadt, F.P. Kroschinsky, F. Re, E. Pulczynski, L. Orsucci, L. Pospiech, M. Deckert, M. Ponzoni, J. Wendler, E. Valk, T. Calimeri, B. Kasenda, M. Trepel, H. Fricker, P. v. Gottberg, E. Burger, G. Ihorst, O. Grishina, C. Hader, E. Zucca, J. Finke and Elisabeth Schorb

On behalf of the German Cooperative Study Group CNS Lymphoma and the International Extranodal Lymphoma Study Group (IELSG)

Treatment algorithm

Induction

2# MATRix (q3w)
Rituximab 375 mg/m² (d 0,-4)
Methotrexat 3.5 g/m² (d 1)
Cytarabin 2x2 g/m²/d (d 2-3)
Thiotepa 30 mg/m² (d4)

Harvest

→ PD: off Study

2# MATRix

→ SD/PD: off Study

Randomization
(Strata: response)

Consolidation

2 cycles R-DeVIC
Rituximab 375 mg/m²/d i.v. (d0)
Dexamethasone 40 mg/d i.v. (d1-3)
Etoposide 100 mg/m²/d i.v. (d1-3)
Ifosfamide 1500 mg/m²/d i.v. (d1-3)
Carboplatin 300 mg/m²i.v. (d1)

ITT

High-dose chemotherapy
BCNU* 400 mg/m² i.v. (d-6)
or: Busulfan, 2x3.2mg/kg
Thiotepa 2 x 5 mg/kg/d i.v. (d-5-(-4))
ASCT (d0)

