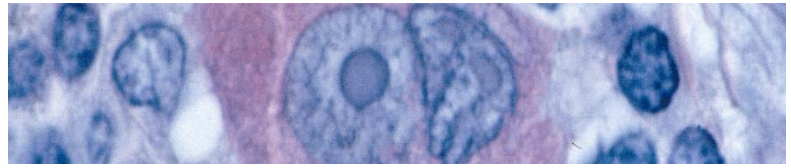
Kompetenznetz Maligne Lymphome

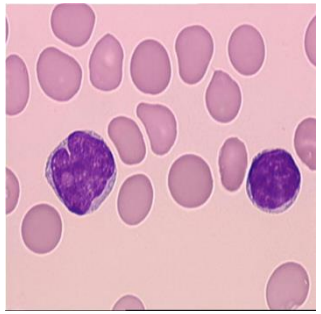
25 Jahre vernetzte Lymphomforschung:

Aktuelle Therapiekonzepte



SPEED REPORT:

MCL, INDOLENTE LYMPHOME



German Lymphoma Alliance

European MCL Network

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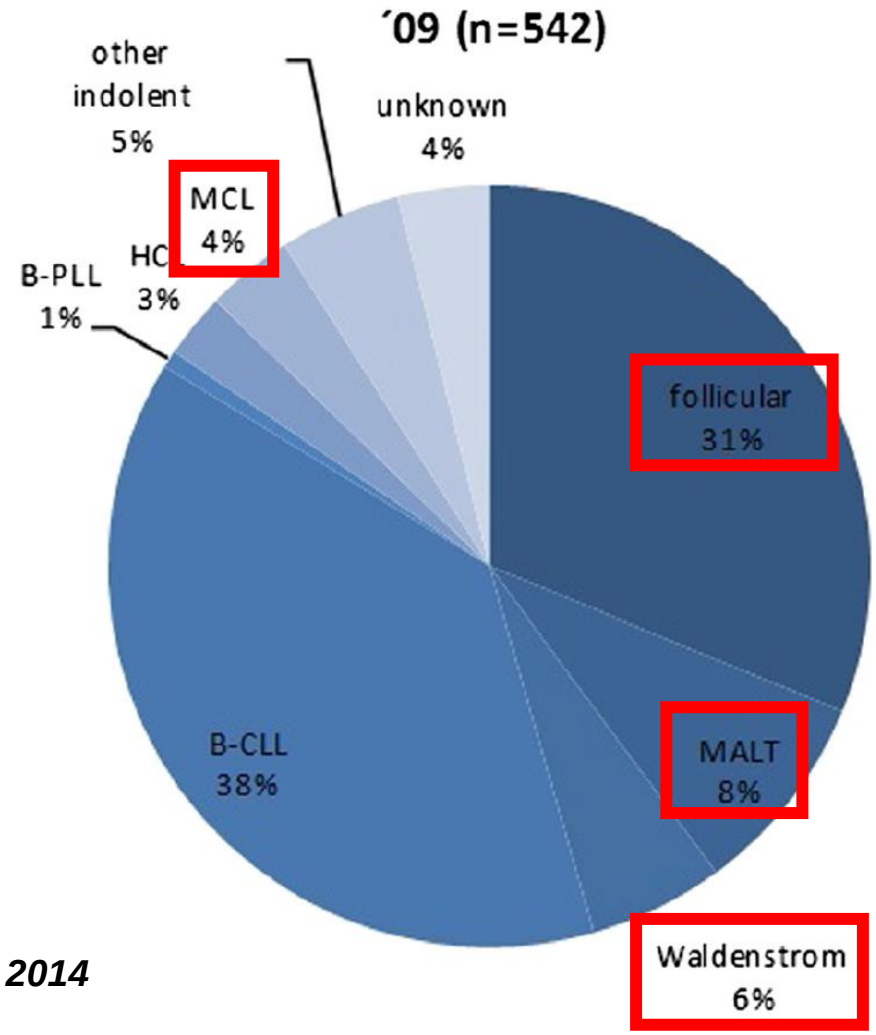
Medizinische Klinik III
LMU München

Mantle cell lymphoma
Disclosures

https://bureaucracyincts.eu

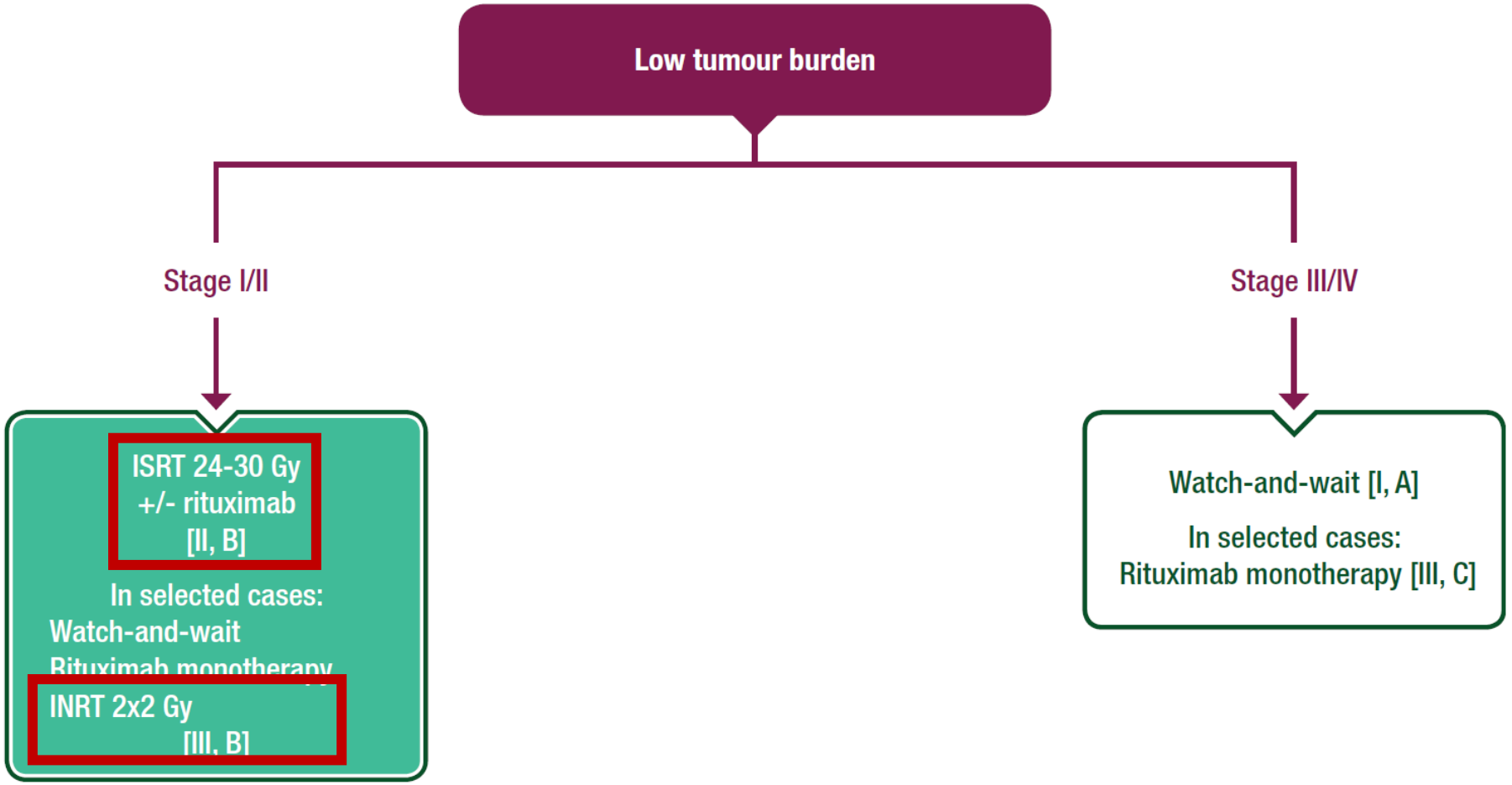
Research Support (institution)	**Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Lilly, Roche**
Employee	**-**
Major Stockholder	**-**
Speakers Bureau	**-**
Speakers Honoraria	**Astra Zeneca, Beigene, Gilead/Kite, Janssen, Lilly, Novartis, Roche**
Scientific Advisory Board	**Abbvie, Astra Zeneca, Beigene,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

