Kompetenznetz Maligne Lymphome

64th ASH Meeting 2022

New Orleans & virtuell

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

Kompetenznetz Maligne Lymphome

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KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

Prof. Dr. med. Martin Dreyling
Klinikum der Universität München

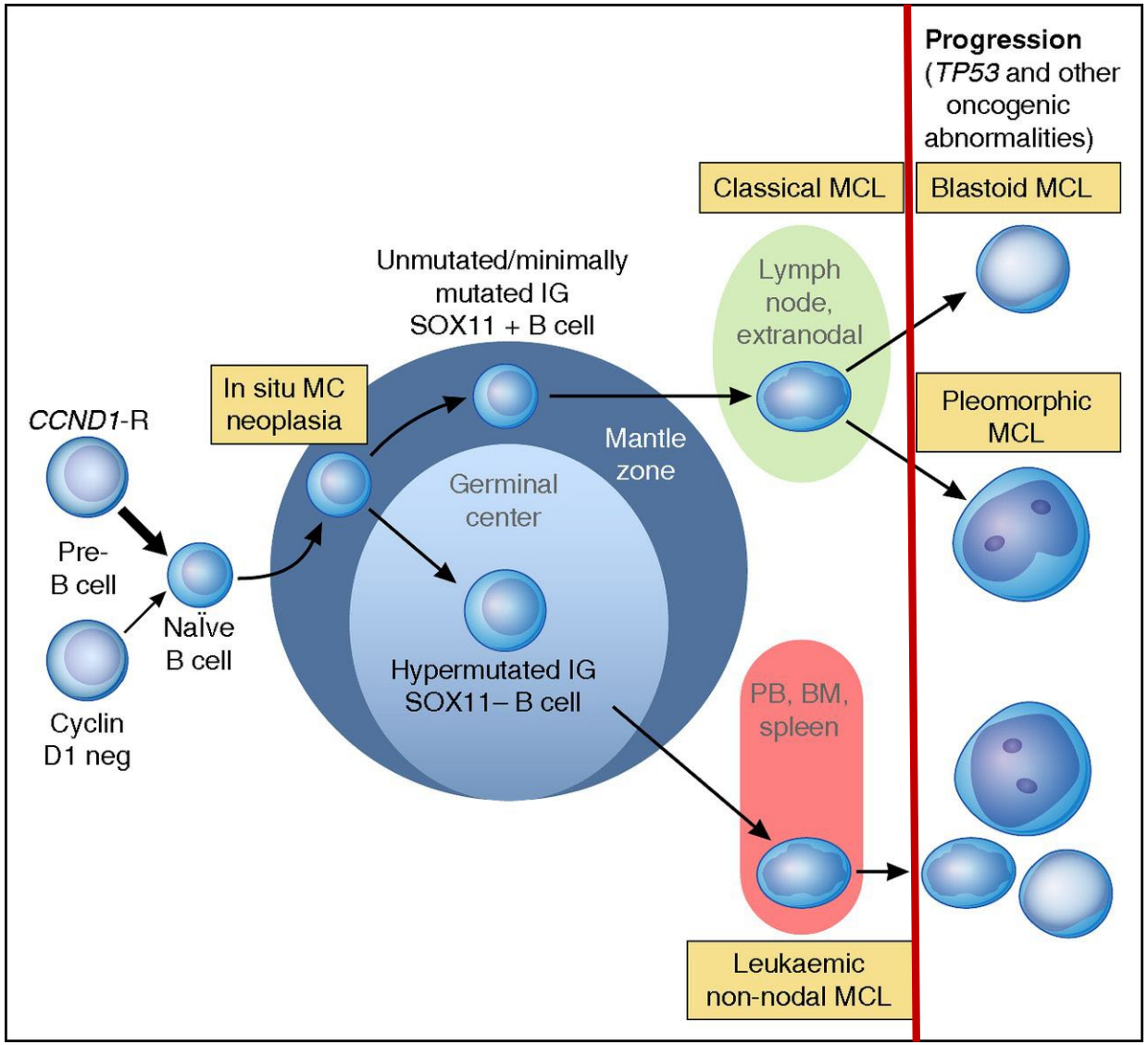
Grußwort Mantelzell-Lymphom (MCL)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2021 wird in Kooperation mit sechs 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	**Amgen, Astra Zeneca, Gilead/Kite, Janssen, Lilly, Novartis, Roche**
Scientific Advisory Board	**Astra Zeneca, Beigene, BMS/Celgene, Gilead/Kite, Janssen, Lilly/Loxo, Novartis, Roche**

MCL: *two kind of diseases*



Dreyling, ESMO CR 2017

Kapitel 1

MCL: Erstlinientherapie

Mantle cell lymphoma
Therapeutic algorithm

LMU KLINIKUM

young patient (≤65)	elderly patient (>65)	compromised patient
First line treatment		
dose-intensified immuno-chemotherapy (R-CHOP, high dose Ara-C) ⇒ Autologous SCT ⇒ Rituximab maintenance	conventional immuno-chemotherapy (VR-CAP, R-CHOP,BR+/-I, R-BAC) ⇓ Rituximab maintenance	Best supportive care? R-Chlorambucil BR (dose-reduced) R-CVP
1. relapse		
immuno-chemotherapy (R-BAC, BR) or targeted approaches ⇓ discuss: - allogeneic SCT	immuno-chemotherapy (BR, R-BAC) or targeted approaches ⇓ discuss: - Rituximab maintenance - radioimmunotherapy	Immuno-chemotherapy (BR) or targeted approaches
higher relapse		
Targeted approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination) Alternatively: repeat previous therapy (long remissions)		

Dreyling, ESMO CR MCL 2017 (updated)

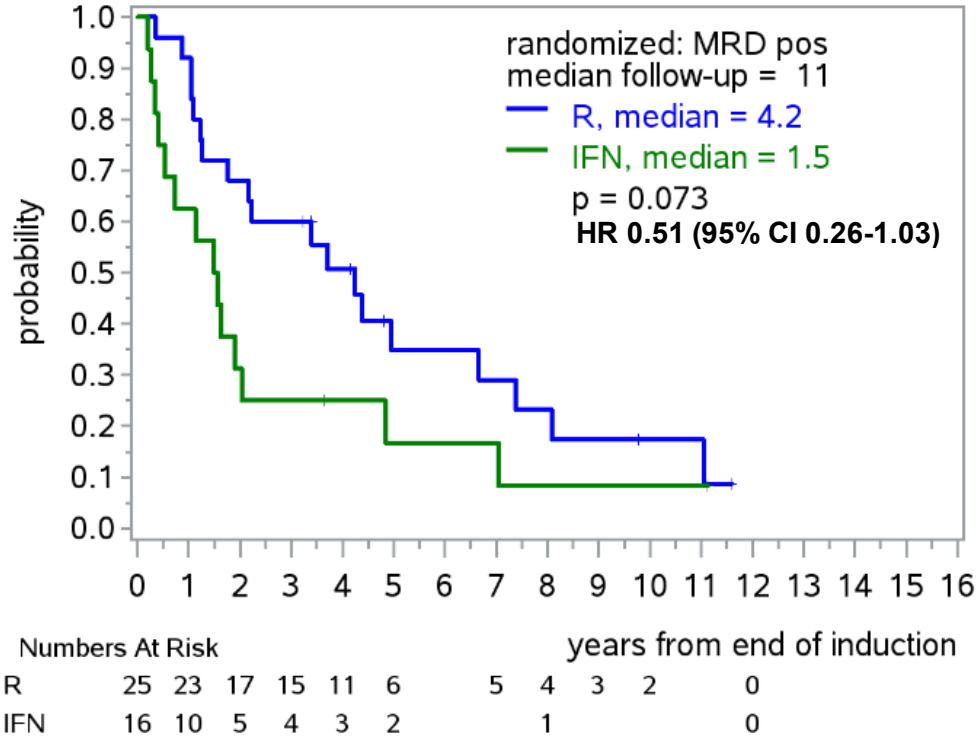
LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN
MEDIZINISCHE FAKULTÄT
INSTITUT FÜR MEDIZINISCHE INFORMATIONSVERARBEITUNG BIOMETRIE UND EPIDEMIOLOGIE (IBE)

Eva Hoster, Marie-Hélène Delfau-Larue, Elizabeth Macintyre, Linmiao Jiang, Stephan Stilgenbauer, Ursula Vehling-Kaiser, Gilles Salles, Catherine Thieblemont, Hervé Tilly, Lothar Kanz, Pierre Feugier, Kai Hübel, Christian Schmidt, Vincent Ribrag, Hanneke Kluin-Nelemans, Martin Dreyling, Christiane Pott

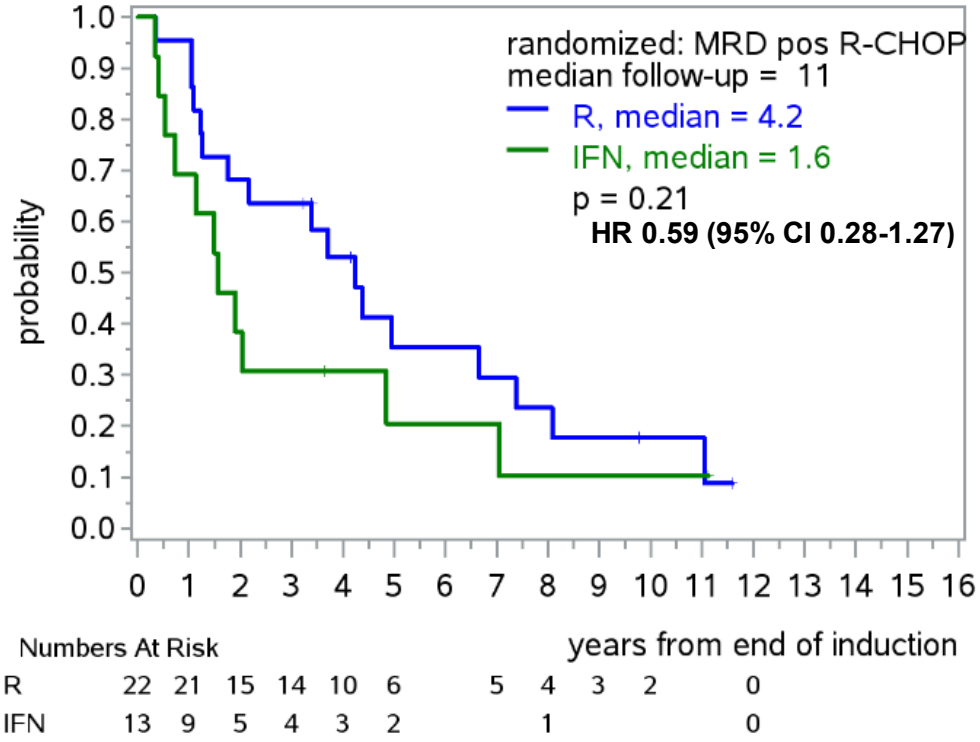
Predictive Value of Minimal Residual Disease on Efficacy of Rituximab Maintenance in Mantle Cell Lymphoma: Results from the European MCL Elderly Trial