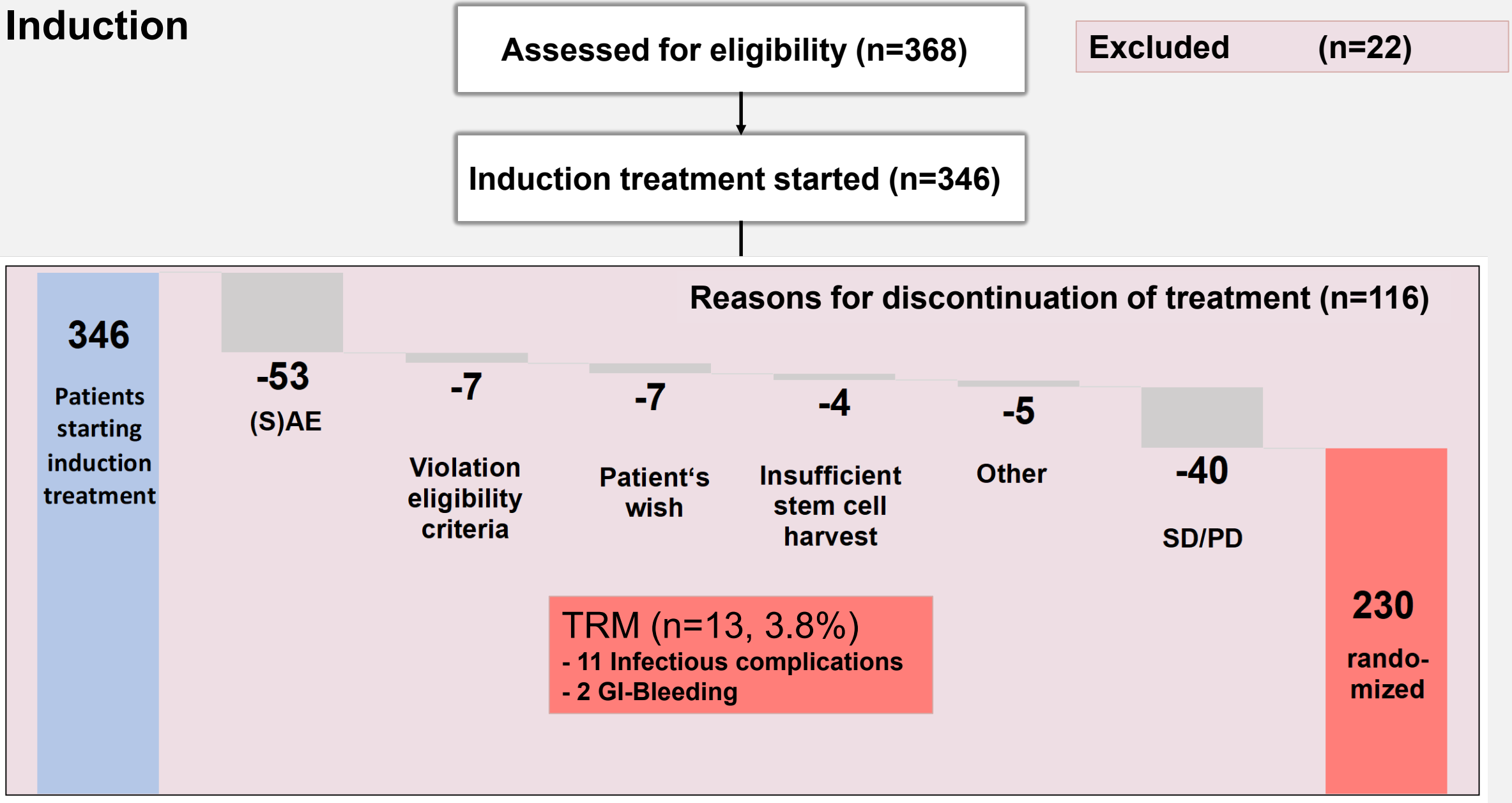
*if BCNU was not availible

MATRix/IELSG43 – Patients' characteristics (ITT)

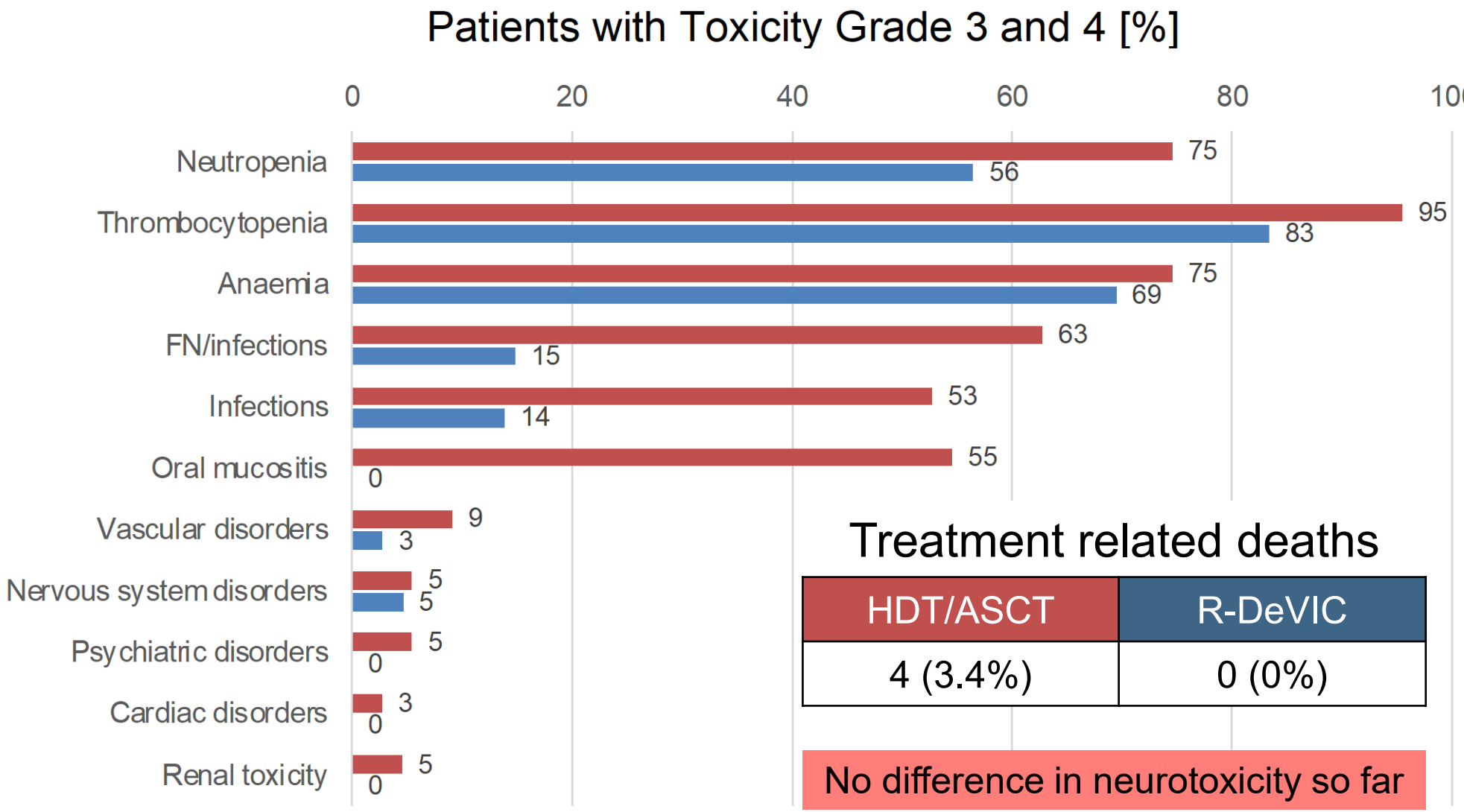
	Arm A (R-DeVIC, n= 115)	Arm B (HDT-ASCT, n= 114)
Median age (range)	59.9 (21-70)	58.5 (24-69)
Age ≥ 65	28 (24.3%)	23 (20.2%)
Histology: DLBCL	111 (98.2%)	111 (97.4%)
Females	53 (46.1%)	49 (43.0%)
ECOG PS >1	26 (22.7%)	32 (28.4%)
Increased LDH	43 (37.4%)	35 (30.7%)
Increased CSF protein	41 (40.6%)	44 (41.1%)
Meningeal involvement (MRI)†	5 (4.4%)	5 (4.4%)
Multiple lesions (MRI)	72 (63.7%)	65 (57.0%)