Indolent Lymphoma
Frequency of subtypes



Schmidt, Leuk Lymph 2014

Follicular lymphoma
ESMO/EHA therapeutic algorithm

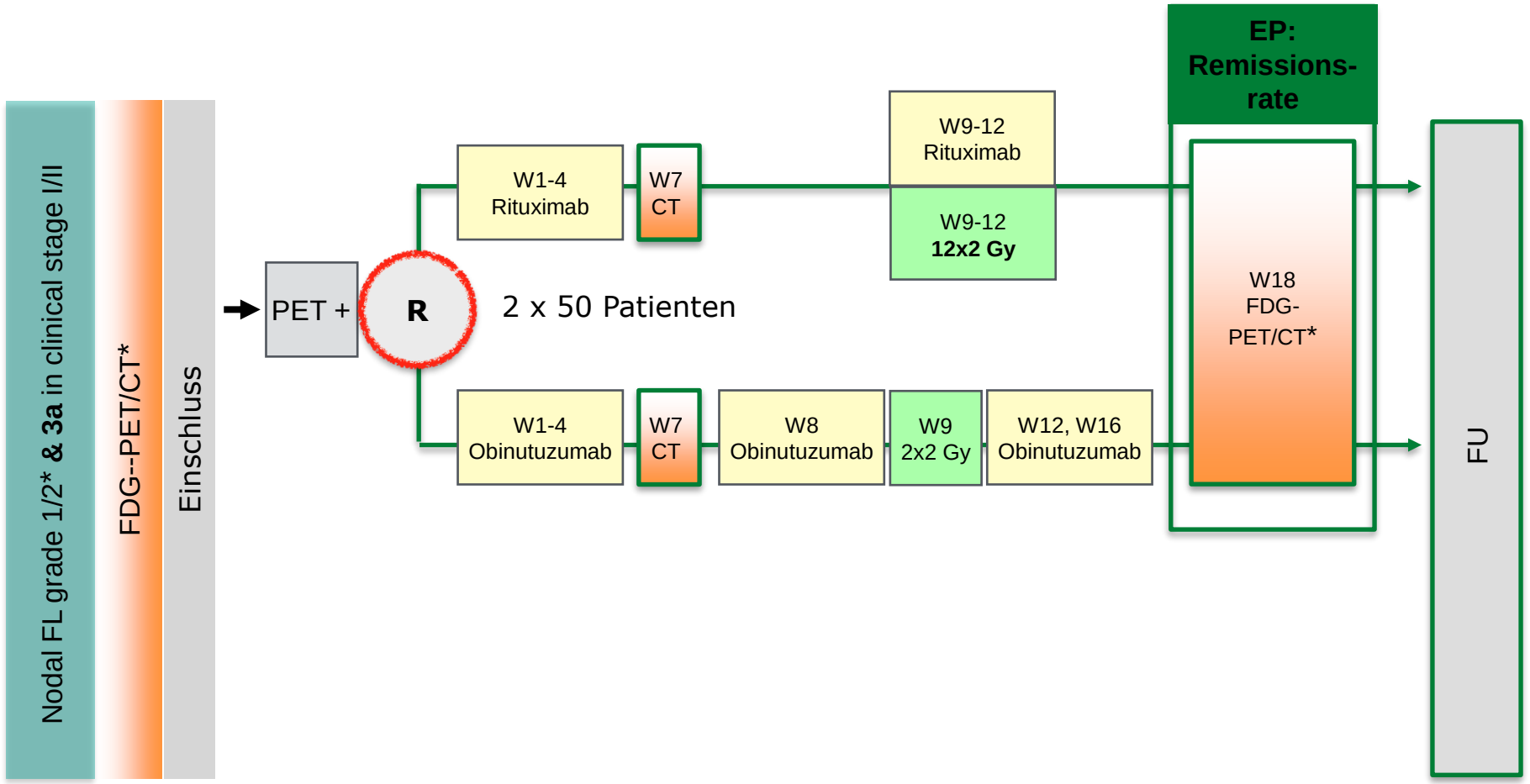


Dreyling, Ann Oncol 2021

FORT*plus*

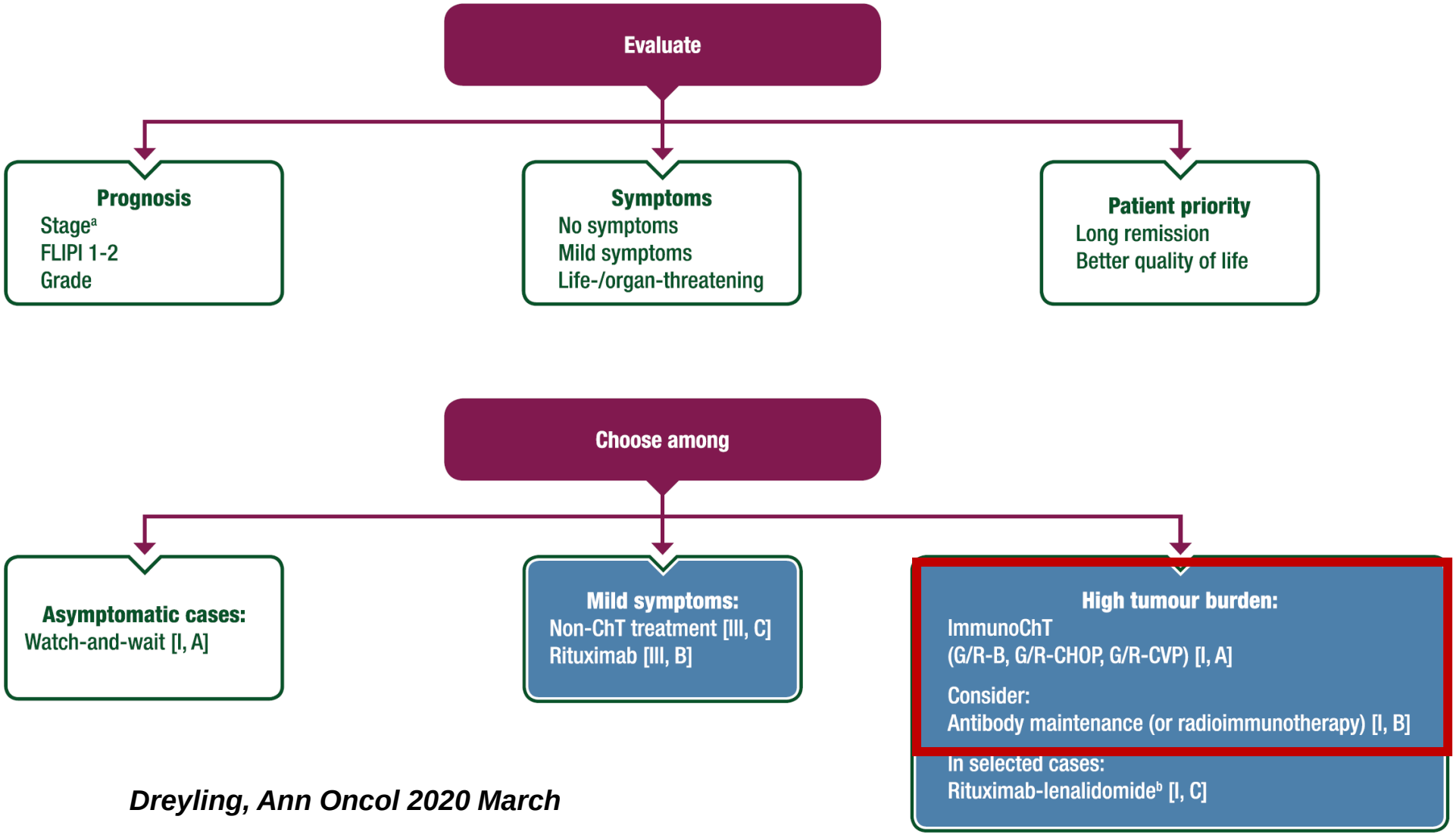
LMU KLINIKUM

Non-inferiority design



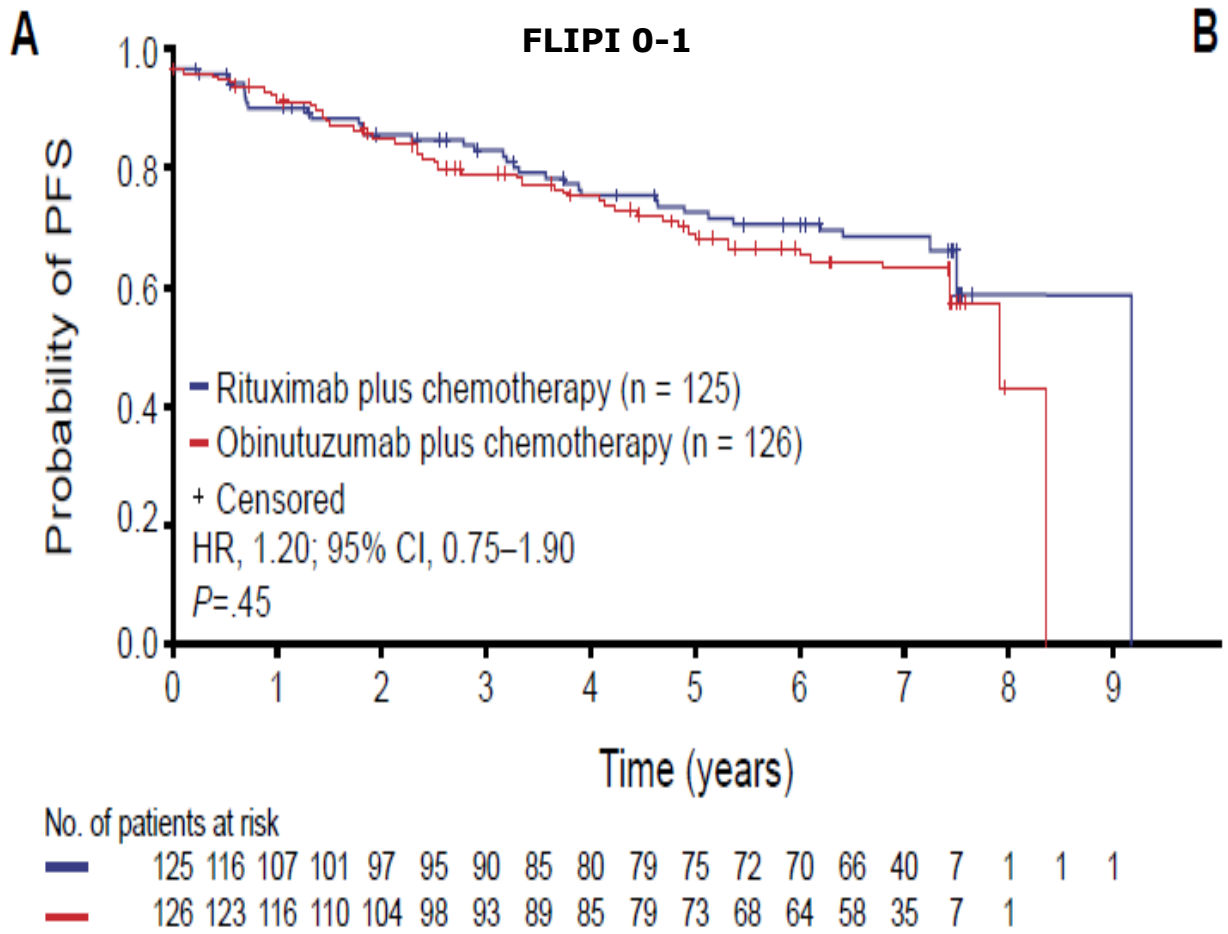
* = centrally reviewed

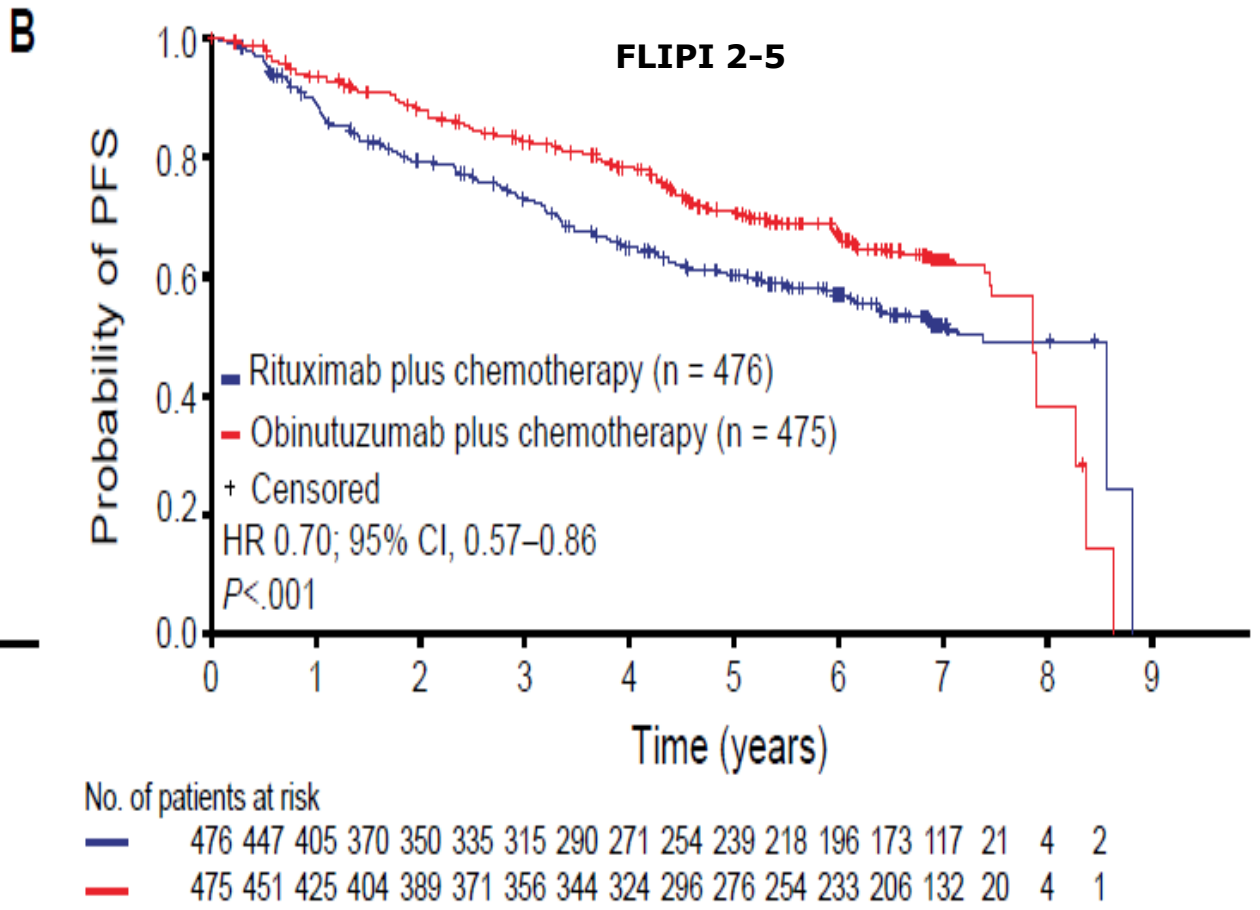
Follicular lymphoma
ESMO/EHA therapeutic algorithm