EUROPEAN mcl NETWORK

Efficacy of R maintenance: MRD positive patients

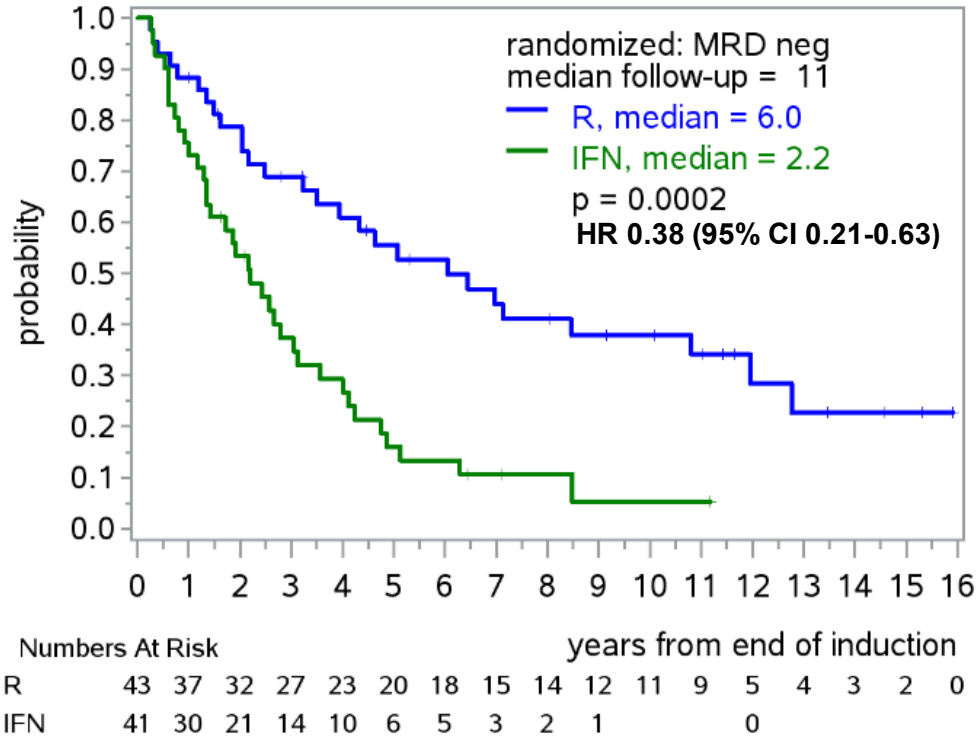


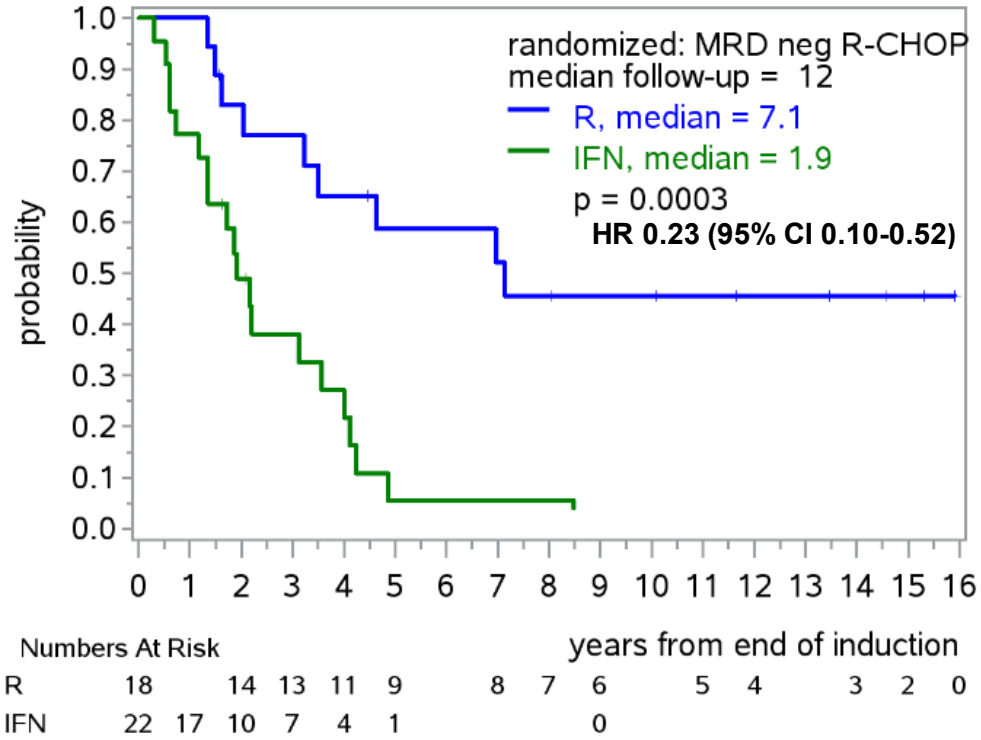
- efficacy of R-maintenance in MRD-positive patients potentially reduced



- especially after R-CHOP

Efficacy of R maintenance: MRD negative patients





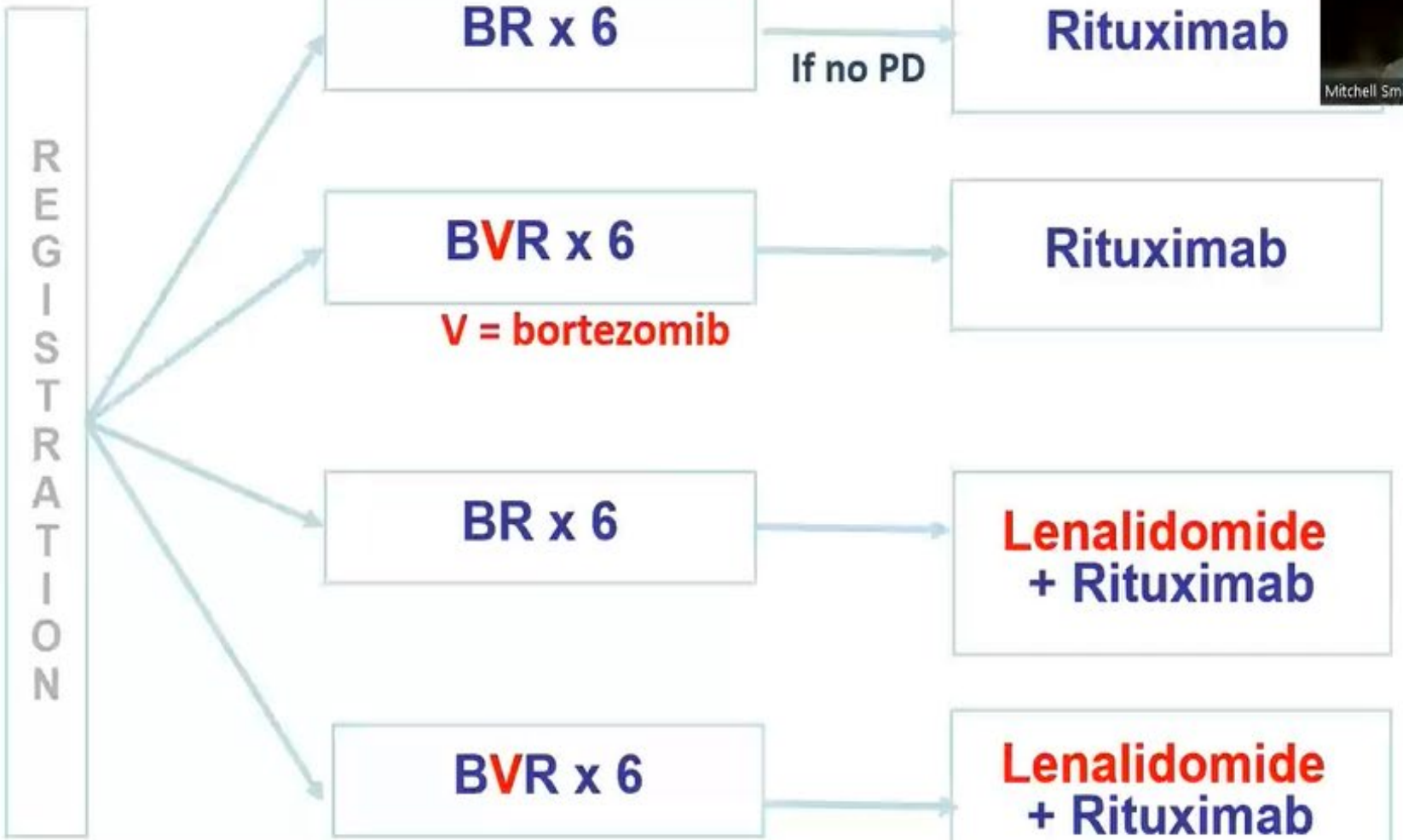
- confirmed efficacy of R-maintenance in MRD-negative patients

Randomized Phase 2 Trial of Front-Line Bendamustine-Rituximab (BR)-Based Induction Followed By Rituximab ± Lenalidomide Consolidation for Mantle Cell Lymphoma

ECOG-ACRIN E1411 NCT01415752

Mitchell R. Smith, Opeyemi Jegede, Peter Martin, Brian G. Till, Samir S. Parekh, David T. Yang, Lale Kostakoglu, Carla Casulo, Nancy L. Bartlett, Paolo F. Caimi, Tarek Al Baghdadi, Kami J. Maddocks, Mark D. Romer, David J. Inwards, Rachel E. Lerner, Lynne I. Wagner, Richard F. Little, Jonathan W. Friedberg, John P. Leonard, Brad S. Kahl

E1411 SCHEMA



Induction:

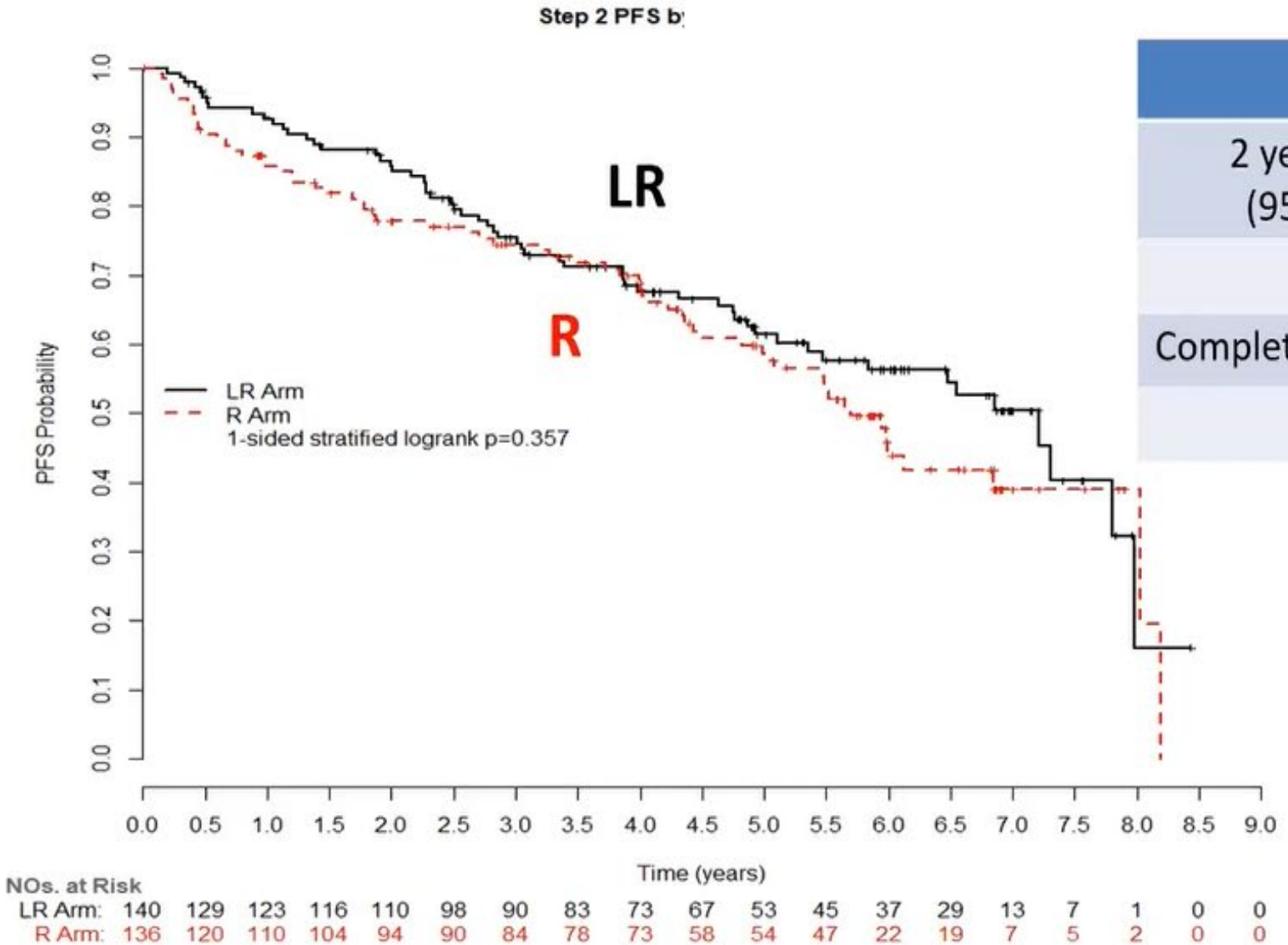
BR = bendamustine 90 mg/m^2/d days 1, 2 + rituximab 375 mg/m^2 day 1, every 28 days x 6

BVR = BR + bortezomib 1.3 mg/m^2 days 1, 4, 8, 11 (later amended to 1.6 mg/m^2 days 1, 8), IV or SQ

Consolidation:

Rituximab 375 mg/m^2 every 8 weeks x 12 doses ± Lenalidomide 15 mg/d on days 21/28 x 24 cycles

PFS BY CONSOLIDATION: R vs LR



	BR/BVR + R	BR/BVR + LR
2 year PFS (95% CI)	78% (70-84%)	86% (79-91%)
p = NS		
Complete Response	87%	84%
P = NS		

Mantle cell lymphoma
Therapeutic algorithm

LMU KLINIKUM

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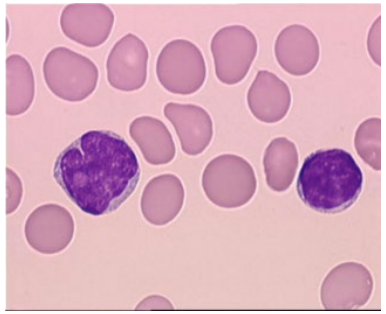
Dreyling, ESMO CR MCL 2017 (updated)

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
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 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*

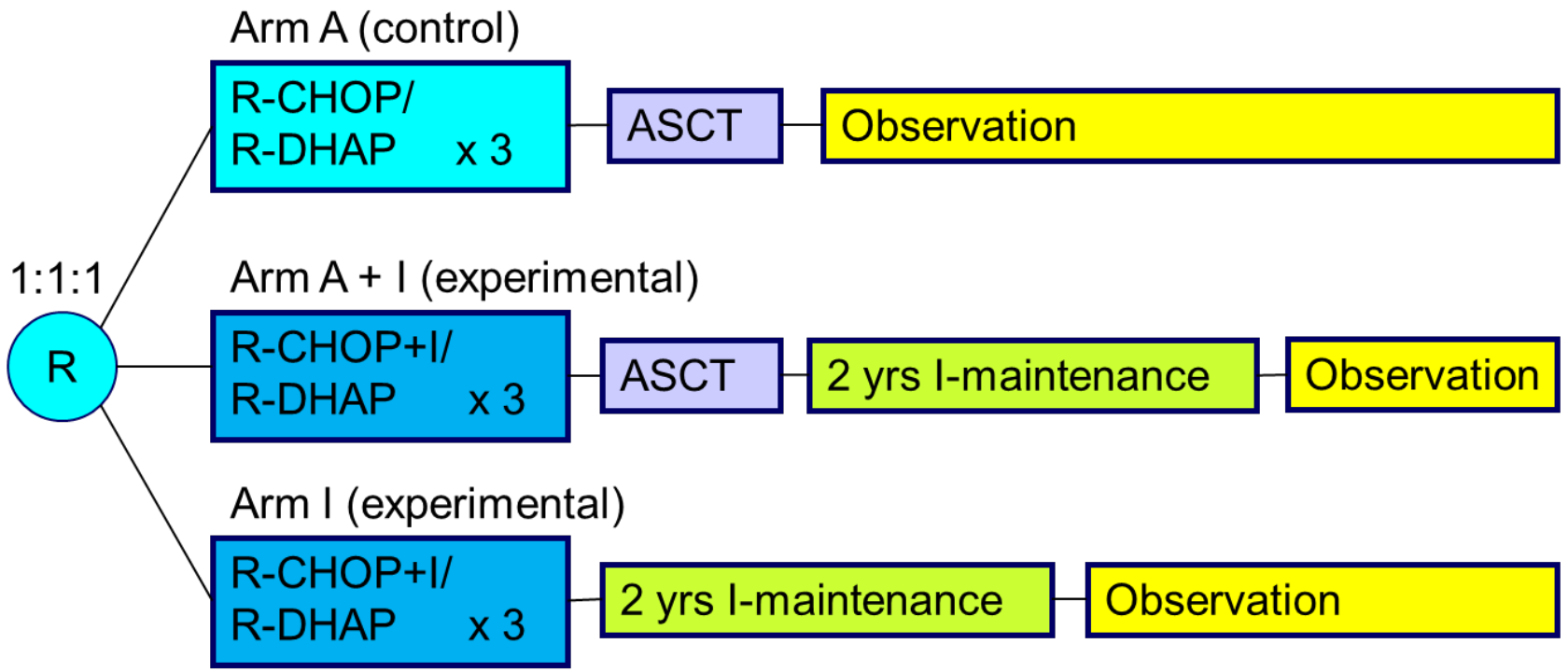
LMU University Hospital Munich, Germany; Erasmus MC Cancer Institute, University Medical Center Rotterdam, Netherlands; Hospital Clinic of Barcelona, Spain; Skane University Hospital and Lund University, Lund, Sweden; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Rigshospitalet, 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