Treatment algorithm

Induction



MATRix/IELSG43 Trial – Toxicity (ITT, ≥ 3°)

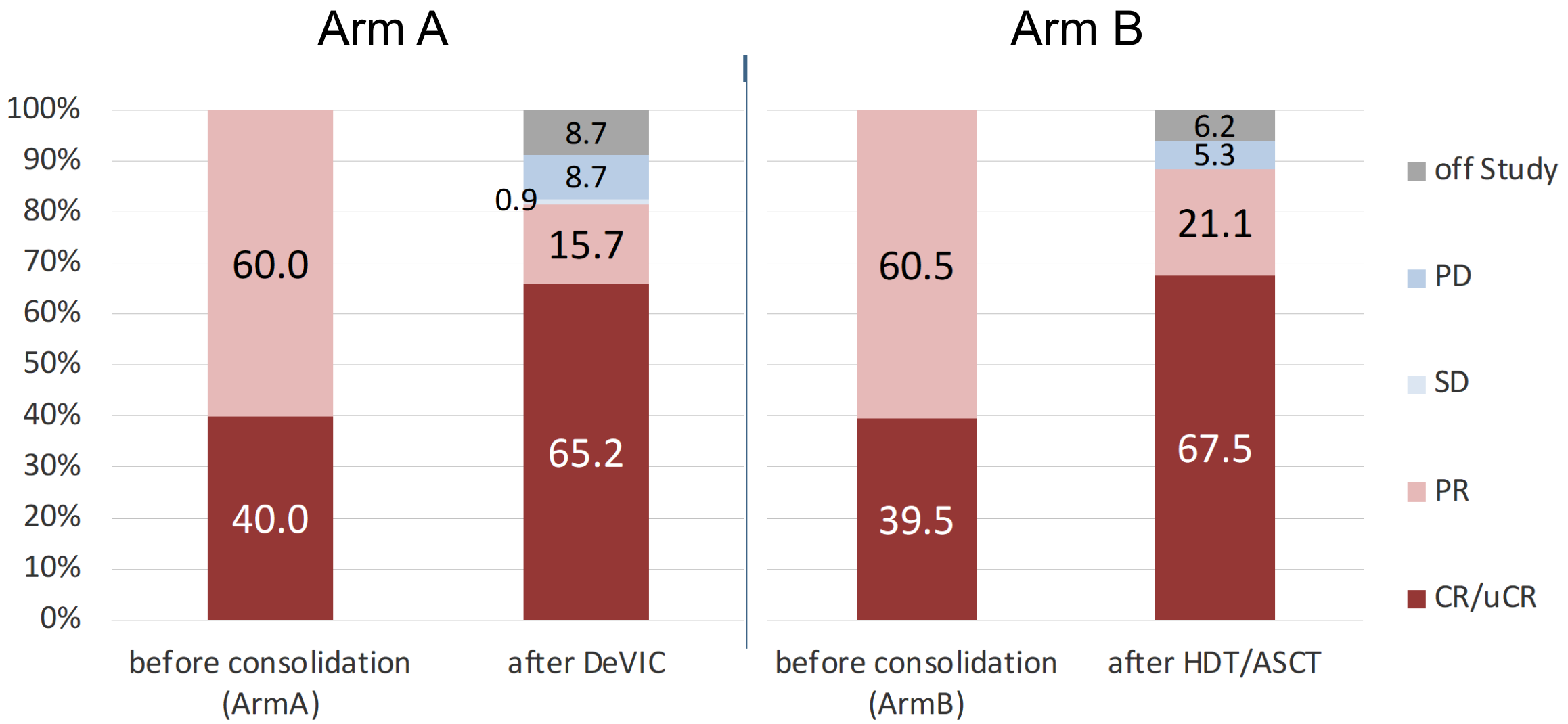


Treatment related deaths

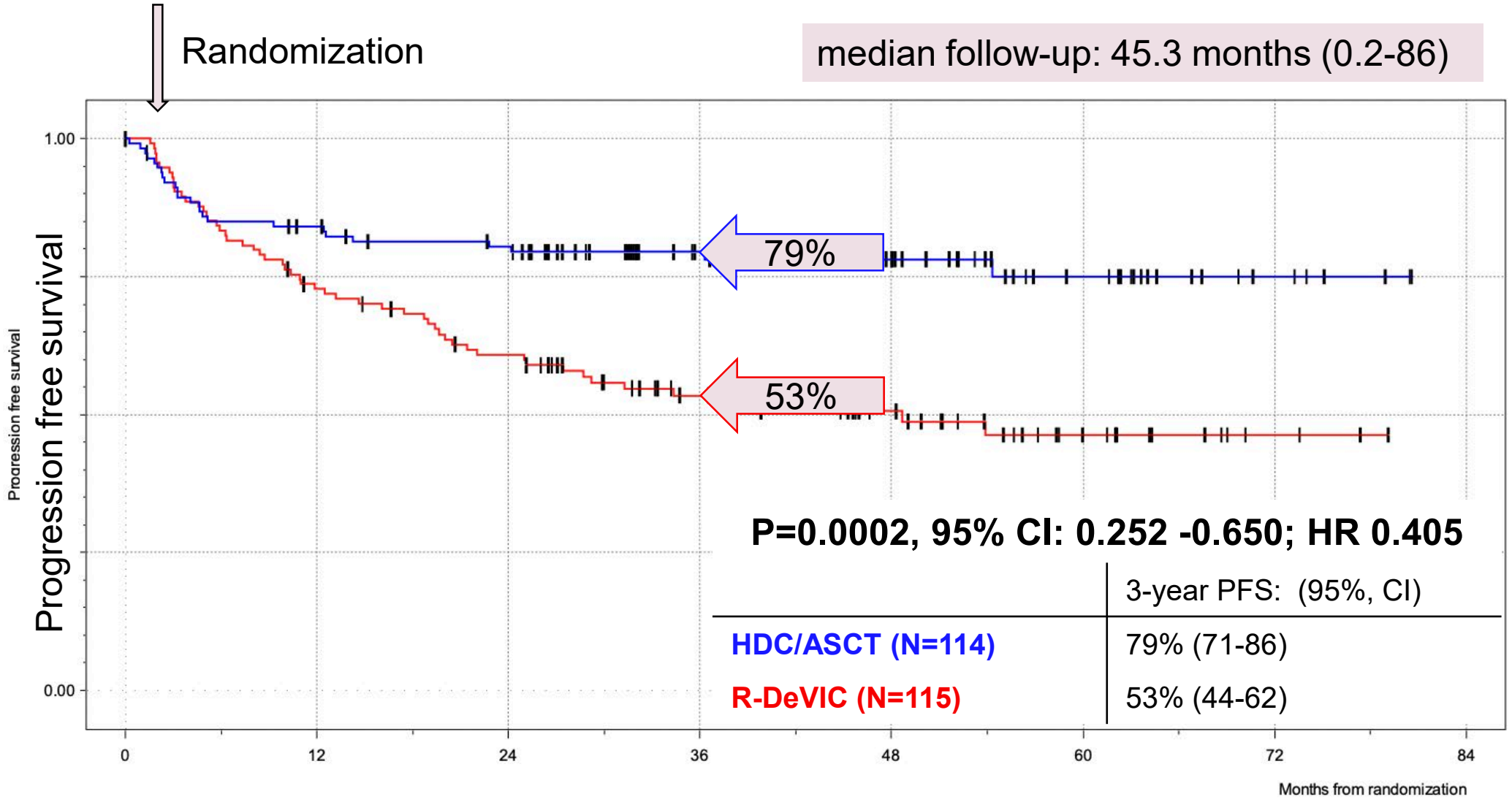
HDT/ASCT	R-DeVIC
4 (3.4%)	0 (0%)