Dreyling, Ann Oncol 2020 March

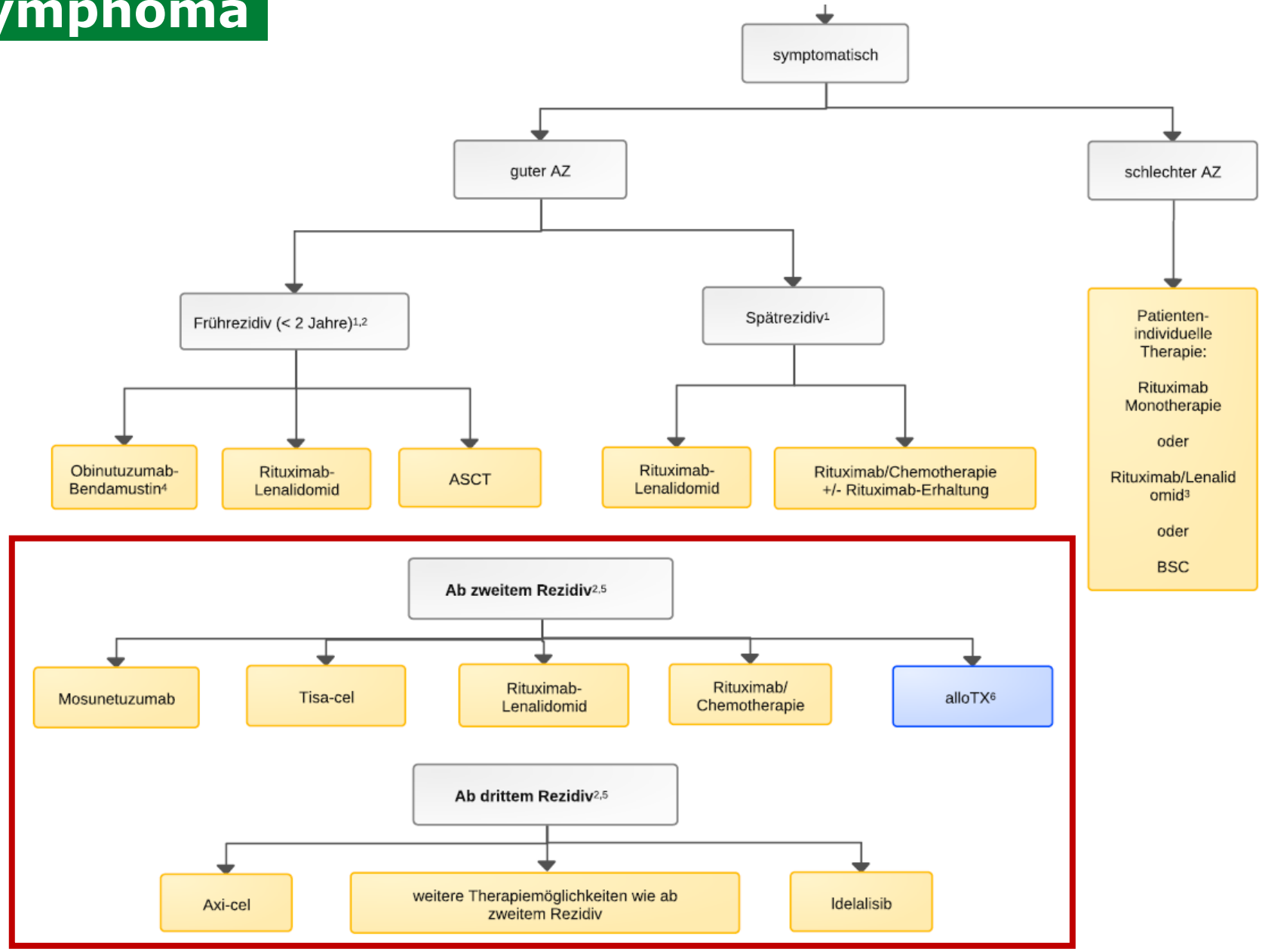
Follicular lymphoma (advanced stage)





Townsend, Hemasphere 2023

Follicular lymphoma (relapsed)



Buske, Onkopedia 2023

Study design

Key inclusion criteria

- CD20+ FL Grade 1–3a
- Previously untreated and require systemic therapy*
- ECOG PS 0–2

Objectives

- Primary: Safety and tolerability of Mosun-Len
- Other: Efficacy (response assessed every 3 cycles,† durability of response), biomarkers, and PK

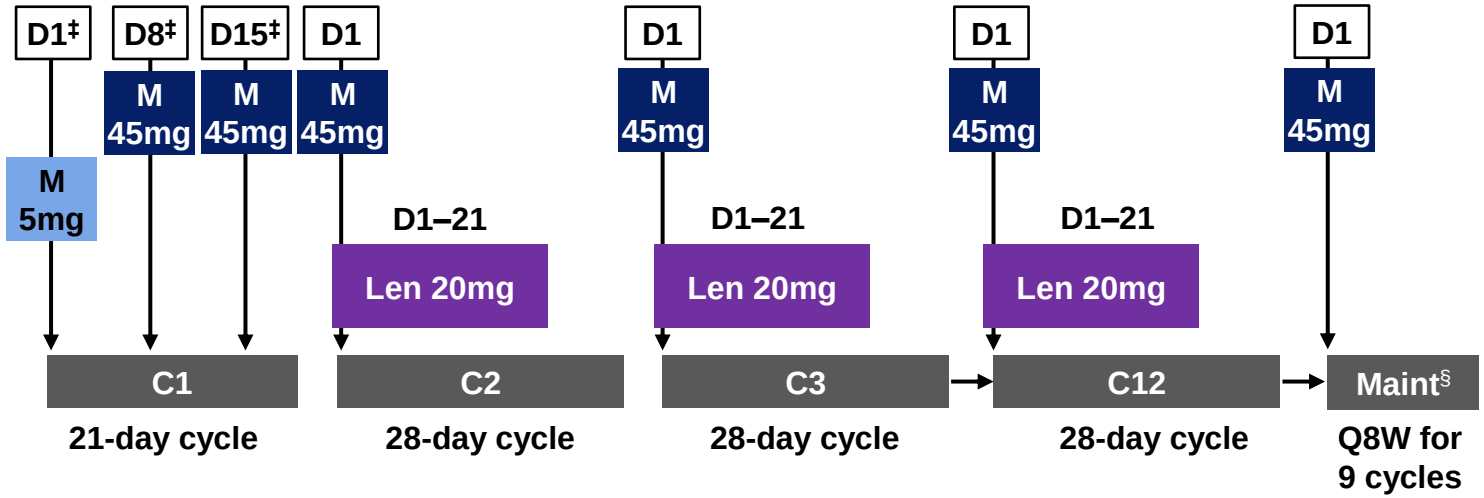
Mosun-Len administration

Mosun

- SC administration for 12 cycles (C1: Q3W; C2–12: Q4W)
- C1 step-up dosing (CRS mitigation)
- No mandatory hospitalization

Len

- Oral administration for 11 cycles (C2–12)



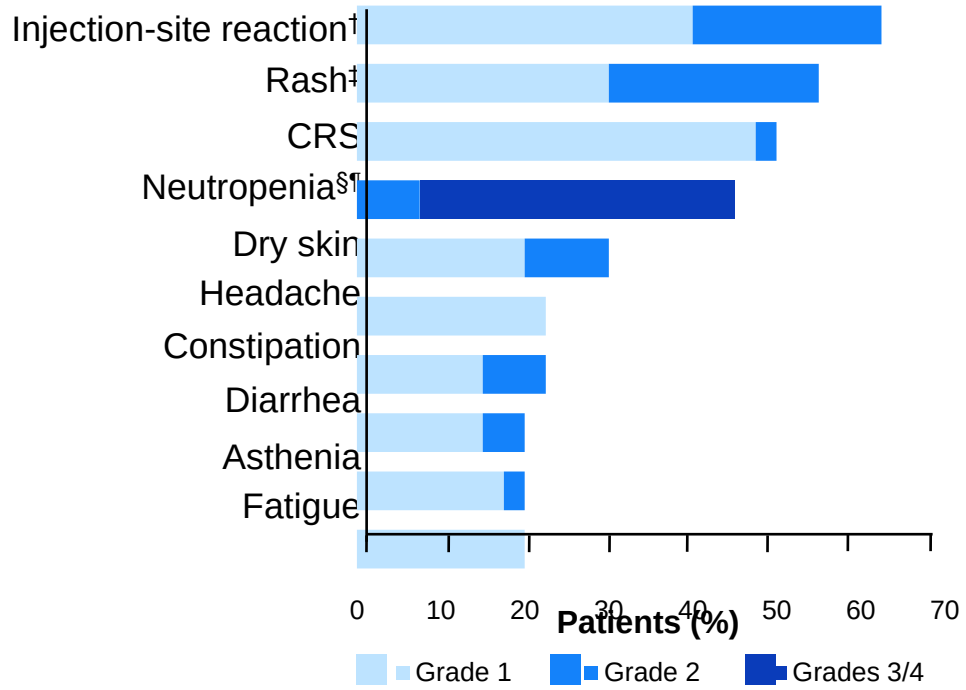
CCOD: July 20, 2023.*Investigator-assessed based on Groupe d'Etude des Lymphomes Folliculaires criteria. †During induction C1–C12. ‡A single dose of oral or IV dexamethasone or methylprednisolone as pre-medication to mitigate risk of CRS was required during C1 and optional after C1. §Mosun monotherapy maintenance option for patients who achieved complete or partial metabolic response after 12 cycles of induction therapy with Mosun-Len.
C, cycle; CCOD, clinical cut-off date; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; M, mosunetuzumab; Q3W, once every 3 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; maint, maintenance; PK, pharmacokinetics.

Summary of adverse events

- 29 patients (72.5%) received at least six cycles of treatment at CCOD

	N=40; n (%)
AEs Related to Mosun/Len	40 (100) 38 (95.0) / 33 (82.5)
Serious AEs Related to Mosun/Len	13 (32.5) 9 (22.5) / 3 (7.5)
Grade 3/4 AEs	22 (55.0)
Serious Grade 3/4 AEs Related to Mosun/Len	3 (7.5) 2 (5.0) / 1 (2.5)
Grade 5 AEs	0
AE leading to dose reduction/modification Mosun Len	 0 9 (22.5)
AE leading to dose delay/interruption Mosun Len	 11 (27.5) 17 (42.5)
AE leading to any treatment discontinuation	2 (5.0)*

Most common AEs (≥20% incidence)



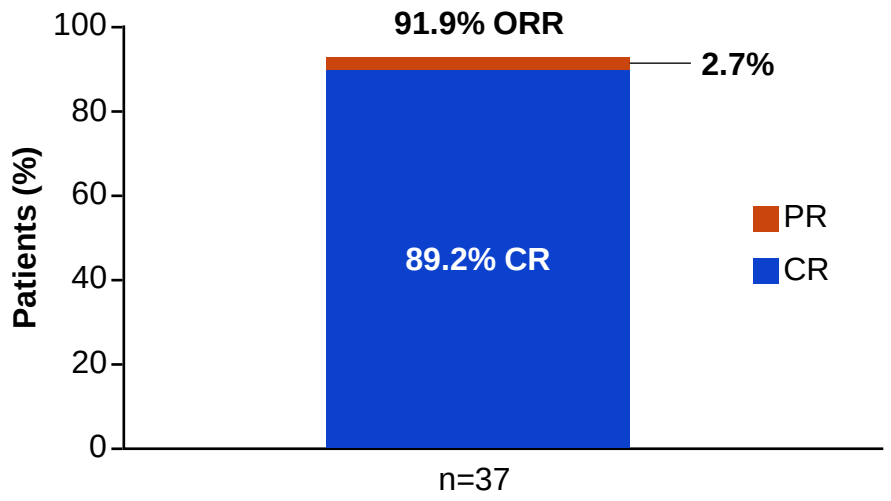
Mosun-Len had a manageable safety profile

CCOD: July 20, 2023. *Both Mosun and Len were discontinued; Grade 1 uveitis AE (n=1) and Grade 2 tumor flare/persistent fever serious AE (n=1). Includes preferred terms: †Injection-site reaction, injection-site rash, injection-site erythema, injection-site inflammation, injection-site edema, injection-site pain; ‡rash, erythema, rash maculo-papular, exfoliative rash, rash erythematous, and rash macular; §neutropenia and decreased neutrophil count.
¶The majority of patients experienced neutropenia events related to lenalidomide. AE, adverse event.