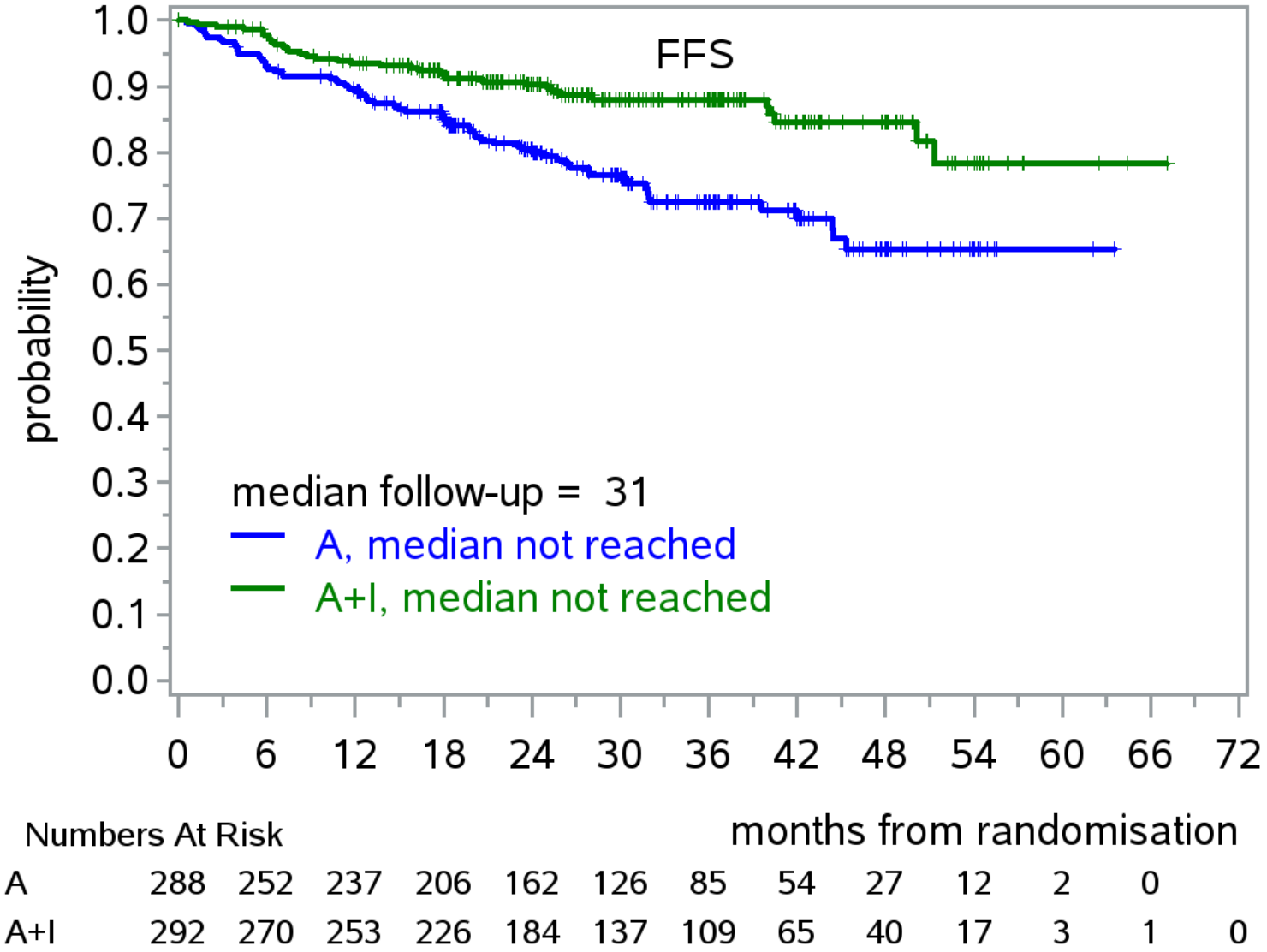
- Primary outcome: FFS

- 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: FFS Superiority of A+I vs. A

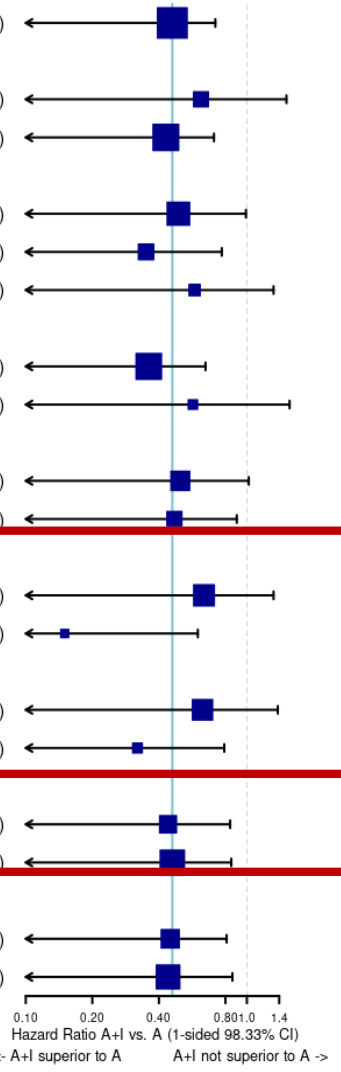


- Superiority of A+I vs. A (FFS) is confirmed
- Kaplan-Meier plots:
  - 3-year FFS A+I: 88%
  - 3-year FFS A: 72%
- p-value (corrected for sequential design) p=0.0008
- HR (A+I vs. A): HR=0.52

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

TRIANGLE: FFS Superiority of A+I vs. A

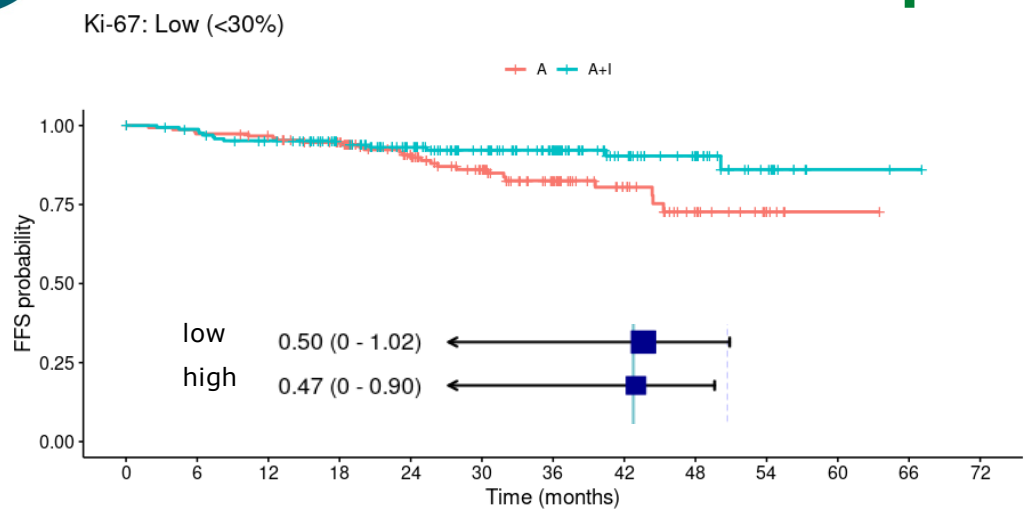
Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% CI)
All	580	103	0.46 (0 - 0.72)
Sex (p=0.0016)			
Female	146	23	0.62 (0 - 1.51)
Male	434	80	0.43 (0 - 0.71)
MIPI			
Low	336	40	0.49 (0 - 0.99)
Intermediate (p=0.49)	159	35	0.35 (0 - 0.77)
High (p=0.69)	85	28	0.58 (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)

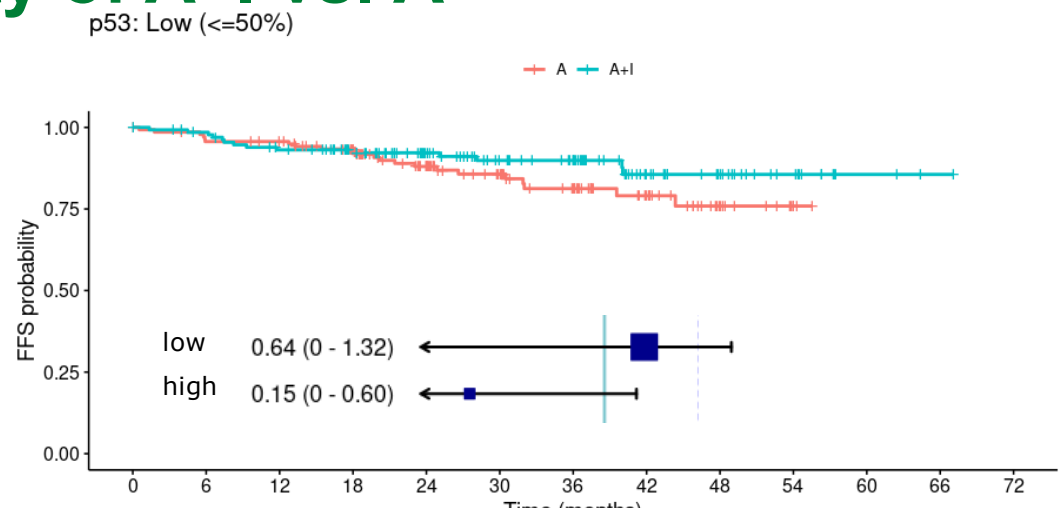


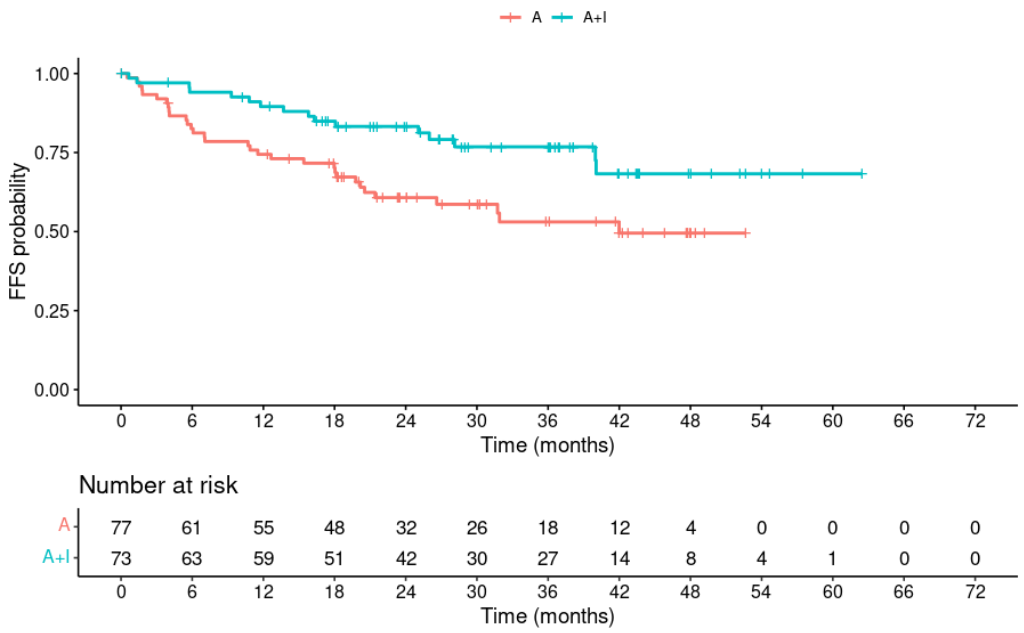
- similar in all MIPI groups
- No differential efficacy according to cytology and Ki-67
- More effective in high p53 expressors
- Trend toward higher efficacy in high risk biology
- No differential efficacy by rituximab maintenance