No difference in neurotoxicity so far

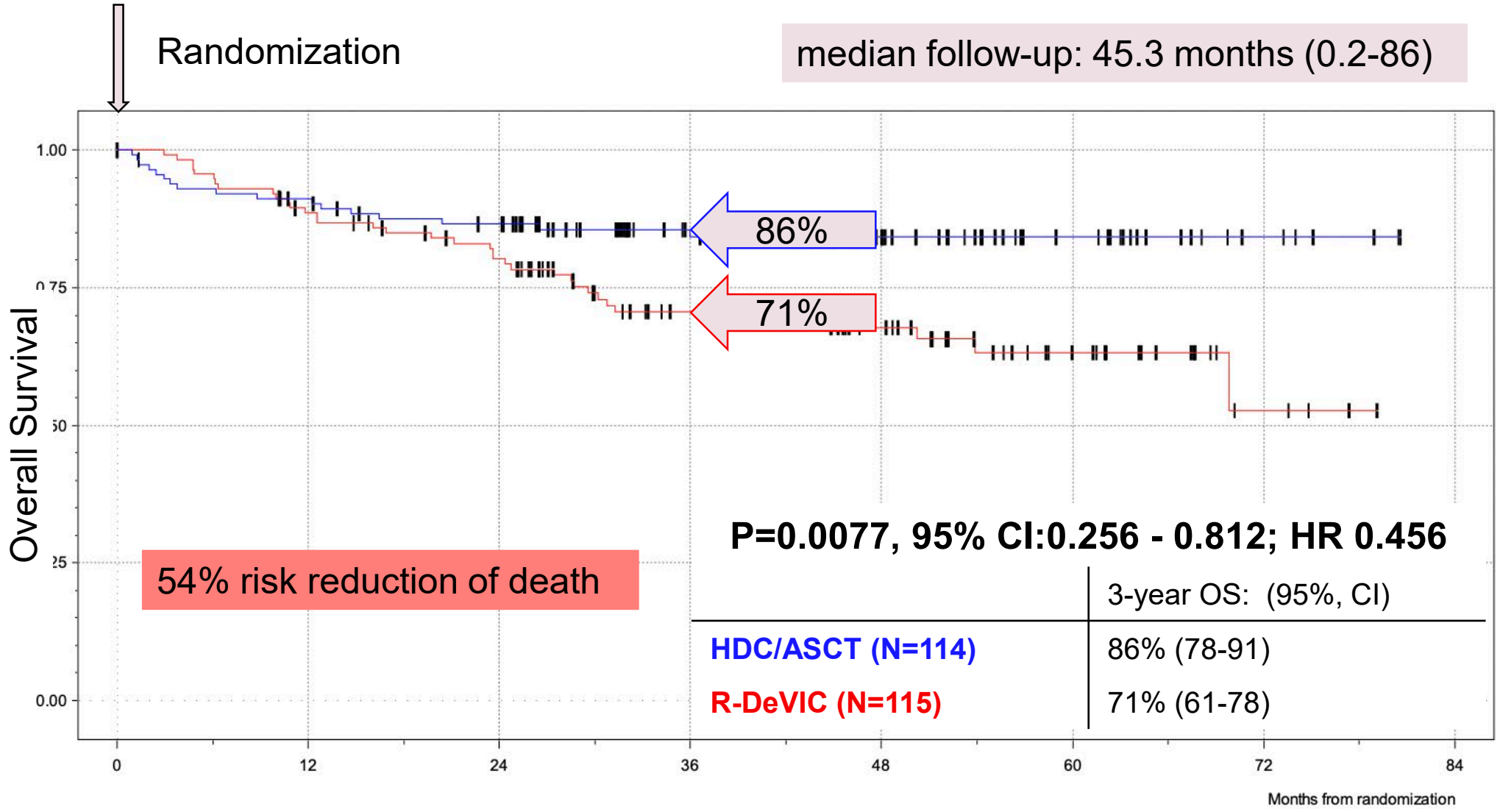
Response (randomized patients)