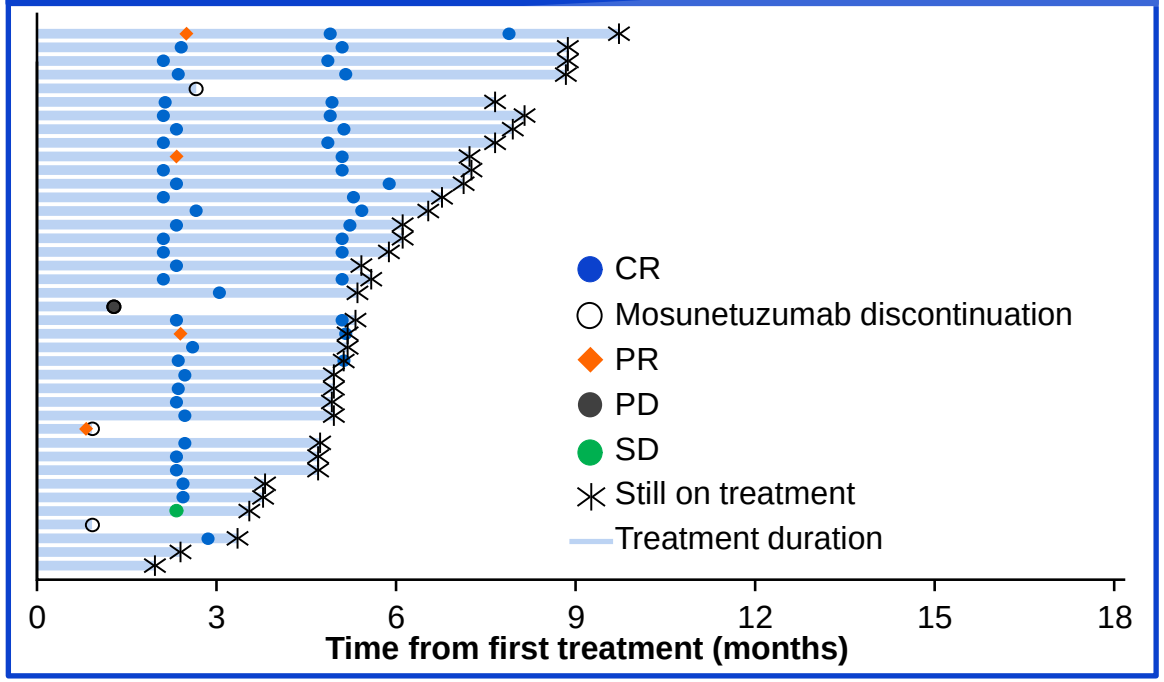
Response

- Median duration of follow-up: 5.2 months (range: 1–10); most patients (95%) had 3–9 months of follow-up at CCOD

Best overall response*



Response timing and duration†



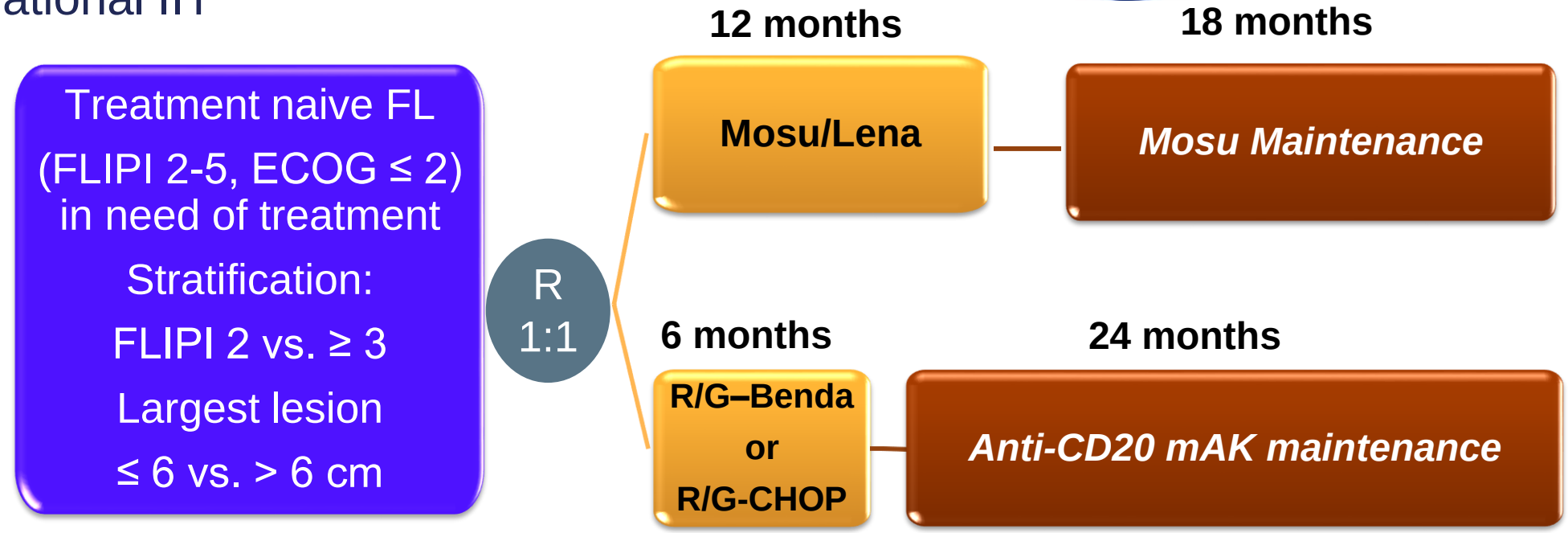
ORR and CR rates were high. All patients who responded were still in response at the CCOD

CCOD: July 20, 2023.
*Thirty-seven patients reached the first treatment assessment (by PET-CT using Lugano 2014 criteria) and were efficacy evaluable. In the efficacy evaluable population one patient (2.7%) each had SD and PD; one patient (2.7%) did not have a response assessment due to early treatment discontinuation for uveitis. Transformed disease was observed in one patient with PR and another with PD during Cycles 1 and 2, respectively.
†Responses were with or without PET.
ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

MorningLyte

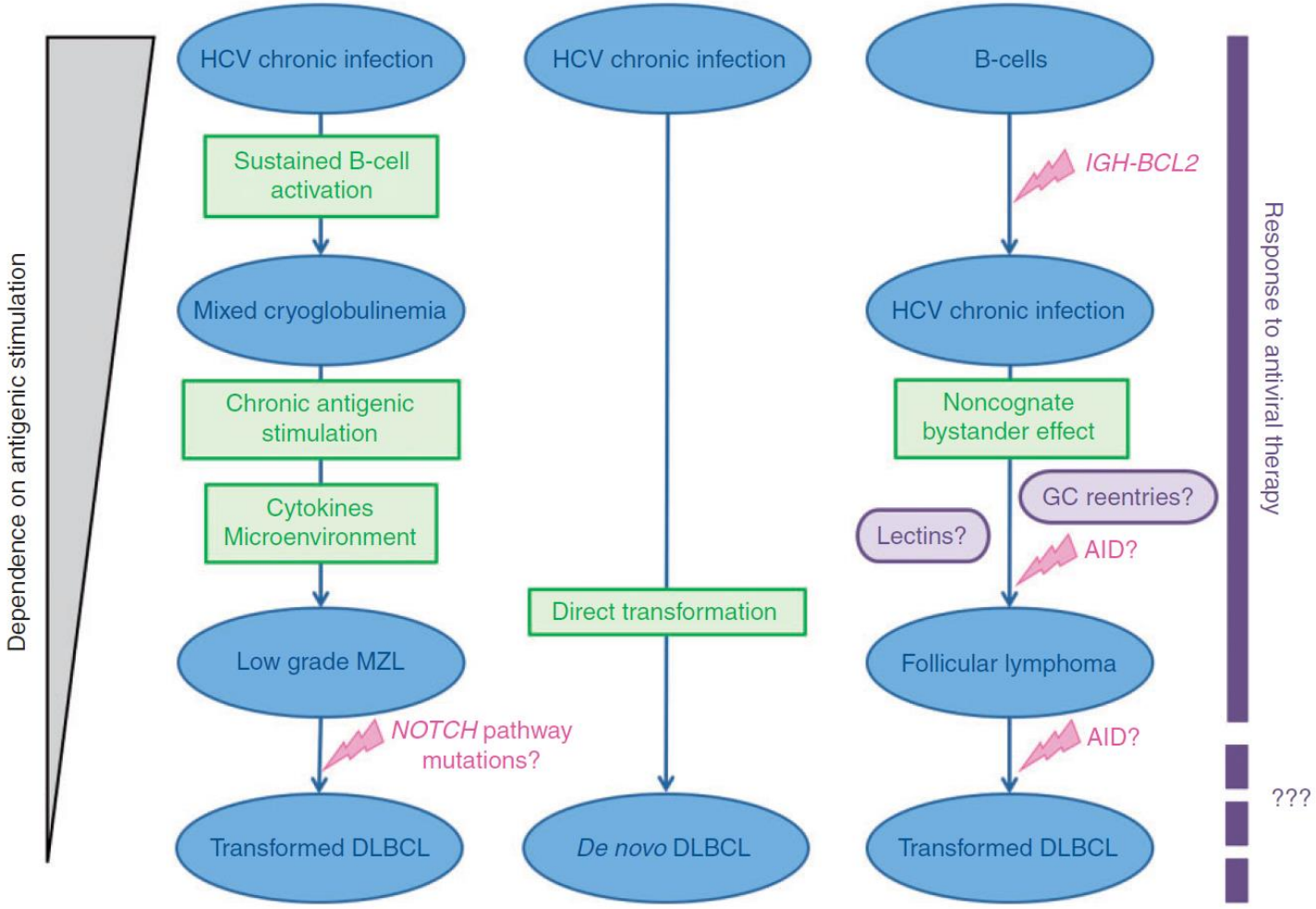
N=790

International IIT



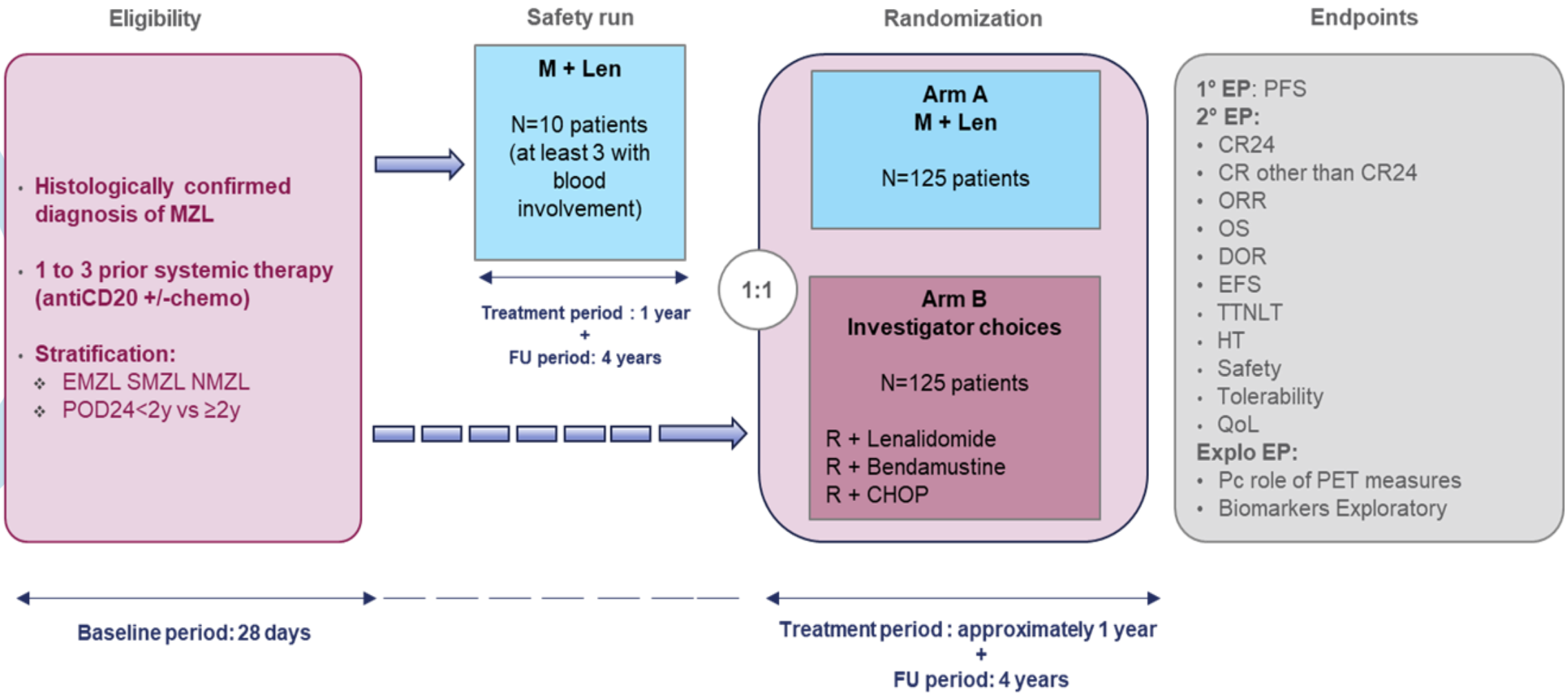
Randomized Phase III
Primary Endpoint PFS

Marginalzonen-Lymphome
Pathogenese



Couronne, Ann Oncol 2018

Study Design



Pathological and biological sample review

NMZL EMZL

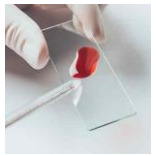
- The paraffin block from the formalin fixed sample that was used to set the diagnosis at relapse (at inclusion). If the relapse material is not available, the initial tumour biopsy will be requested.
- Immunohistochemistry slides
- Exceptionally if blocks are not available for a patient, 20 unstained slides will be requested.