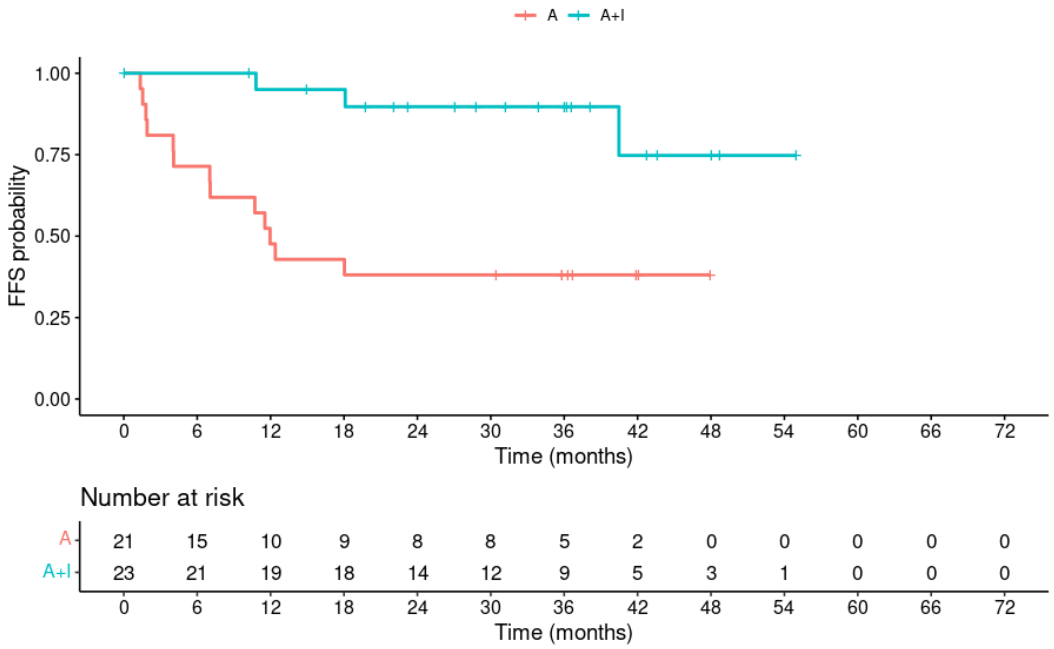
A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

TRIANGLE: FFS Superiority of A+I vs. A



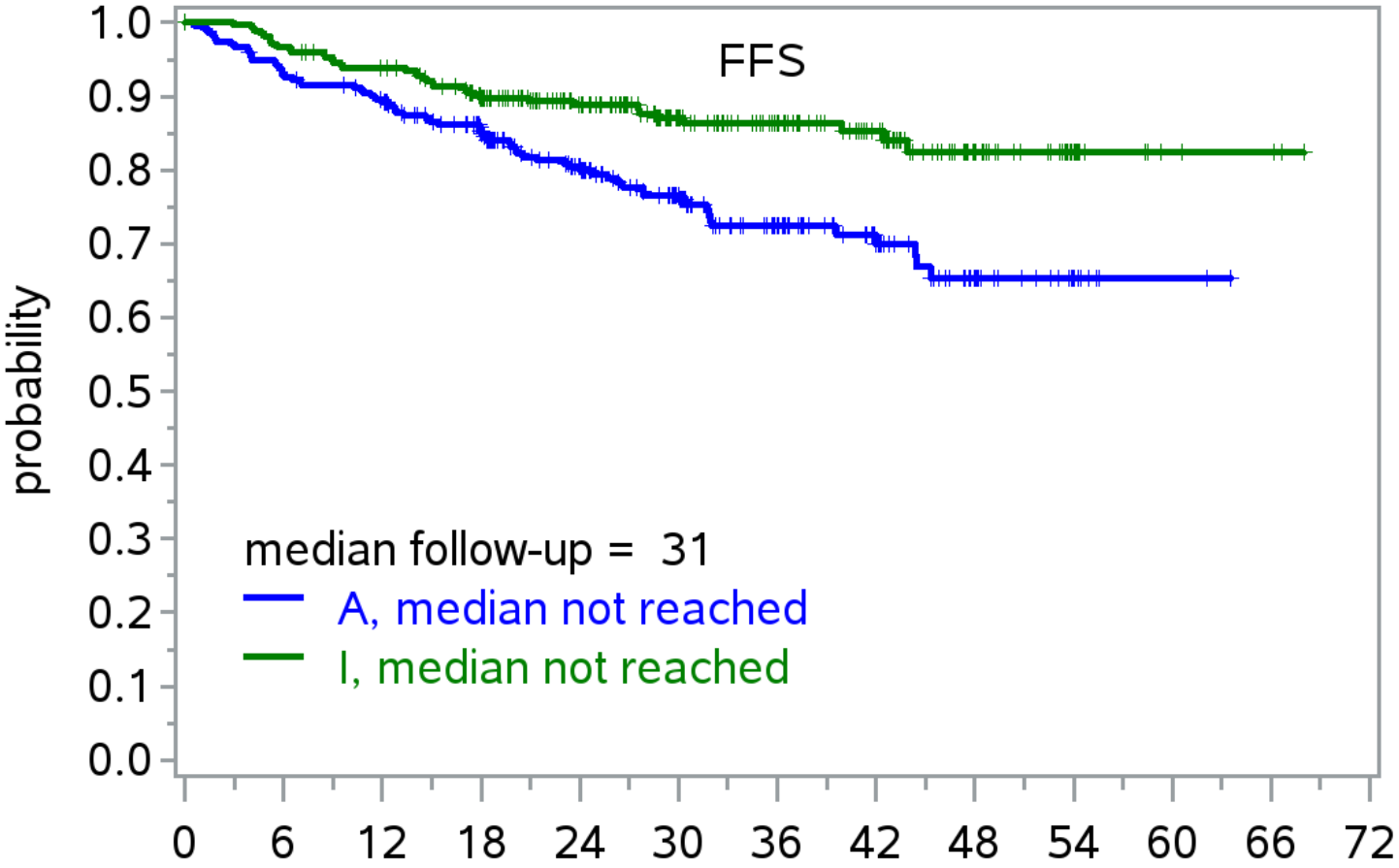






A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

TRIANGLE: No FFS Superiority of A vs. I



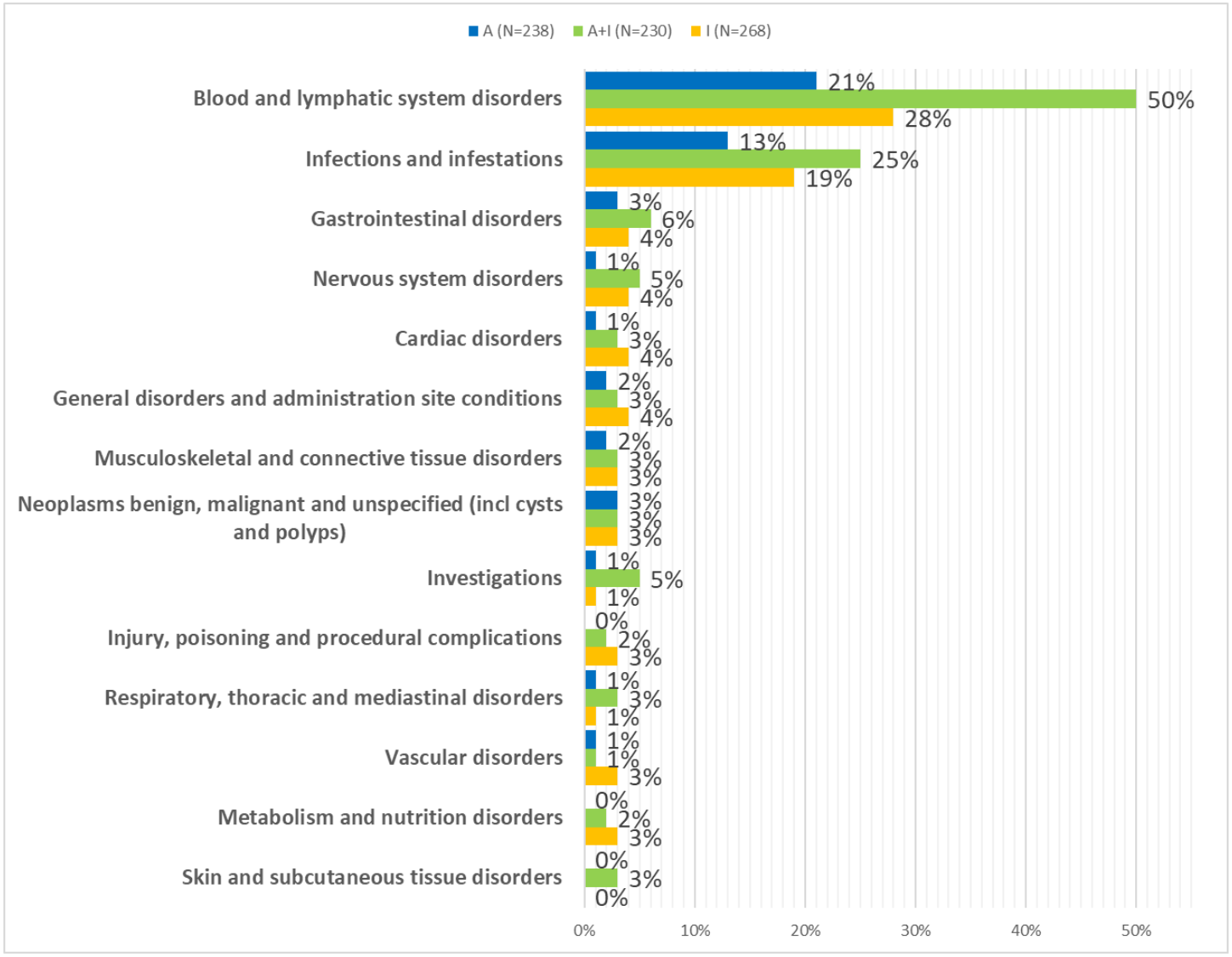
Numbers At Risk

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: 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%