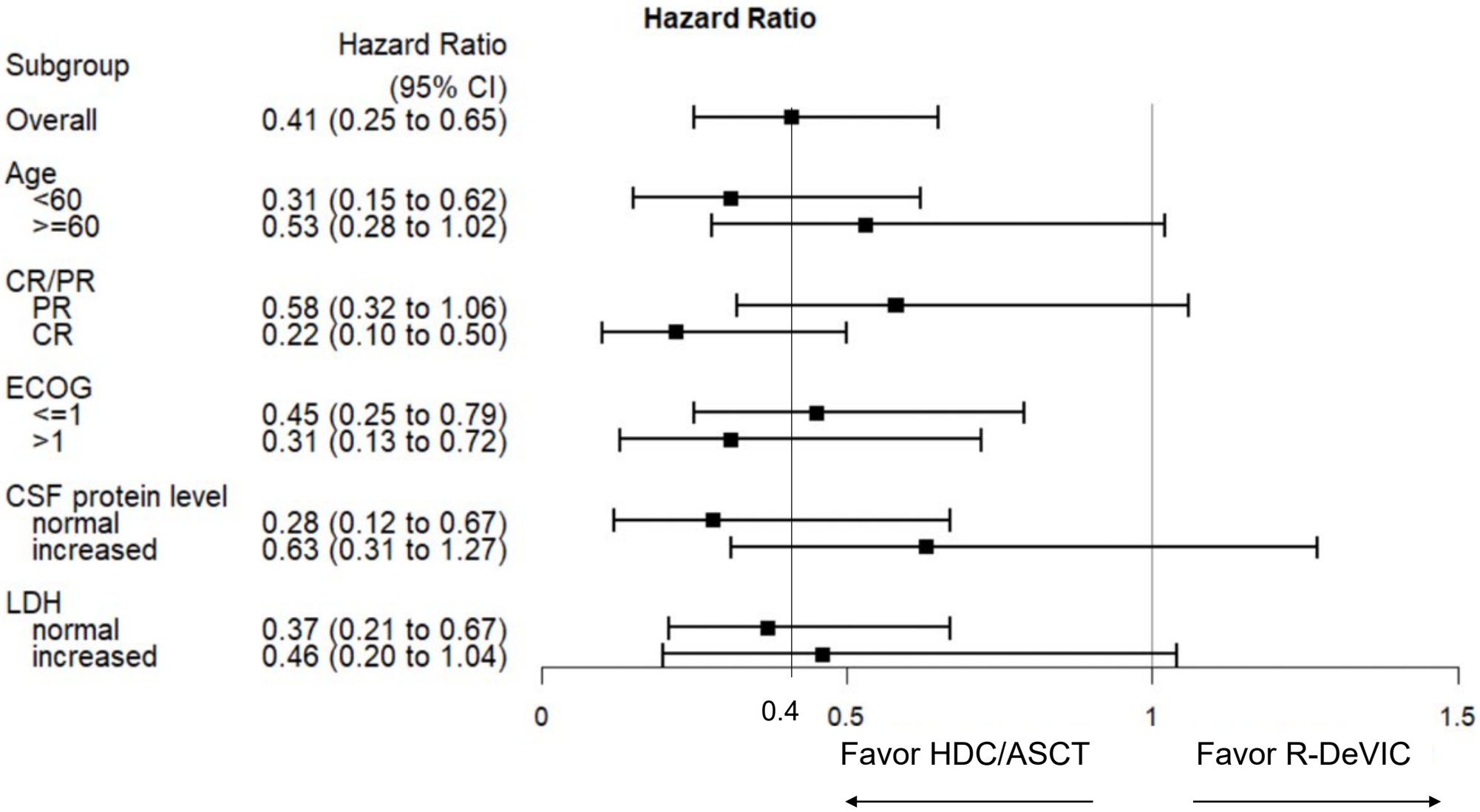
MATRix/IELSG43 Trial – PFS (ITT)



MATRix/IELSG43 Trial – OS (ITT)



Subgroup Analysis (PFS)



PCNSL: IELSG43 AutoSCT

- AutoSCT improves PFS & OS compared to conventional chemo
  - 3 yr PFS 79% (HR 0.40) and OS 86% (HR 0.45)
- Benefit maintained in age 60-70
- Cognitive data not shown

- Comparison to Low Dose WBRT strategy?