LYSA-P Créteil France

Centralized review

SMZL

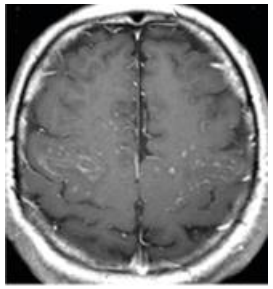
- Mandatory :
  - Local graphic results of flow cytometry diagnosis based on an antibodies panel : Matutes, CD20, CD11c, CD180, CD43, et CD200 markers,
    - 15 ml of Blood on EDTA for Flow Cytometry analysis and banking at *Baseline* only for centers that don't do CD20, CD11c, CD180, CD43, et CD200 markers.



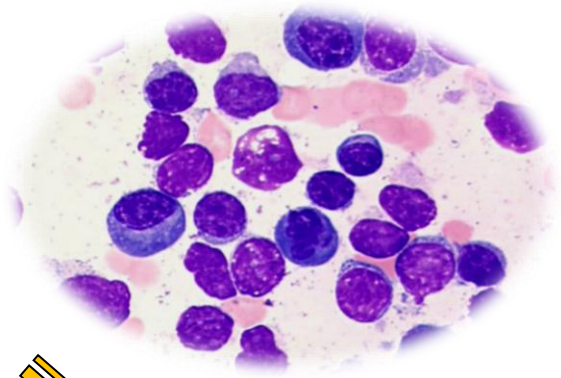
  - Blood and bone marrow slides at Baseline for a centralized cytological review

- **Confirmation of diagnosis before randomization :**
  - **Centralized cytological review**
  - **Flow Cytometry**

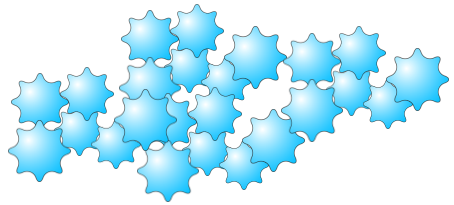
Waldenstroem
Clinical presentation



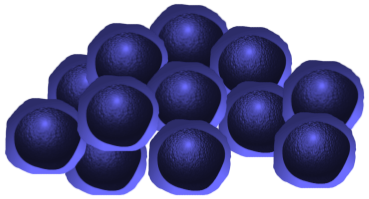
Bing-Neel



BM

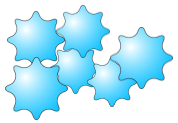


Symptomatic Hyperviscosity
IgM >5,0g/l
Viscosity > 4,0 cp



Lymphadenopathy
Splenomegaly
≤20% firstline
50-60% Relapse

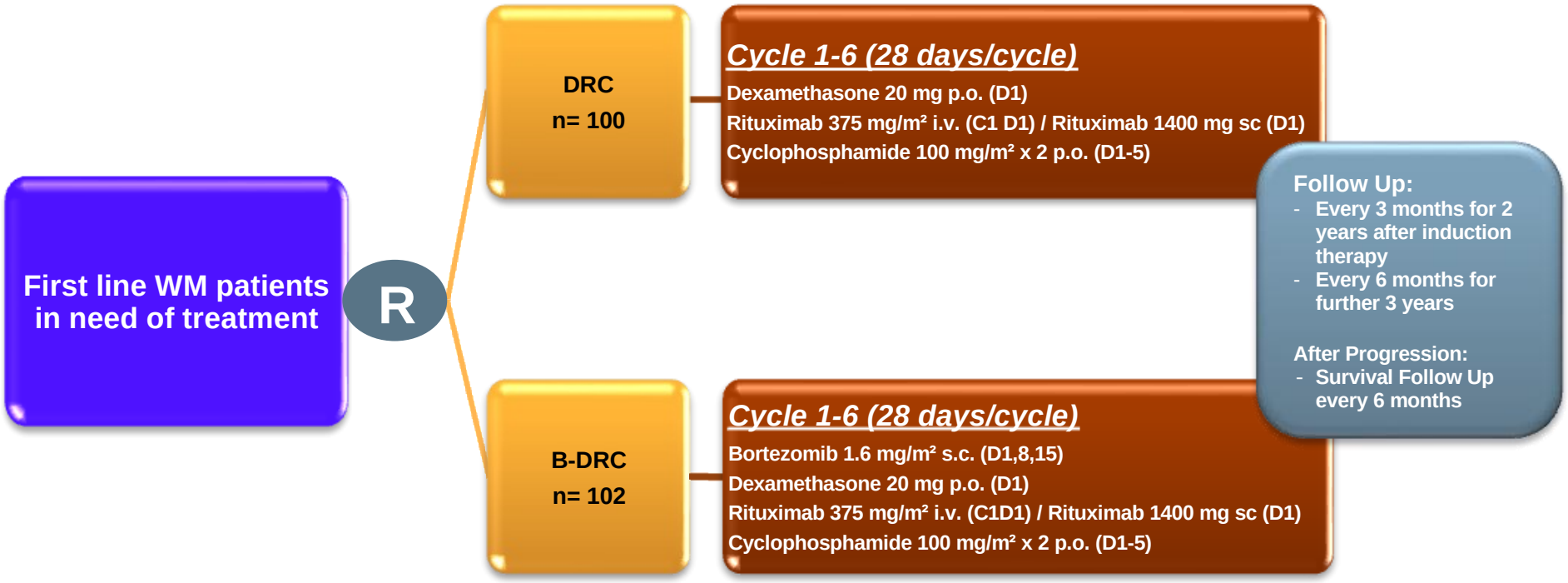
Hepcidin
↓ IDA



IgM Neuropathy (22%)
Cryoglobulinaemia (10%)
Cold agglutinimaemia(5%)

Treon, Hematol Oncol 2013

ECWM-1 Study Design

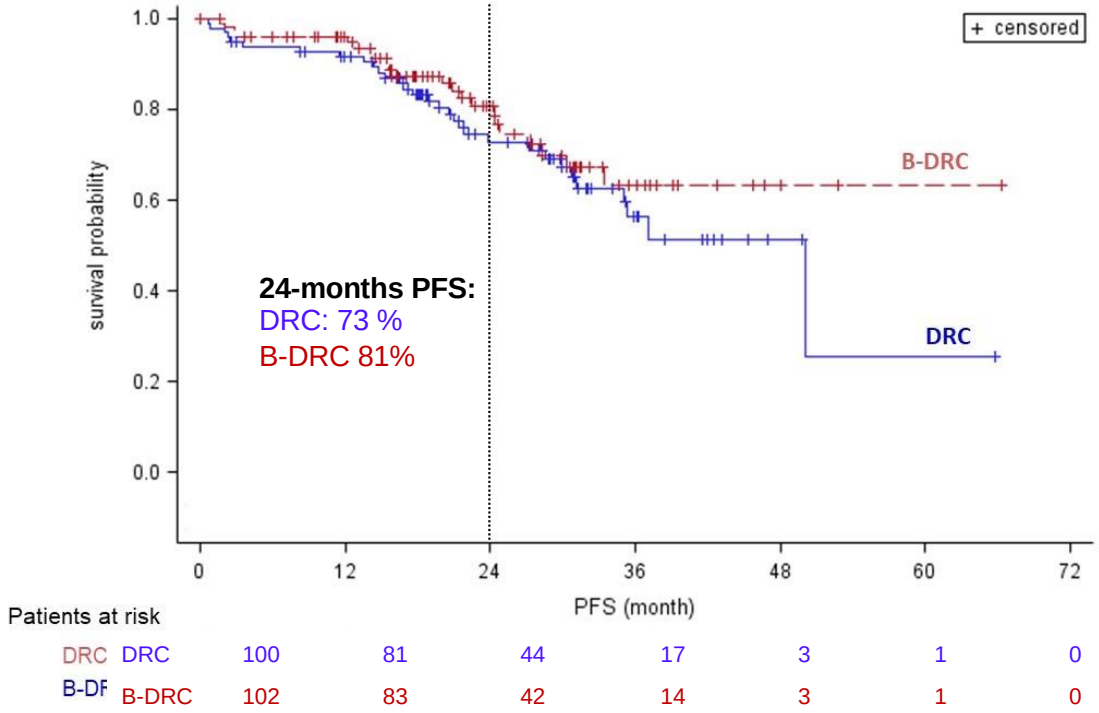


Randomized Phase II
Endpoints: PFS, response rates, OS, safety

Buske et al., JCO, 2023

Progression-Free Survival

Median follow-up was 27.5 months at the time of the data cut.



	DRC	B-DRC
Median PFS, months (95% CI)	50.1 (31.2-n.a.)	n.a. (33.5-n.a.)
HR (95% CI)	0.759 (95% CI: 0.439; 1.311)	
Logrank p-value	P=0.32	

Buske et al., JCO, 2023

ECWM-2 - Quartal III 2018

first line WM – single arm phase II

Key eligibility criteria

- Confirmed WM (N=53)
- Measurable disease
  (serum IgM > 0.5 g/dL)
- In need of treatment
- ECOG PS status of 0–2
- Genotyped for MYD88/CXCR4

Treatment

Induction

- Bortezomib SC 1.6/m^2 d1,8,15 cycle 1-6
- Rituximab 375 mg/m2 IV cycle 1, 1400 SC cycle 1-6
- Ibrutinib 420 mg PO continuously

Maintenance

- Rituximab 1400 SC every 2nd month x 12
- Ibrutinib 420 mg PO continously

Primary Endpoint: 1-year PFS

Sponsor: Ulm
Participating countries: Germany, Greece, France
Activated: actively recruiting

41 von 53 Patienten eingeschlossen

VIWA-1: Study Design

European multinational phase II trial, multicenter (GER, FRA, GRC), two – arm, open label randomized for treatment naive Waldenström's Macroglobulinemia

Key eligibility criteria

- Proven clinicopathological WM
- De novo WM independent of the genotype
- In need of treatment
- No prior treatment with Venetoclax or any BCL-2 inhibitor

1:1 Randomization (N=80)

Stratification

MYD88 and CXCR4 mutation

Arm A: Venetoclax/ Rituximab

Cycle 1 (28-days cycle):
Venetoclax: 200 mg/d QD PO on d1-7
400 mg/d QD PO on d8-14
800 mg/d QD PO on d15-28
Cycle 2-12:
Rituximab: 375 mg/m^2 i.v. on d1
Venetoclax: 800 mg/d QD PO on d1-28

Arm B: DRC

Cycle 1-6:
Dexamethasone: 20 mg PO on d1
Rituximab: 375 mg/m^2 i.v. on d1
Cyclophosphamide: 100 mg/m^2 BID on d1-5