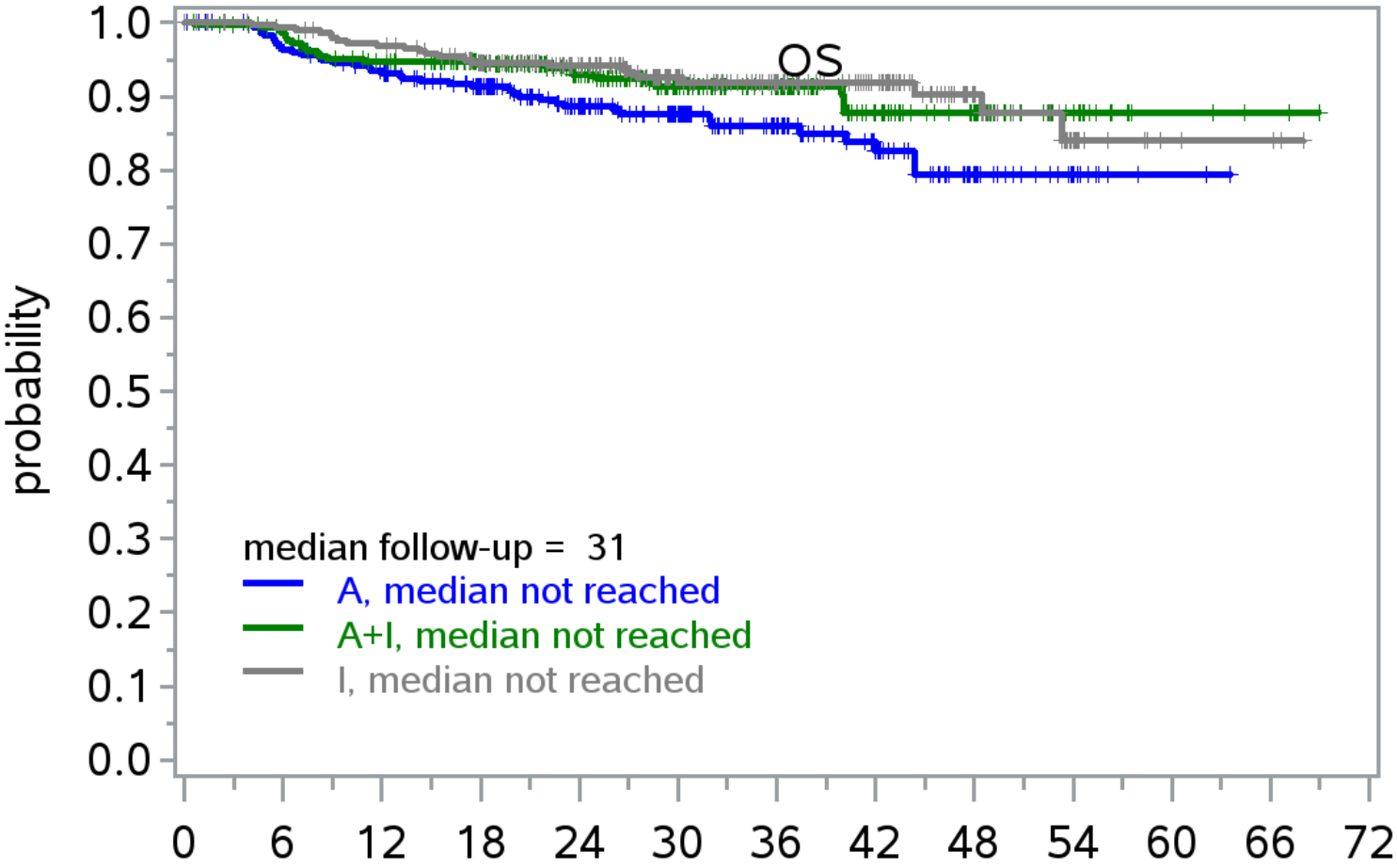
Grade 5

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

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

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 Ibrutinib only**

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

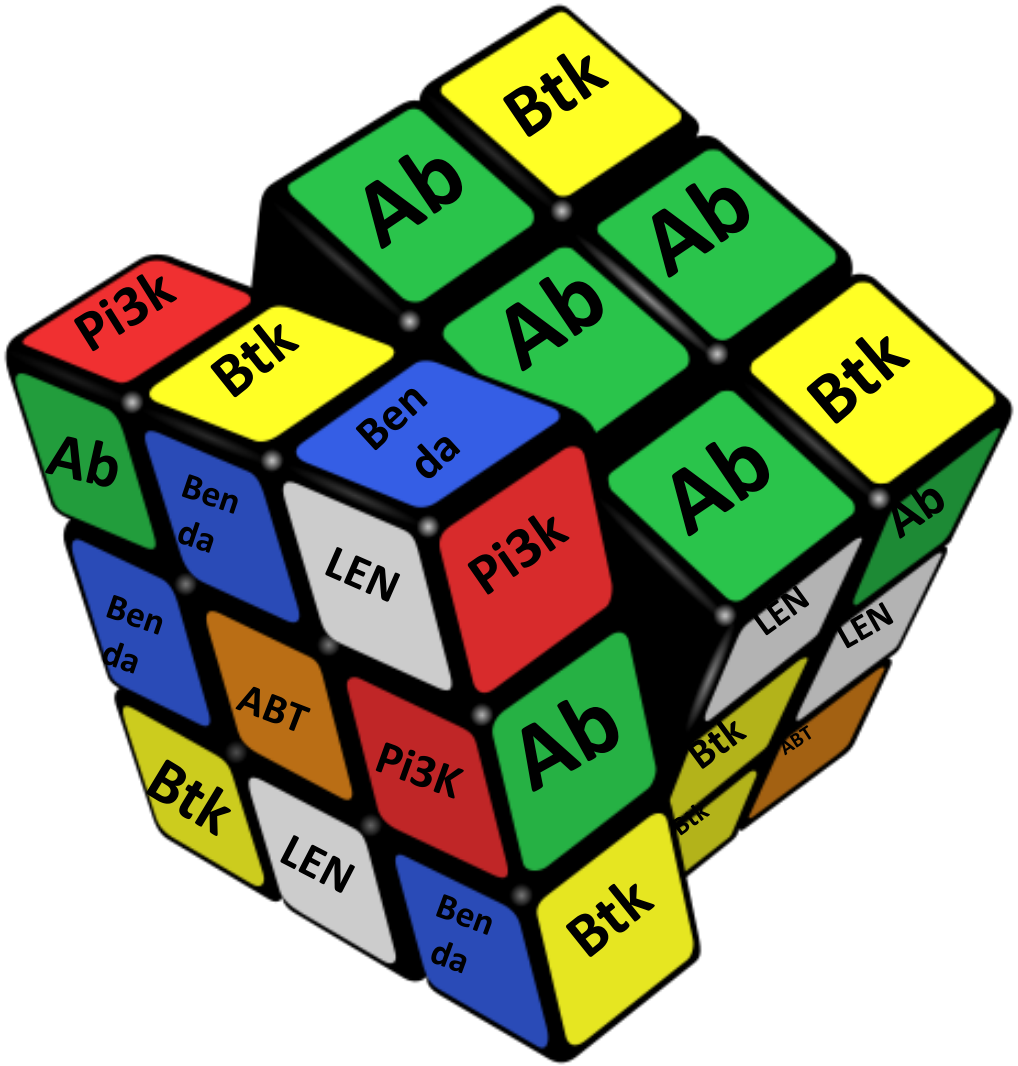
A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Kapitel 2

Rezidiviertes MCL:

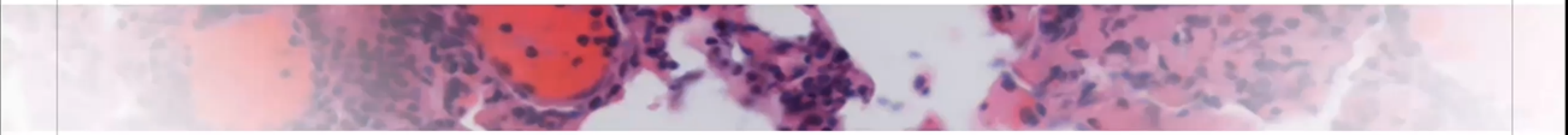
BTK-Kombinationen

Mantle cell lymphoma
The era of combinations



American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



PHASE 1/2 STUDY OF ZILOVERTAMAB AND IBRUTINIB IN MANTLE CELL LYMPHOMA (MCL), CHRONIC LYMPHOCYTIC LEUKEMIA (CLL), OR MARGINAL ZONE LYMPHOMA (MZL)

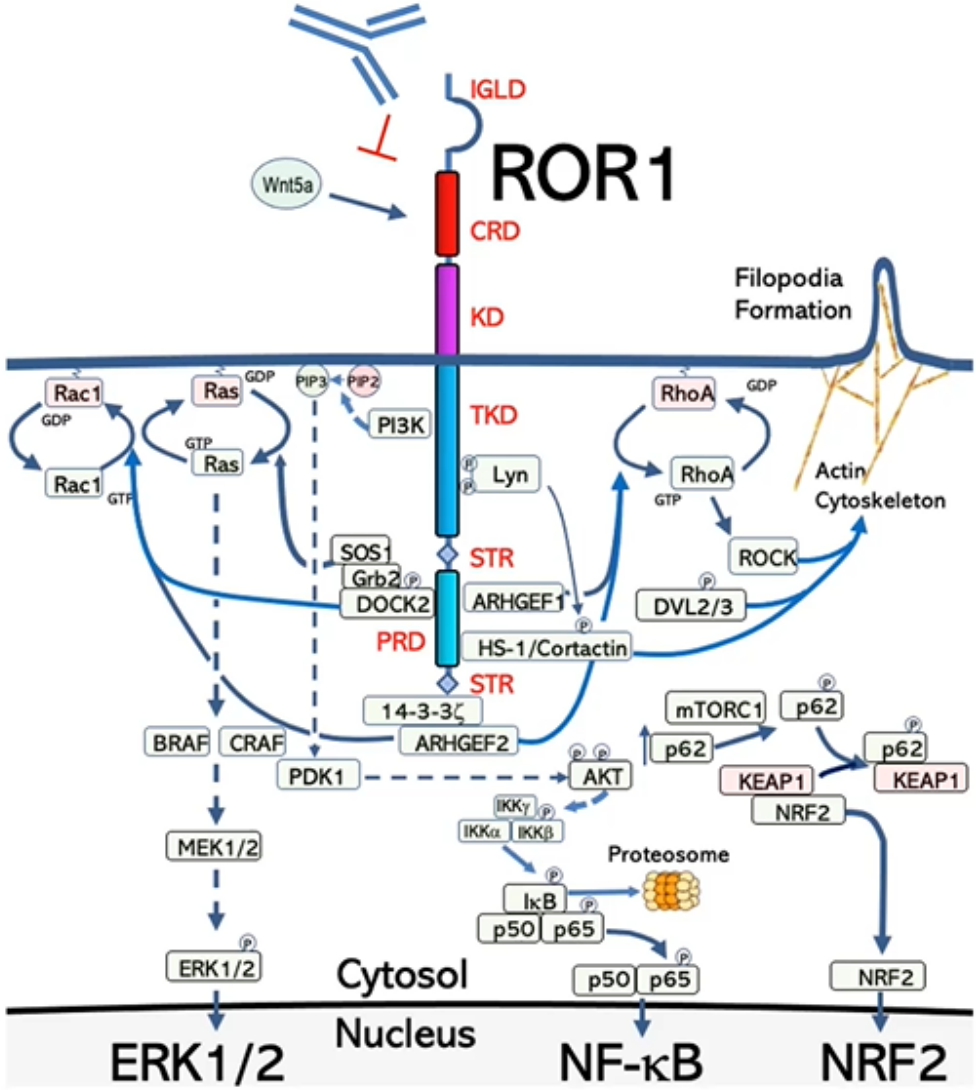
HJ. LEE[1], M. CHOI[2], T. SIDDIQI[3], J. RHODES[4], W. WIERDA[5], I. ISUFI[6], J. TUSCANO[7], N. LAMANNA[8], S. SUBBIAH[9], J. KOFF[10], L. LESLIE[11], A. GOLDENBERG[12], G. CHUNG[13], J. BREITMEYER[14], S. YAZJI[14], M. WANG[1], C. JAMIESON[2] and T. KIPPS[2]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]University of California San Diego, La Jolla, CA, [3]City of Hope, Duarte, CA, [4]Northwell Health, Manhasset, NY, [5]University of Texas M.D. Anderson Cancer Center, Houston, TX, [6]Yale University School of Medicine, New Haven, CT, [7]University of California, Davis, CA, [8]Columbia University Medical Center, New York, NY, [9]LSU, New Orleans, LA, [10]Emory University, Atlanta, GA, [11]John Theurer Cancer Center, Hackensack, NJ, [12]Manhattan Hem Onc Associates, New York, NY, [13]The Christ Hospital, Cincinnati, OH, [14]Oncternal Therapeutics, San Diego, CA.

Data cut for all data presented is 11Oct2022

Background

- ROR1 is an onco-embryonic kinase-like receptor that is expressed at high levels in many solid and hematologic malignancies, including MCL, CLL, and MZL, but not on normal adult tissues.
- Wnt5a can activate ROR1-signaling, which enhances expression of genes induced by activation of ERK1/2, NF-kB, and NRF2 that can promote cancer-cell growth, migration, self-renewal, and resistance to therapy
- Zilovertamab (formerly cirmtuzumab) is a fully humanized anti-ROR1 mAb designed to inhibit ROR1-signaling
- Zilovertamab inhibits CLL-cell expression of genes induced by activated ERK1/2, NF-kB, STAT3, and NRF2 that may promote the survival and growth of CLL cells with mutated TP53 of patients treated with inhibitors of Bruton Tyrosine Kinase (BTK) (e.g. ibrutinib)

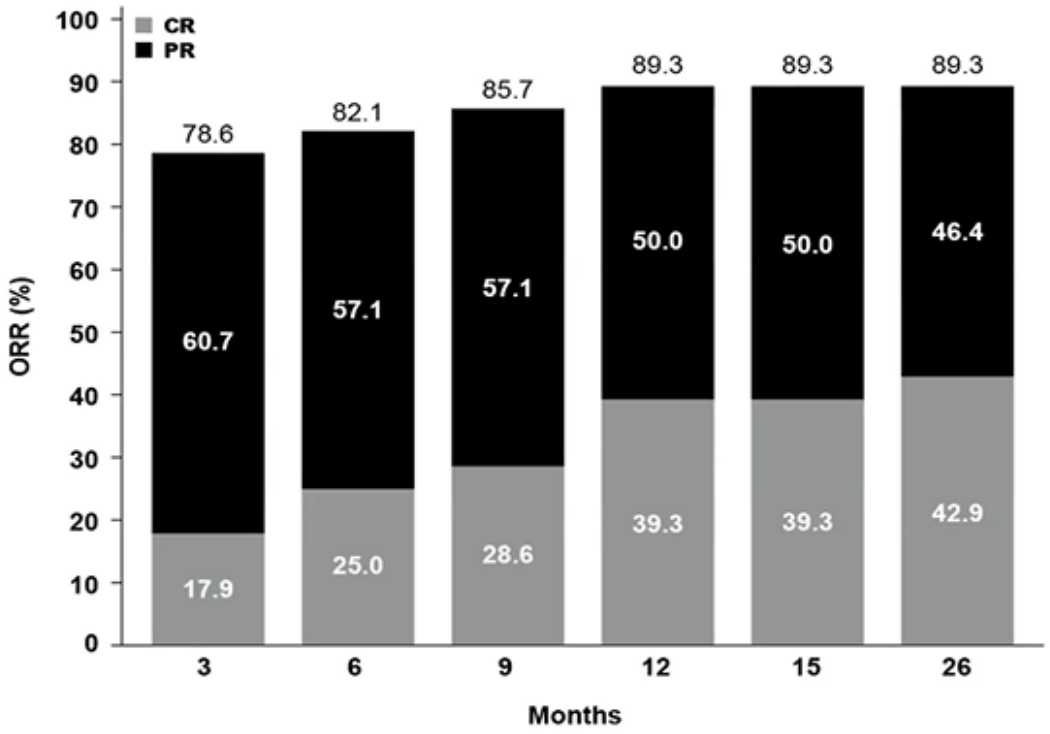


Source: Kipps, Blood 2022

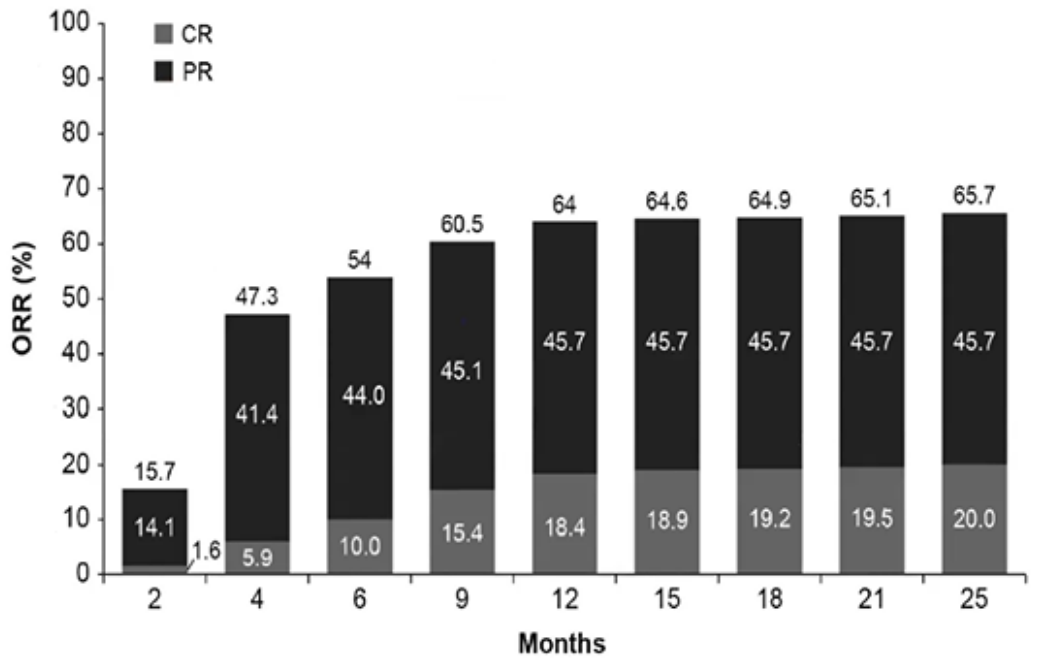
MCL Efficacy: Clinical Response Rates Over Time