Follow Up

- every 3 months for 2 years
- every 6 months until end of study or death

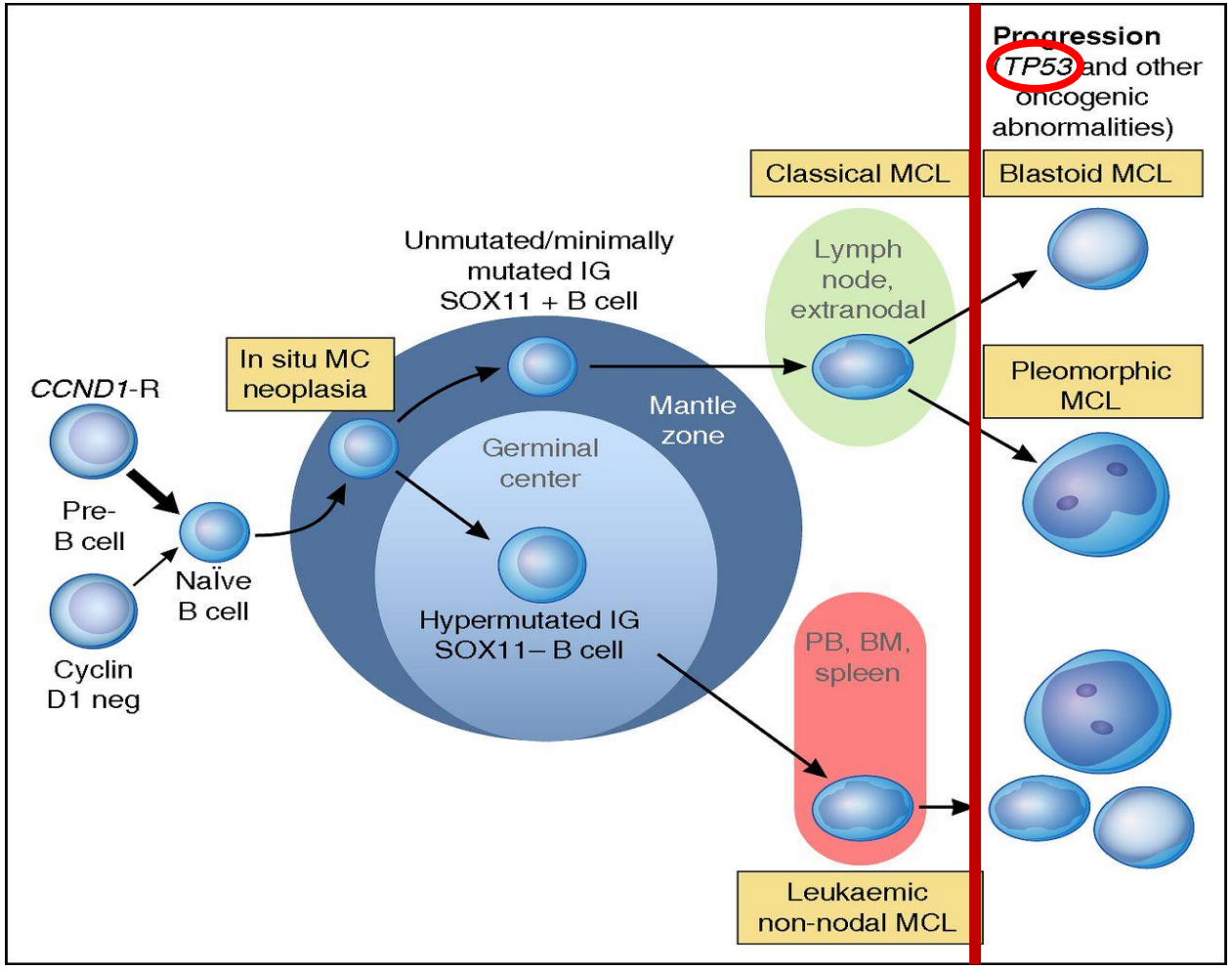
Primary endpoint

The primary endpoint is the rate of CR/VGPR 12 months after randomization (CR/VGPR12) using the modified response criteria updated at the Sixth IWWM. Besides patients with PR, MR or SD at 12 months from randomization, patients who died or progressed within 12 months from randomization are considered as non-CR/non-VGPR.

Secondary endpoints

Major Response rate and overall response at staging visits, Best response + Time to first response + Event free survival + PFS + Response Duration + Lymphoma specific survival + Overall survival + Safety + QoL

Mantelzell-Lymphom
Spektrum der Erkrankung



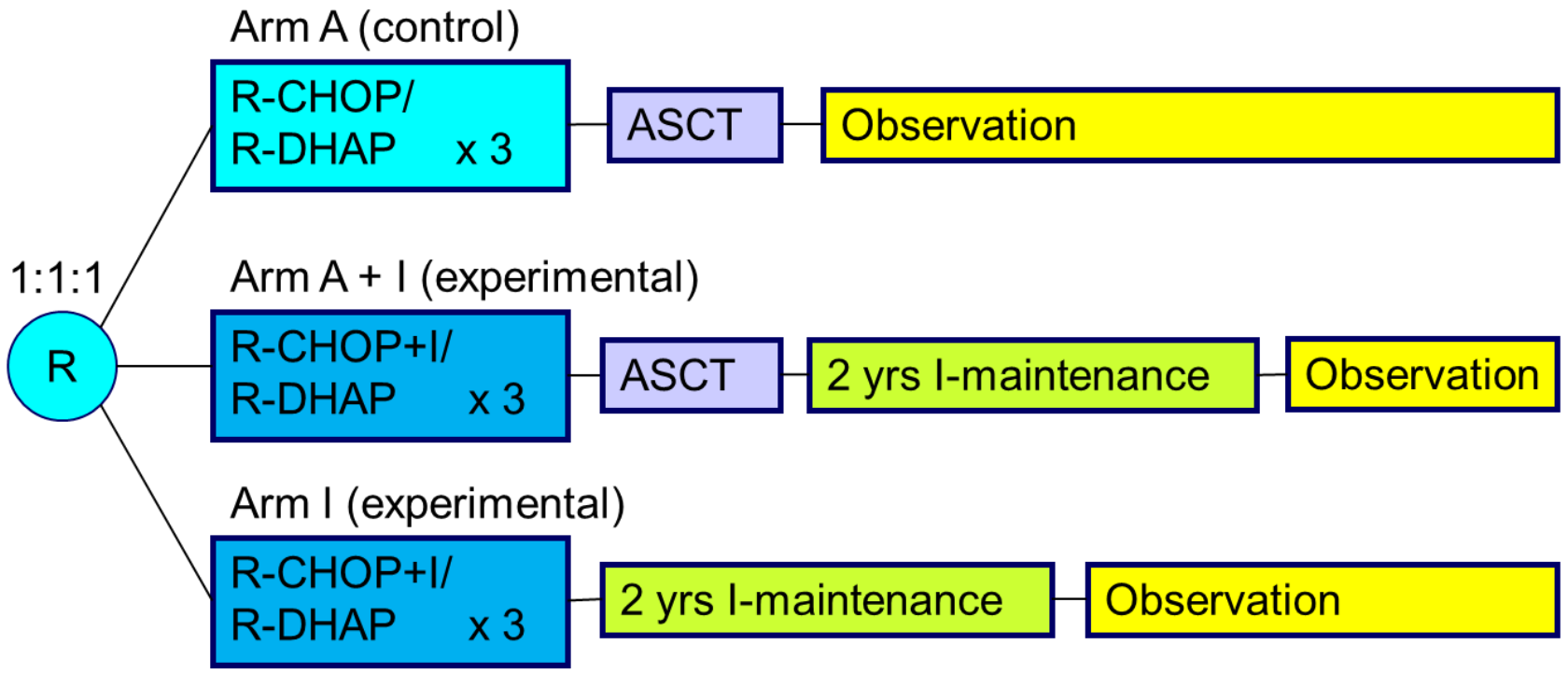
Dreyling, Ann Oncol 2017

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

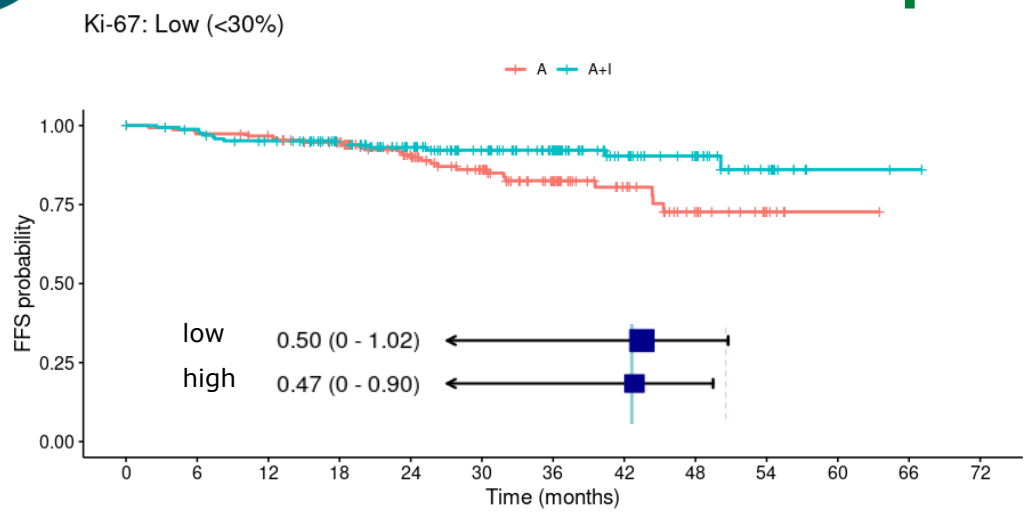
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety

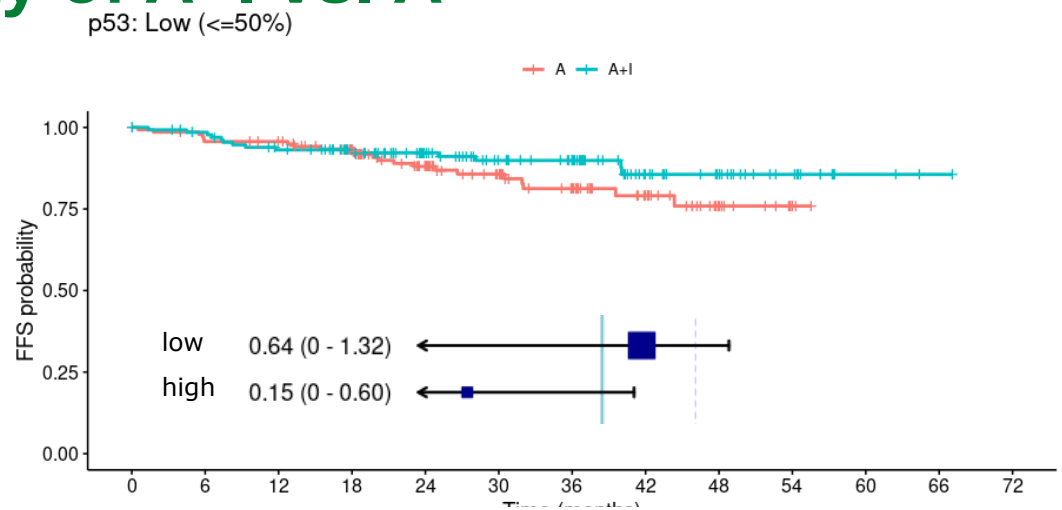


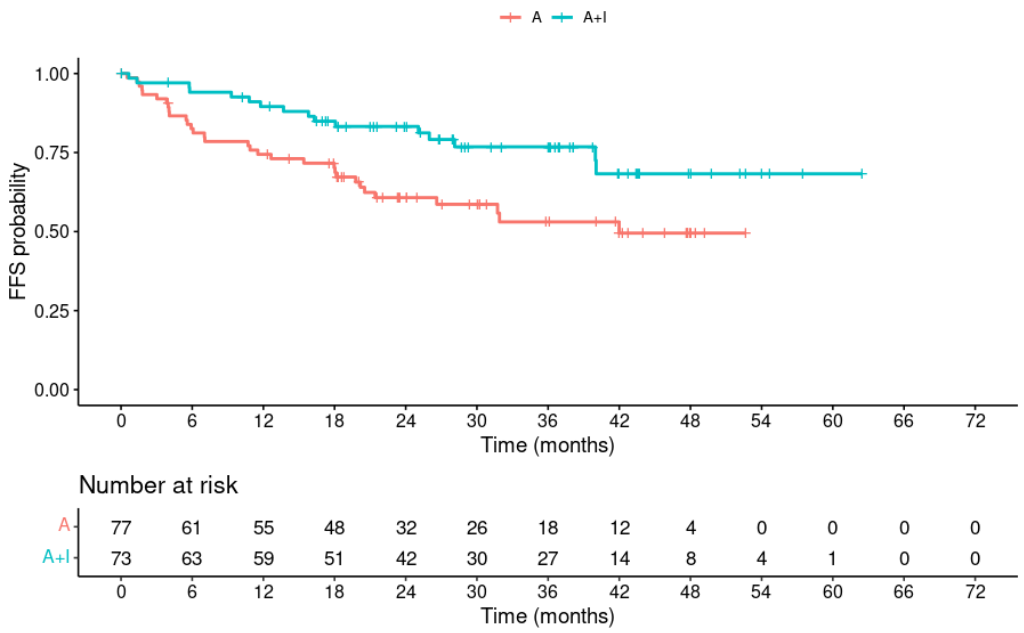
- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

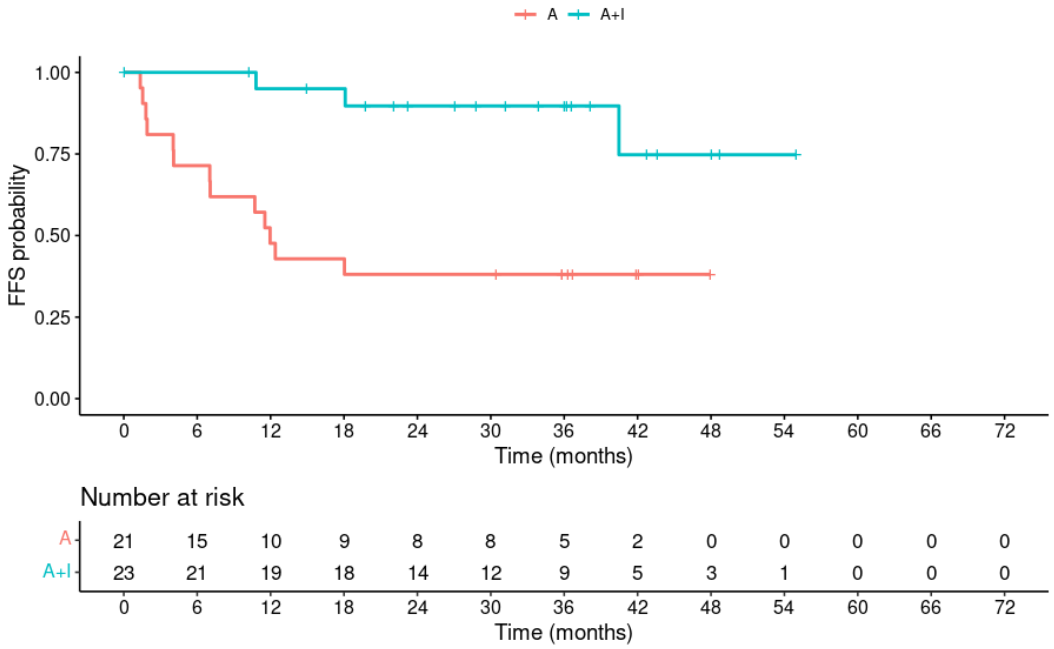
Dreyling, ASH 2022

TRIANGLE: FFS Superiority of A+I vs. A



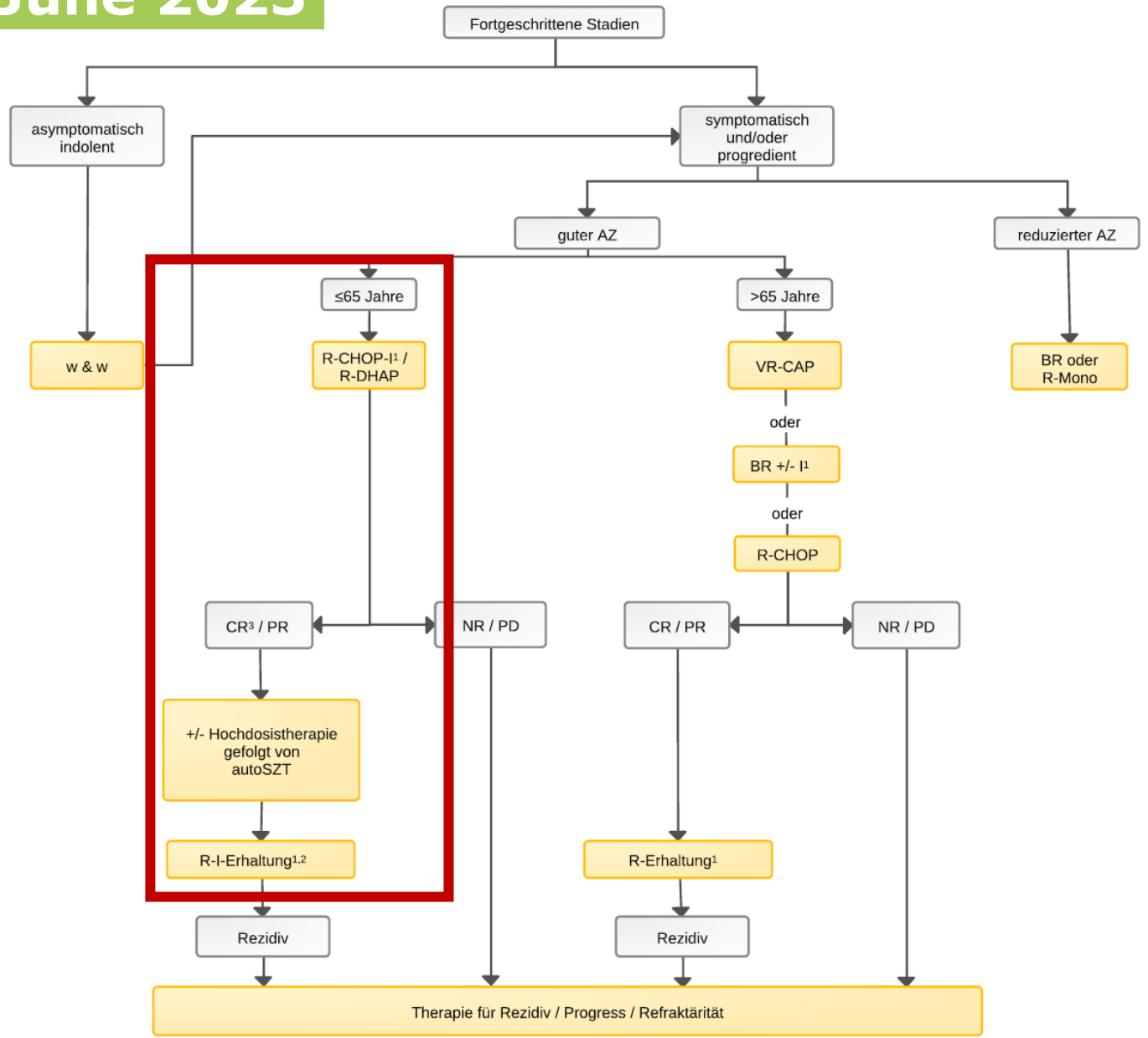




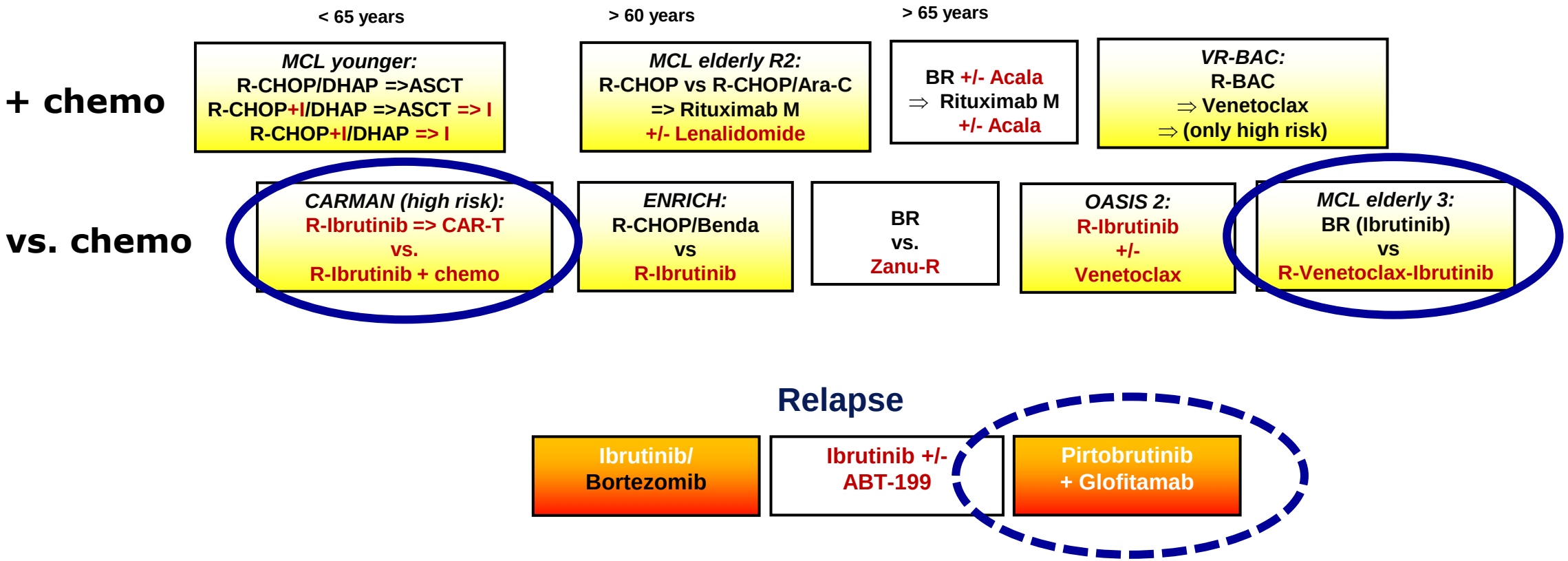


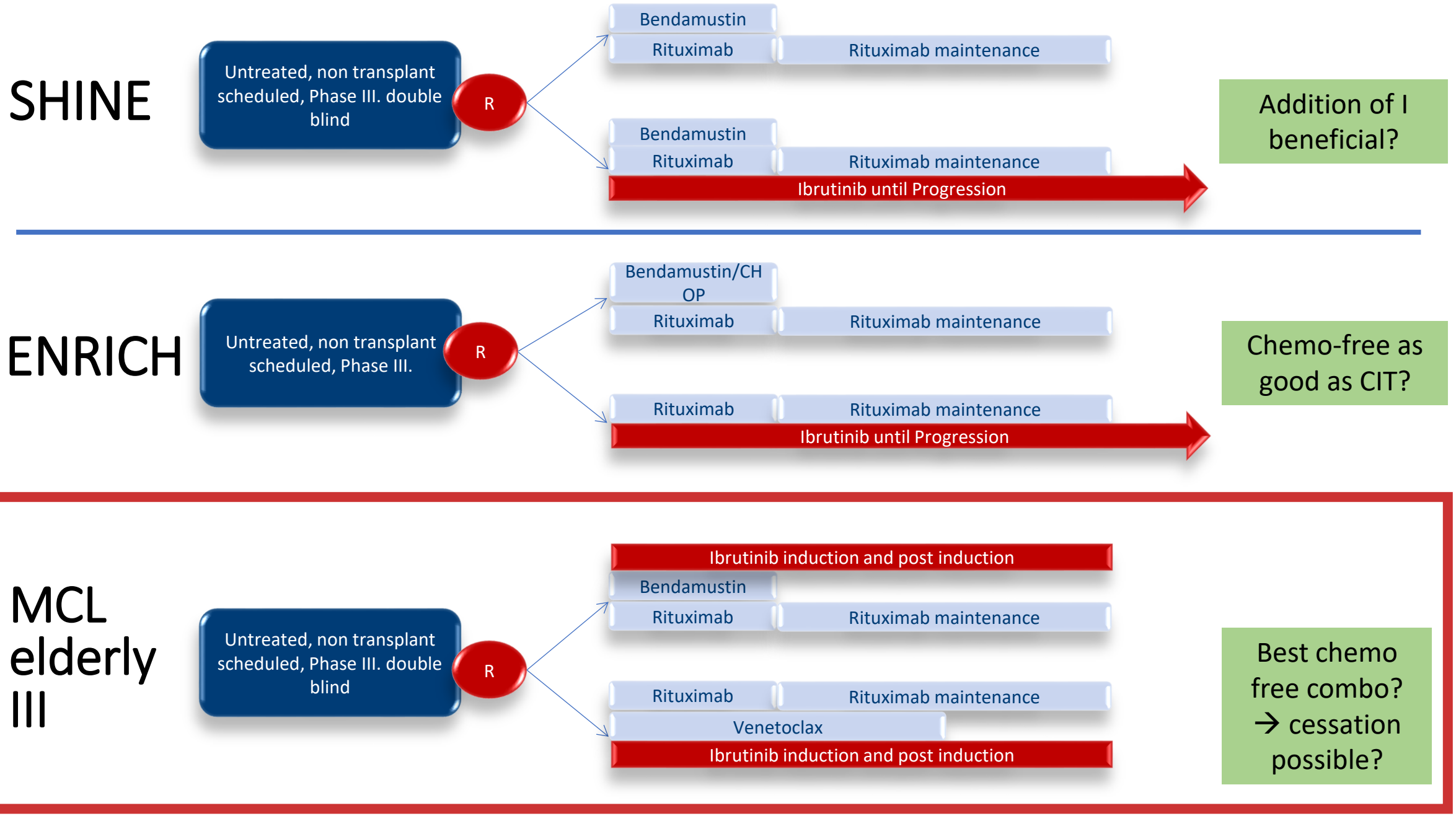
A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