Zilovertamab + ibrutinib combination demonstrates rapid achievement of response

Zilovertamab + ibrutinib



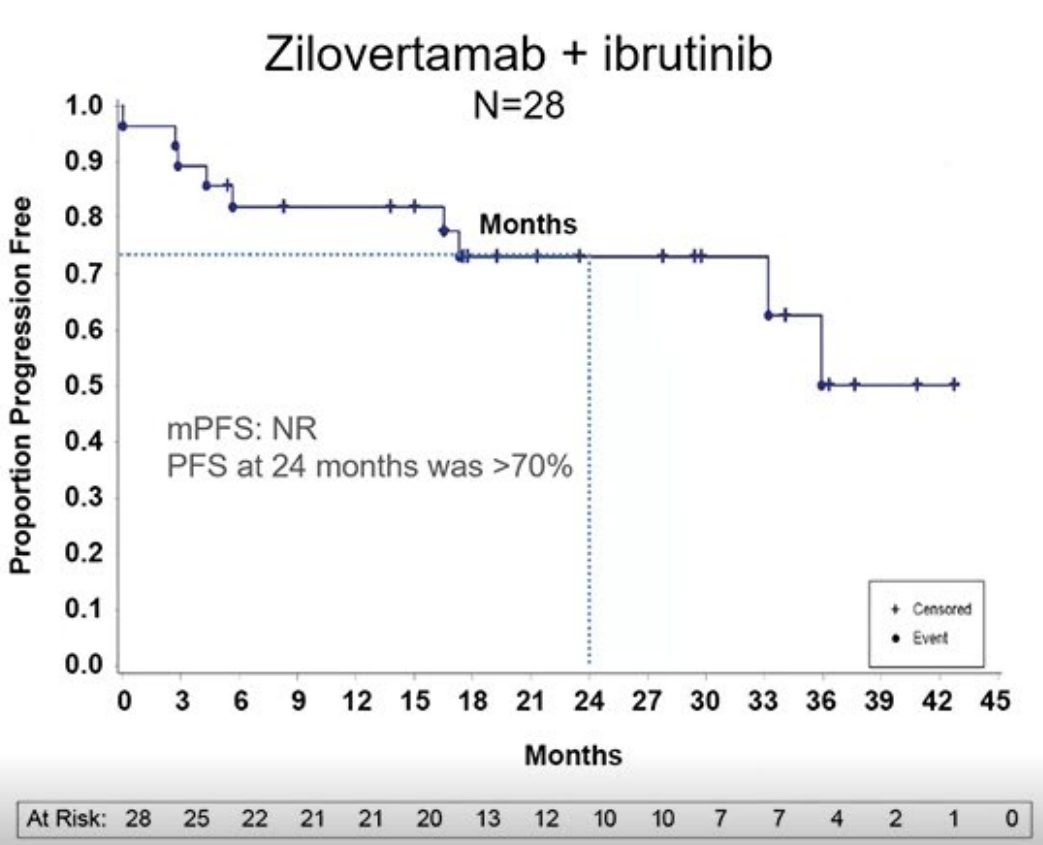
Historical ibrutinib, Rule 2017[a]

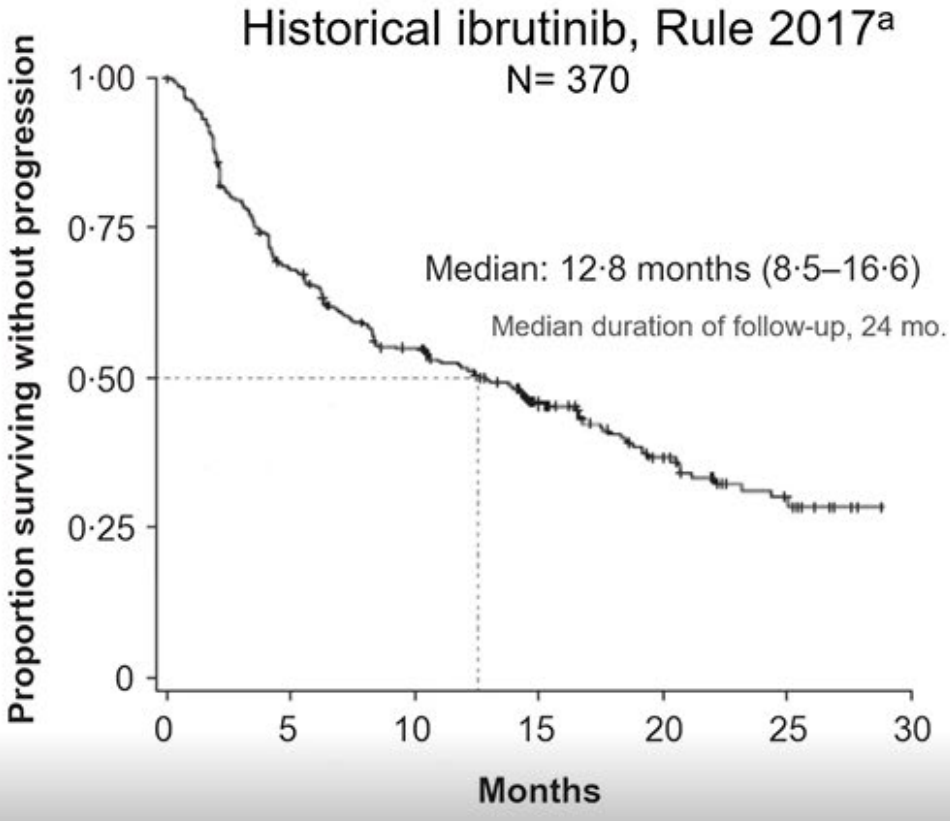


[a] Rule, British Journal of Haematology, 2017

MCL Efficacy: Progression Free Survival

Zilovertamab + ibrutinib combination provides favorable PFS benefit compared to historical ibrutinib treatment alone





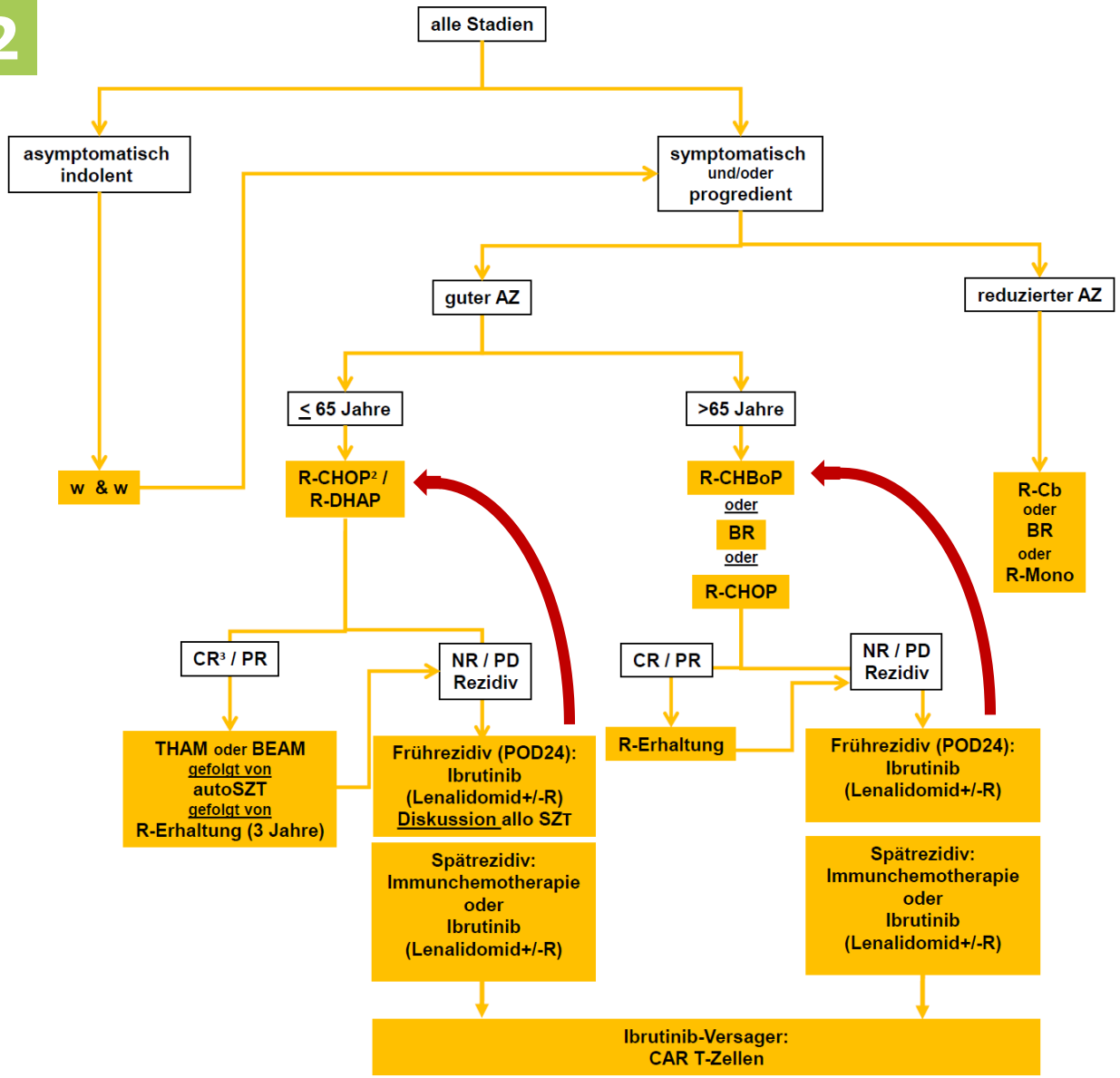
[a] Rule, British Journal of Haematology, 2017

Kapitel 3

Rezidiviertes MCL:

BTKi-Versager

Mantle cell Lymphoma
Onkopedia 2022



TARMAC: Combination of time-limited ibrutinib and tisagenlecleucel in relapsed or refractory mantle cell lymphoma

Phase II primary analysis results

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Study overview

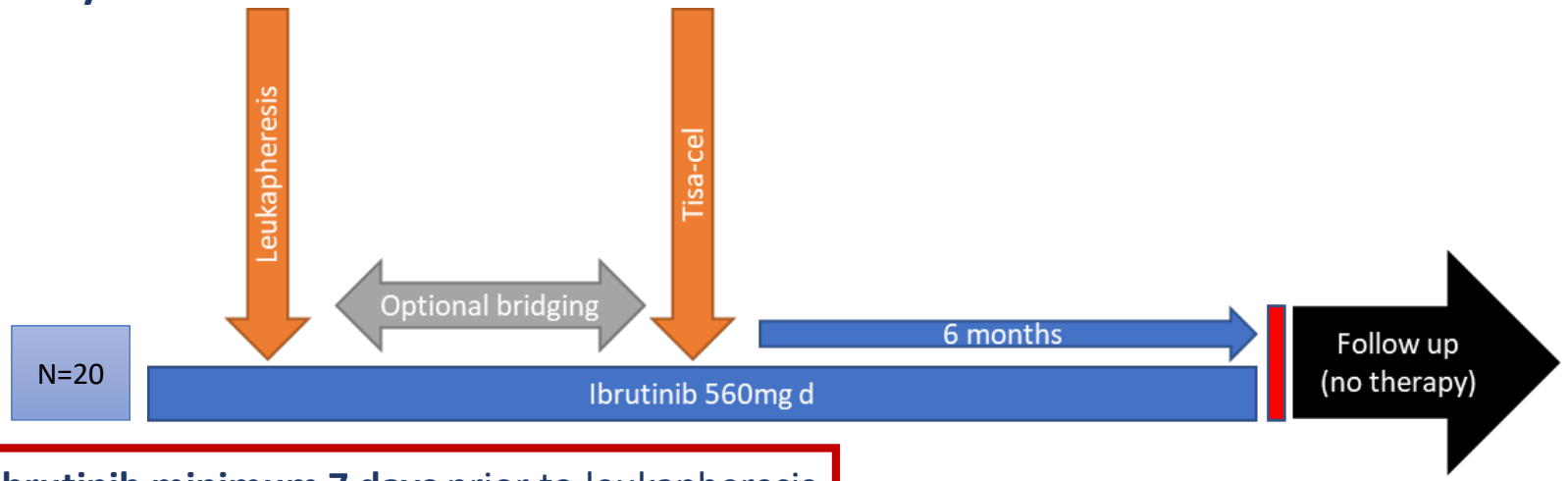
Key inclusion criteria:

- MCL[1]
  - Relapse after 1 line *or*
  - Insufficient response to induction[2]
- >18yo
- Radiographically assessable or bone marrow phase disease

Key exclusion criteria:

- Prior allogeneic transplant
- Active CNS involvement

Study Schema:



Ibrutinib minimum 7 days prior to leukapheresis

Lymphodepletion with fludarabine/cyclophosphamide x 3 days

Tisagenlecleucel median $3.0x10^8$ infused (range 1.3-4.6)

Time-limited therapy: ibrutinib ceased at 6 months if measurable residual disease (MRD) negative by flow cytometry

Primary endpoint: Complete response rate at 4 months post tisagenlecleucel[3]

Key secondary endpoints: Safety, objective response rate, progression free survival, duration of response, overall survival, subgroup analysis based on *TP53* status

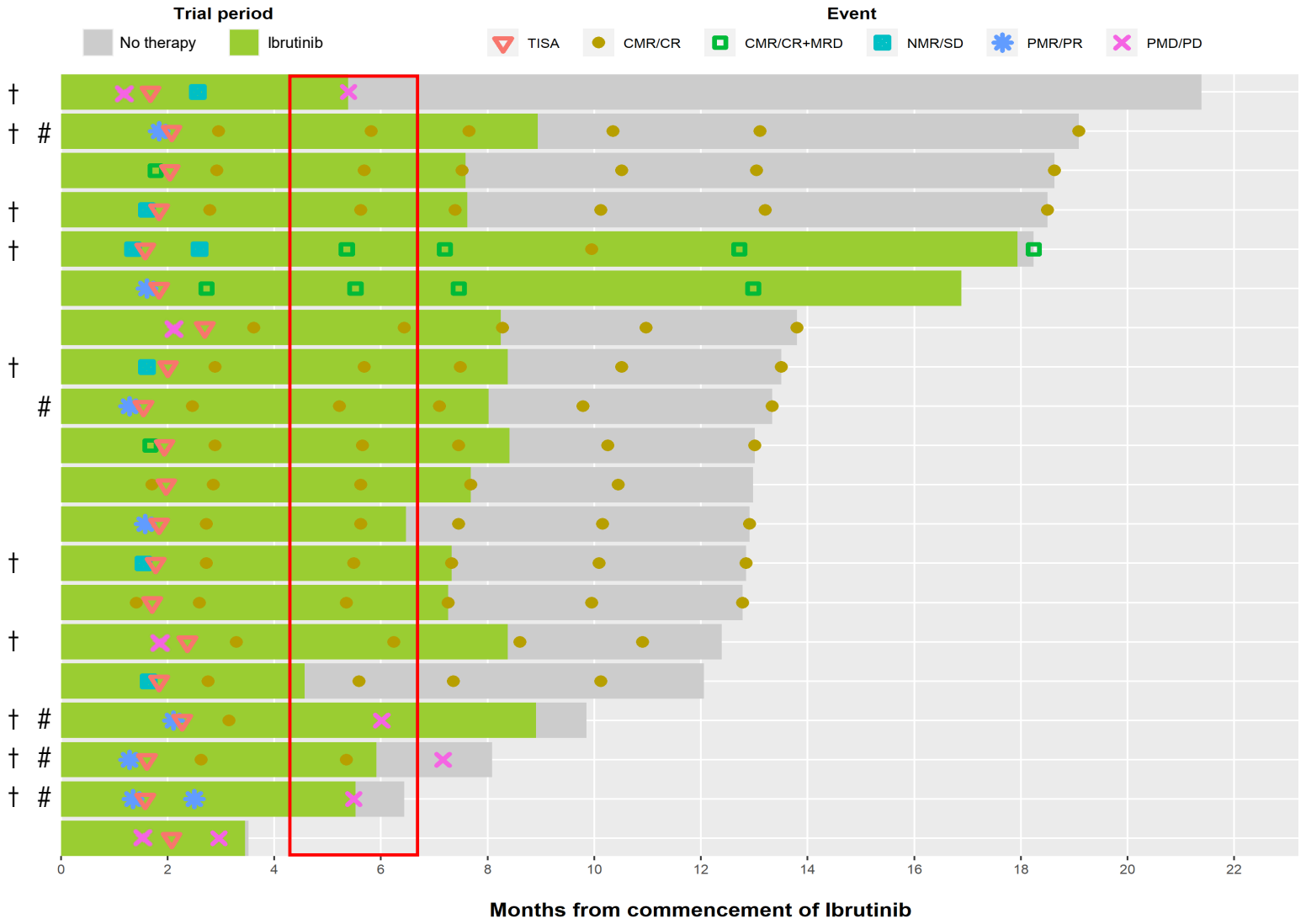
Null hypothesis:

Ibrutinib naïve: CR rate of 9% at M4 and 20% overall with ibrutinib

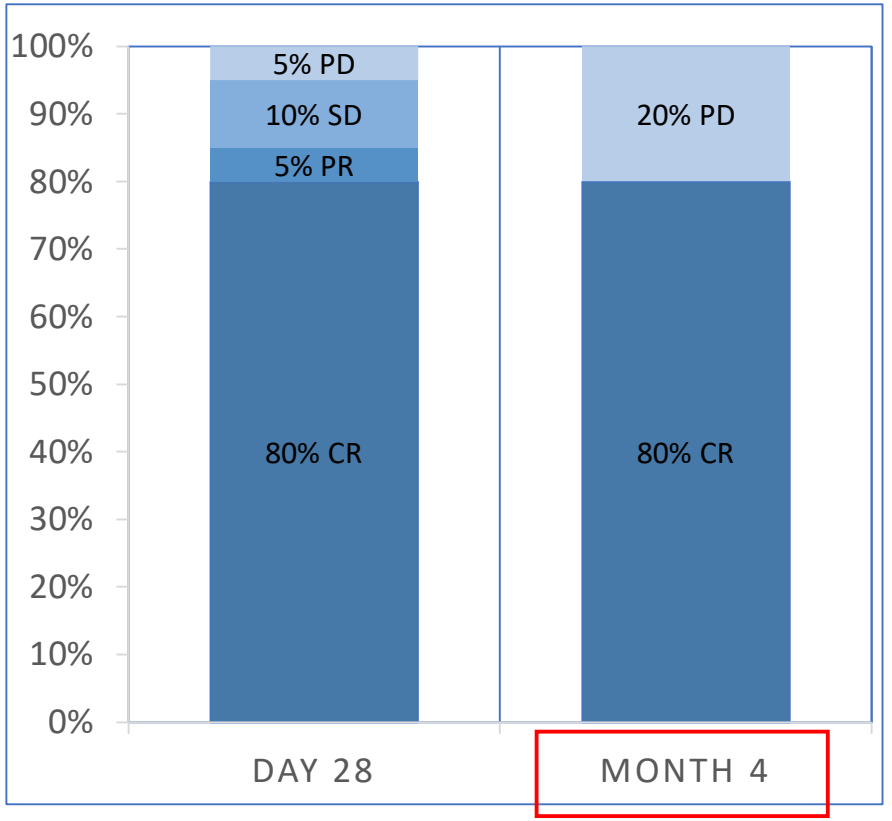
Ibrutinib exposed: CR rate of ~20% with chemotherapy

[1]Confirmed centrally by presence of t(11;14) on fluorescent in-situ hybridisation; [2] No patient was enrolled due to insufficient response to induction, all patients had relapsed after at least one line of treatment; [3]Response assessed at Month 4 with PET/CT by Lugano 2014 criteria, including bone marrow biopsy

Primary endpoint – response at 4 months



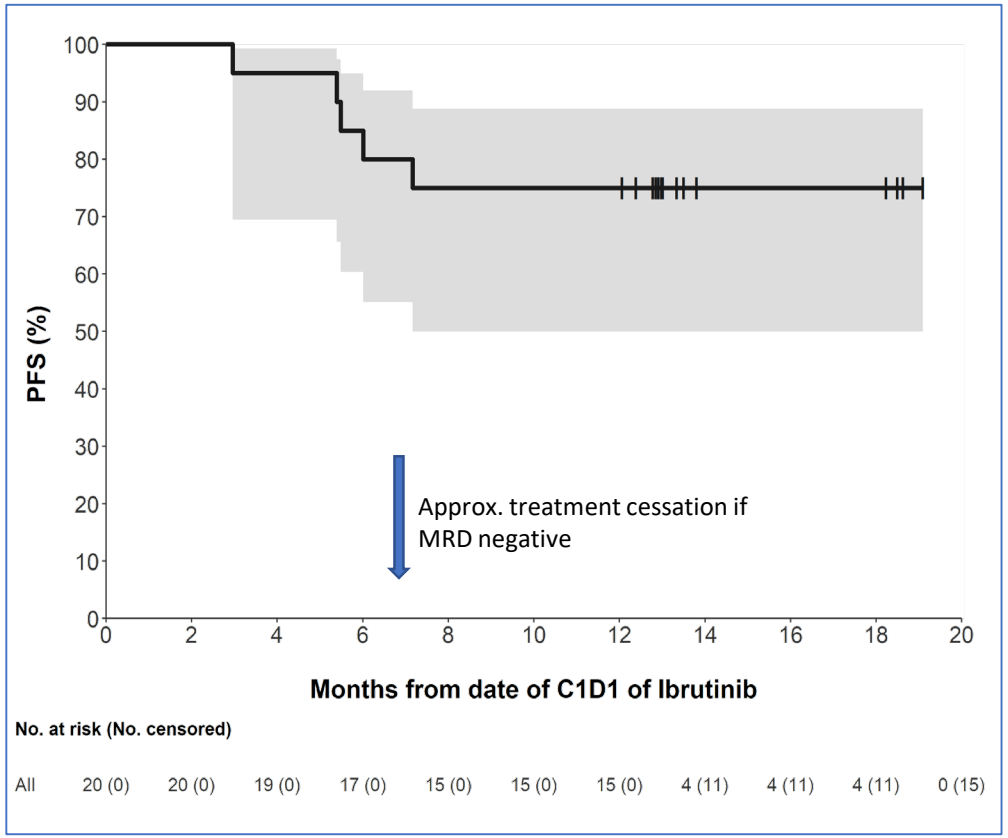
Efficacy endpoint (n=20)	Rate
Complete response rate[1]	80%



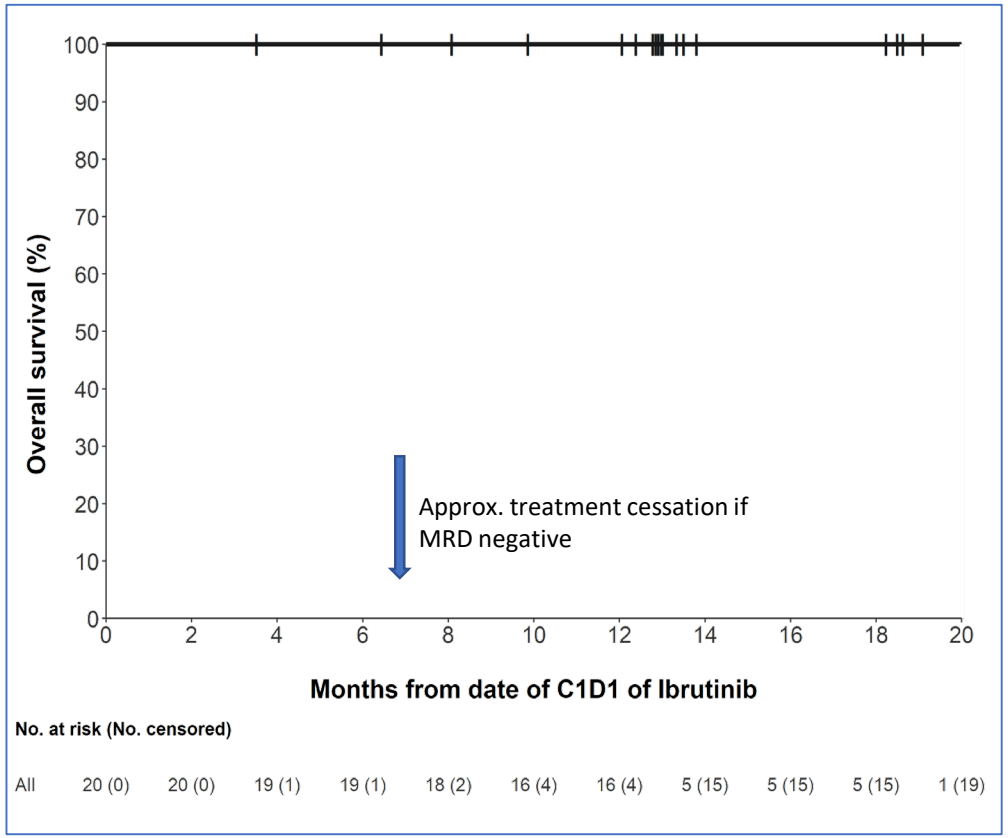
† BTKi exposed; # Bridging therapy

Survival outcomes

PFS



OS



	N=20
Median follow up, mo (range)	13.0 (3.5-21.4)
Median PFS	Not reached (7.2-NE)
6 month event-free rate, % (95% CI)	85% (60-95%)
12 month event-free rate, % (95% CI)	75% (50-89%)