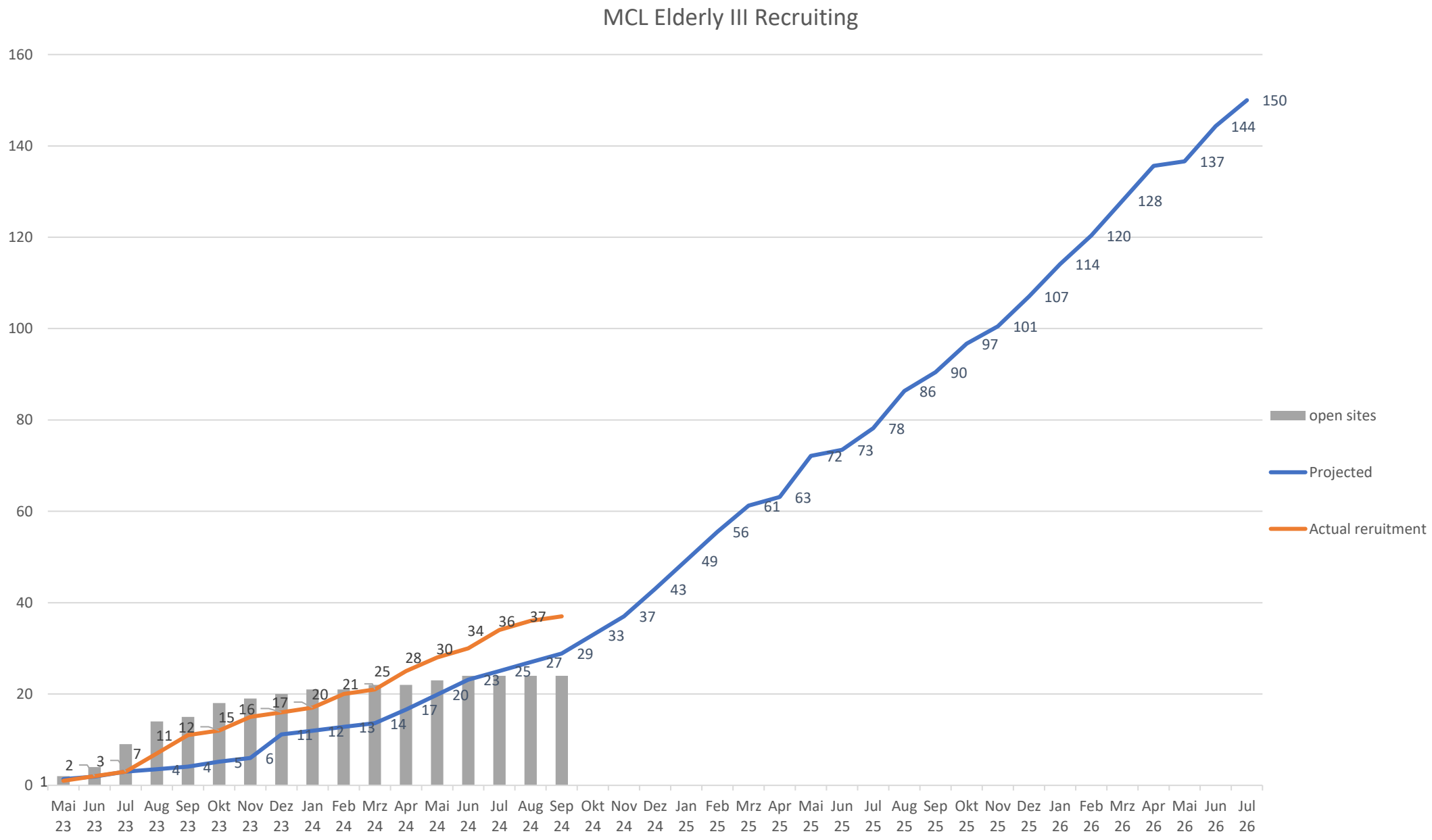
Mantle cell Lymphoma
Onkopedia June 2023



European MCL Network
Study generation 2024




SHINE
Untreated, non transplant scheduled, Phase III. double blind
R
Bendamustin
Rituximab
Rituximab maintenance
Bendamustin
Rituximab
Rituximab maintenance
Ibrutinib until Progression
Addition of I beneficial?
ENRICH
Untreated, non transplant scheduled, Phase III.
R
Bendamustin/CHOP
Rituximab
Rituximab maintenance
Rituximab
Rituximab maintenance
Ibrutinib until Progression
Chemo-free as good as CIT?
MCL elderly III
Untreated, non transplant scheduled, Phase III. double blind
R
Ibrutinib induction and post induction
Bendamustin
Rituximab
Rituximab maintenance
Rituximab
Rituximab maintenance
Venetoclax
Ibrutinib induction and post induction
Best chemo free combo? → cessation possible?


MCL Elderly III Recruiting
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120
100
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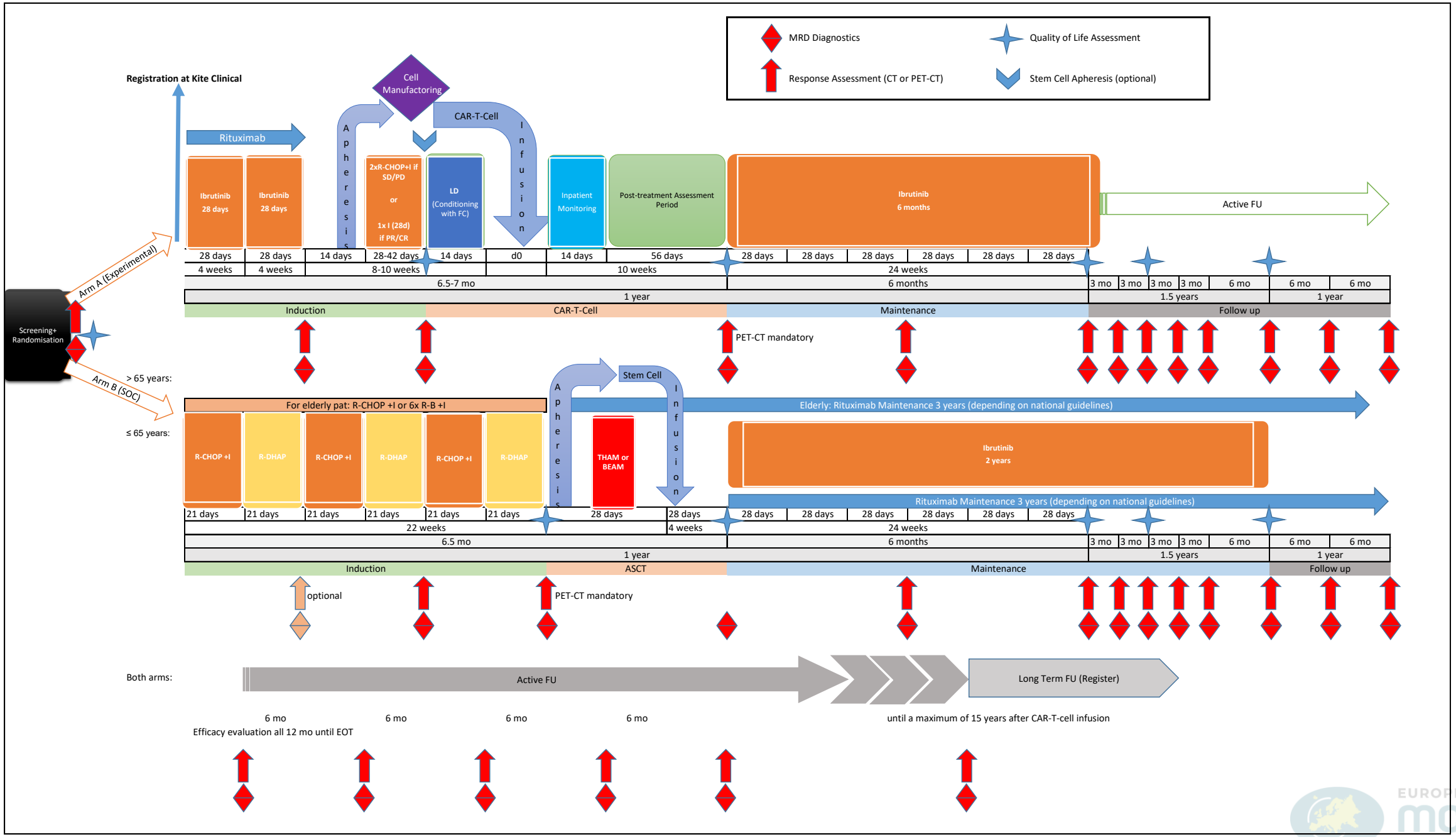
open sites
Projected
Actual reruitment


MRD Diagnostics
Quality of Life Assessment
Response Assessment (CT or PET-CT)
Stem Cell Apheresis (optional)
Registration at Kite Clinical
Cell Manufactoring
Rituximab
Apheresis
CAR-T-Cell
Infusion
Ibrutinib 28 days
Ibrutinib 28 days
2xR-CHOP+I if SD/PD or 1x I (28d) if PR/CR
LD (Conditioning with FC)
Inpatient Monitoring
Post-treatment Assessment Period
Ibrutinib 6 months
Active FU
Arm A (Experimental)
Screening+ Randomisation
Arm B (SOC)
> 65 years:
≤ 65 years:
28 days
28 days
14 days
28-42 days
14 days
d0
14 days
56 days
28 days
28 days
28 days
28 days
28 days
28 days
4 weeks
4 weeks
8-10 weeks
10 weeks
24 weeks
6.5-7 mo
6 months
3 mo
3 mo
3 mo
3 mo
6 mo
6 mo
6 mo
1 year
1.5 years
1 year
Induction
CAR-T-Cell
Maintenance
Follow up
PET-CT mandatory
For elderly pat: R-CHOP +I or 6x R-B +I
Stem Cell
Elderly: Rituximab Maintenance 3 years (depending on national guidelines)
R-CHOP +I
R-DHAP
R-CHOP +I
R-DHAP
R-CHOP +I
R-DHAP
THAM or BEAM
Ibrutinib 2 years
Rituximab Maintenance 3 years (depending on national guidelines)
21 days
21 days
21 days
21 days
21 days
21 days
28 days
28 days
28 days
28 days
28 days
28 days
28 days
22 weeks
4 weeks
24 weeks
6.5 mo
6 months
Induction
ASCT
Maintenance
Follow up
optional
PET-CT mandatory
Both arms:
Active FU
Long Term FU (Register)
6 mo
6 mo
6 mo
6 mo
until a maximum of 15 years after CAR-T-cell infusion
Efficacy evaluation all 12 mo until EOT

KML Studien in Indolenten Lymphomen
Take home messages 2024

LMU KLINIKUM

- **Follikuläres Lymphom (Erstlinie, randomisiert):**
  - Frühe Stadien: Radiatio (*2Gray/Obi vs 24 Gray/R*)
  - Erstlinie: Mosu + Len (*MorningLyte*)
- **Marginalzonen-Lymphom (Rezidiv, randomisiert):**
  - Rezidive: Mosu + Len (*MARSUN*)
- **Waldenstroem (Erstlinie, randomisiert):**
  - Chemo-freie Konzepte (VIWA)
- **Mantelzell-Lymphom (Erstlinie, randomisiert):**
  - Ibru/Ven/Ritux (MCL elderly 3)
  - CAR-T +Ibru/Ritux (Carman)

Studientreffen 2022, Berlin