Glofitamab dosing schedules

Phase I dose escalation in R/R MCL

Glofitamab IV administration

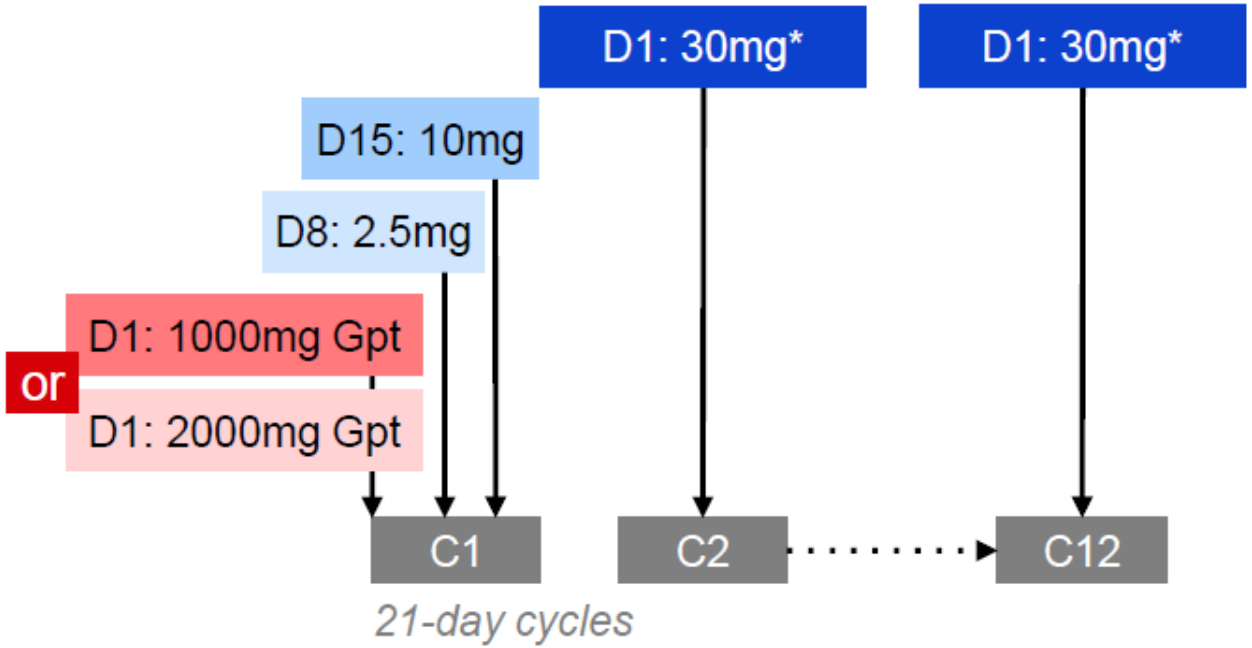
- Fixed-duration treatment: maximum 12 cycles

CRS mitigation

- Obinutuzumab pretreatment (1 x 1000mg or 1 x 2000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

Population characteristics:

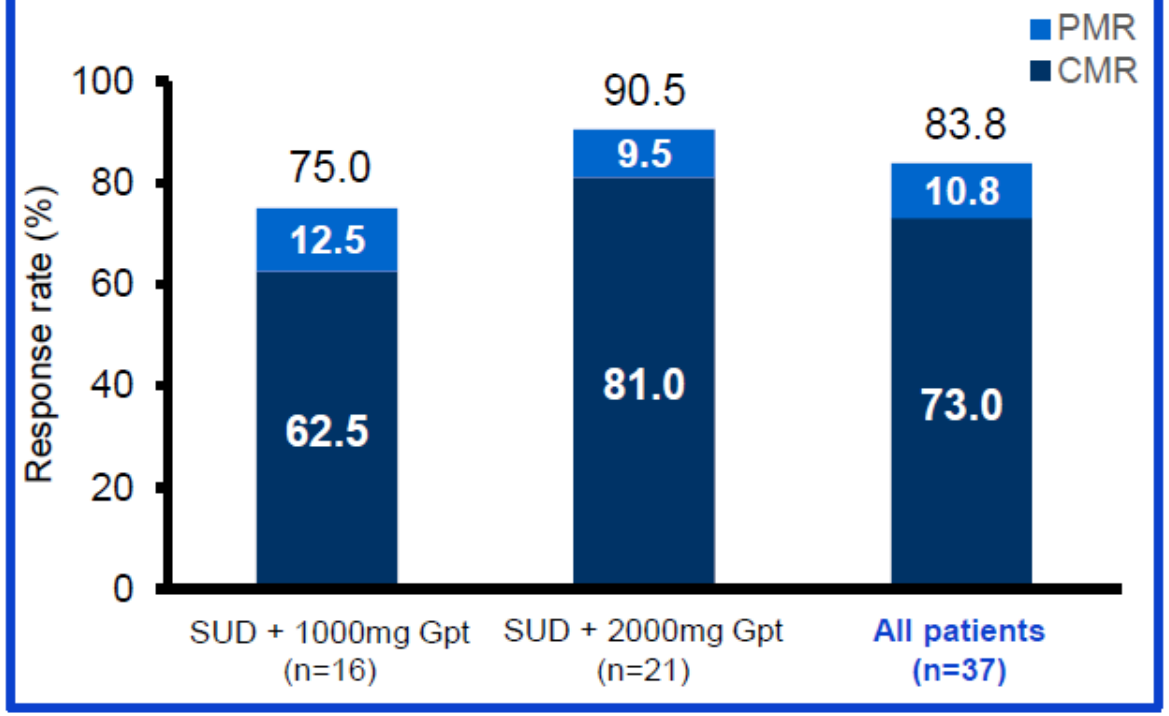
- Age ≥18 years
- ≥1 prior systemic therapy
- ECOG PS ≤1



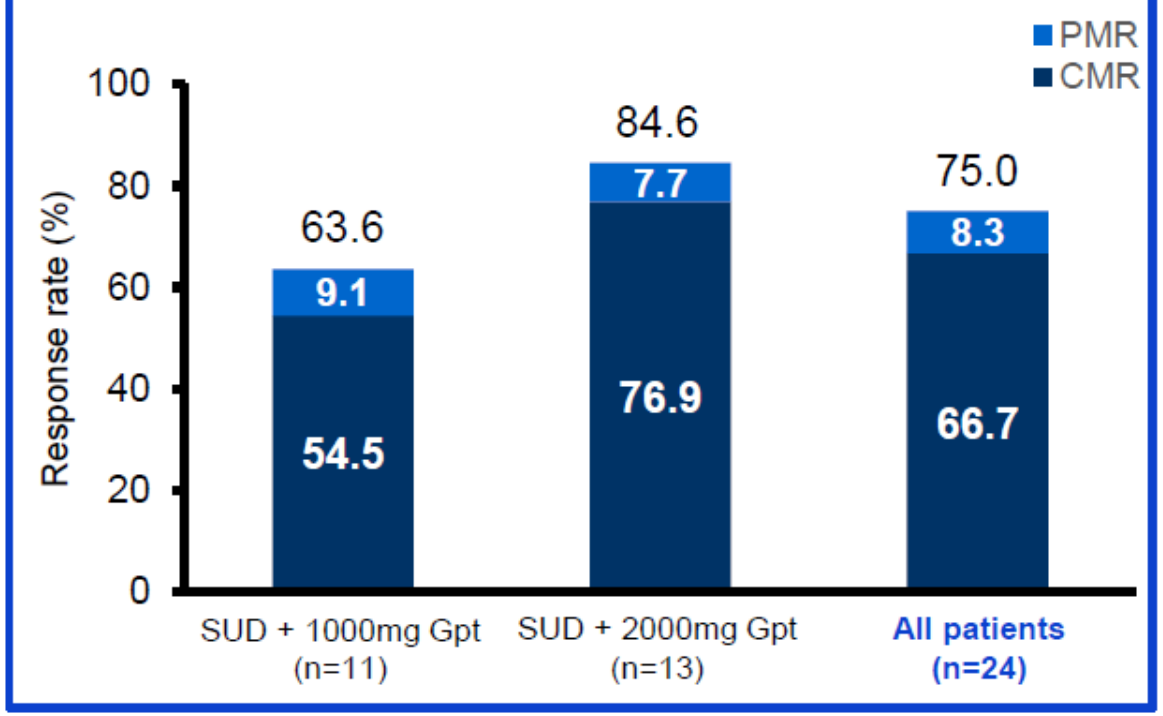
Clinical cut-off date: March 14, 2022; *In the glofitamab SUD + 1000mg Gpt cohort, two patients had 16mg glofitamab as their target dose.

Response rates by glofitamab regimen

All patients*



Patients with prior BTKi



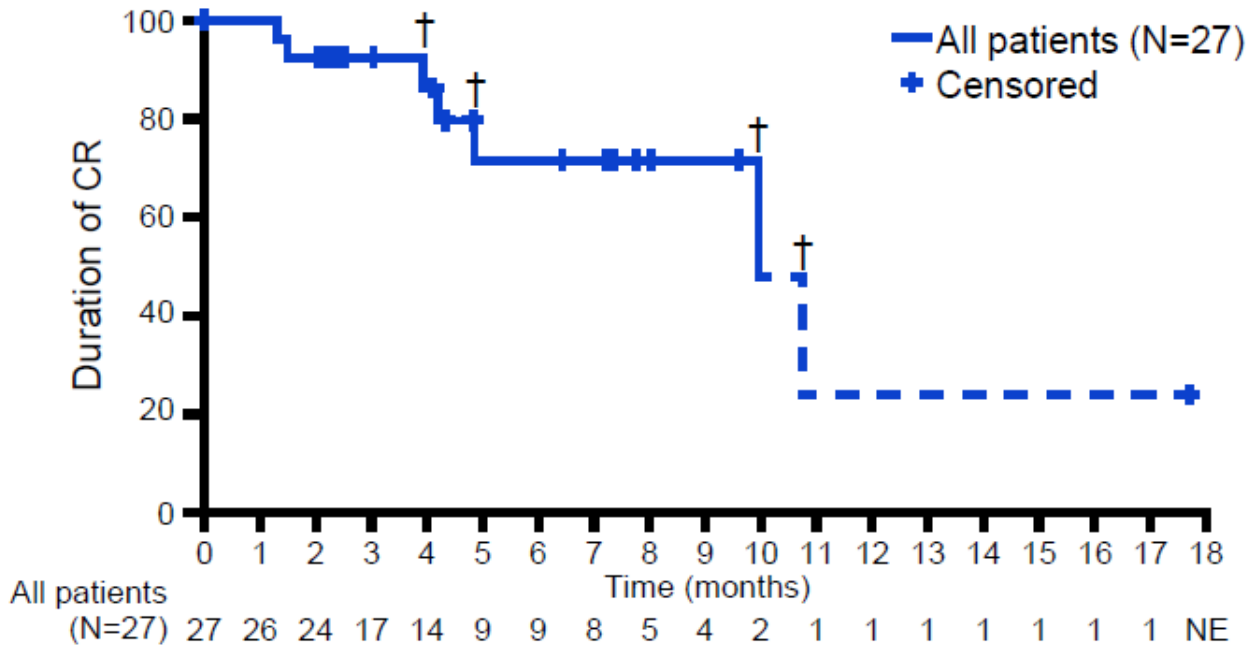
High response rates with glofitamab monotherapy in patients with R/R MCL

*Efficacy results are reported for the secondary efficacy population (includes all patients who had a response assessment performed, withdrew early from treatment or study, or are on still on treatment at the time of their first scheduled response assessment). Prior lines of therapy ranged from 1–5 in both the responder and non-responder groups. CMR, complete metabolic response; PMR, partial metabolic response.

Cheson et al. J Clin Oncol 2014.

Duration of complete response

Duration of CR*

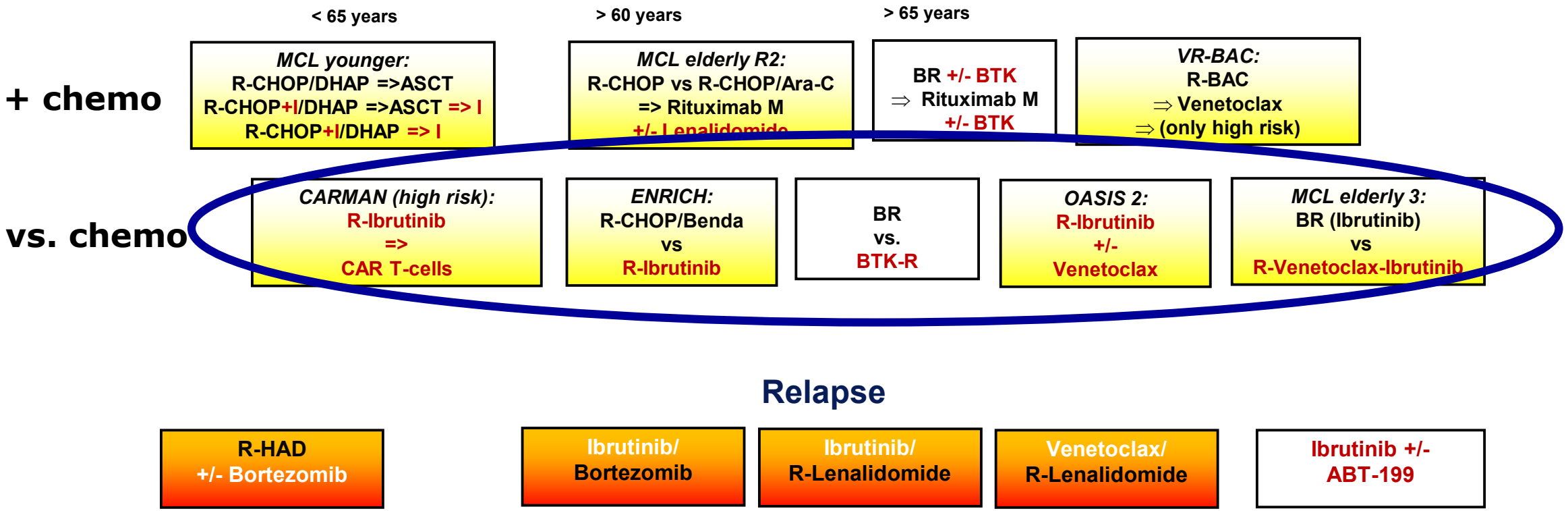


- Median DOCR follow-up: 5.1 months (range, 0.0–18.0)
- Median DOCR: 10.0 months (95% CI: 4.9–NE)
- At data cut-off, **74.1%** (20/27) of patients with a CR remained in remission
- Durable CRs were maintained after cessation of therapy
- Four events due to COVID-19 deaths; when excluded, median not reached and 87% (20/23) CRs were ongoing

The majority of CRs were ongoing at data cut-off

*DOCR is measured from the date of first complete response to the date of progression or death from any cause; †Death due to COVID.
DOCR, duration of complete response.

European MCL Network
Study generation 2022



Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2022

Für den Inhalt verantwortlich:

Prof. Dr. med. Martin Dreyling

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Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

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