The young side of LYMPHOMA

gli under 40 a confronto

Verona, Centro Congressi Camera di Commercio
26-27 settembre 2025

FONDAZIONE ITALIANA LINFOMI

DBMSS
Dipartimento di Biotecnologie Molecolari e Scienze per la Salute

Attualità nella terapia di I linea nel paziente giovane con MCL

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UNIVERSITÀ DI TORINO

Disclosures of Simone Ragaini

Company name	Research support	Employee	Consultant	Stockholder	Speakers honoraria	Advisory board	Other
Pierre Fabre					x		
Beigene					x		
Roche					x		
Novartis					x		
Astrazeneca					x		
Gilead/Kyte							x

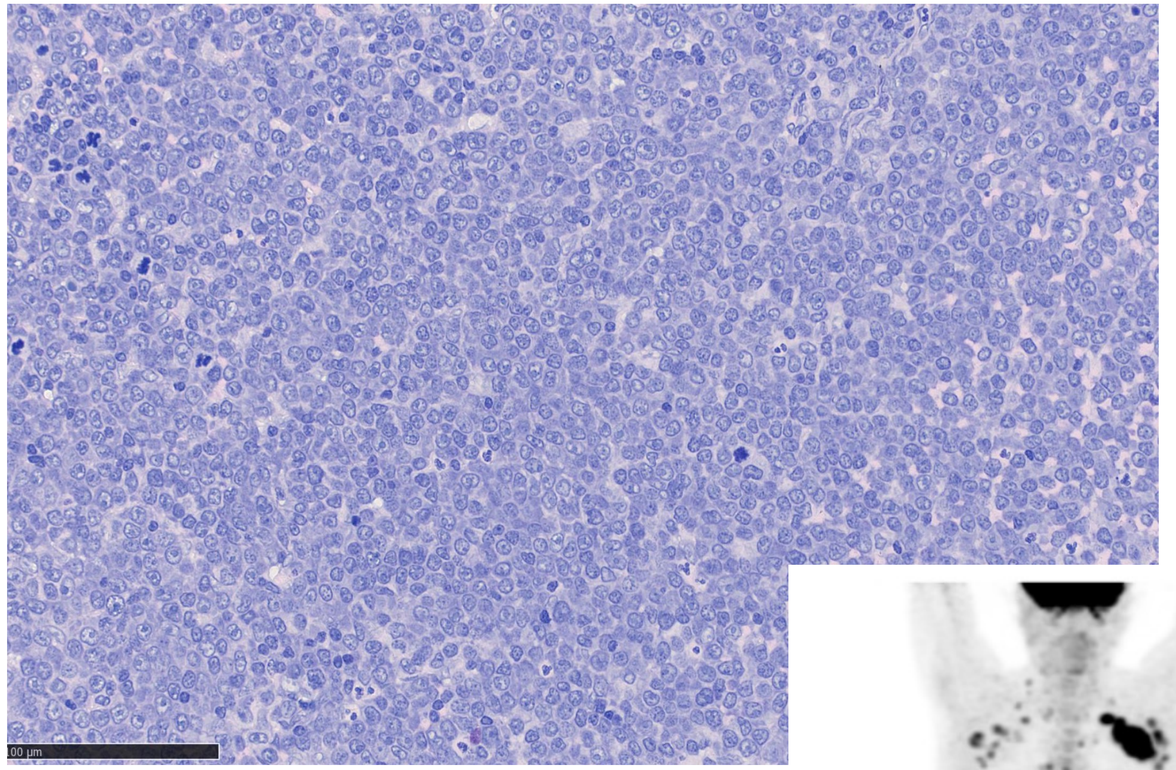
Break the mold in young MCL patients

- **ASCT**: dead or alive? (its long-term efficacy was demonstrated in the pre-rituximab and pre-cytarabine era)
- Is **risk-adapted treatment** in MCL feasible?
- Is **tailored monitoring** in MCL feasible?

Martin Dreyling, Blood 2005
Anna-Katharina Zoellner, The Lancet Haematology 2021

Male, 46 y.o.

- Previous smoker - Fit
- Familiarity for colo-rectal cancer
- Lawyer
- January 2024: weight loss, onset of palpable adenopathies

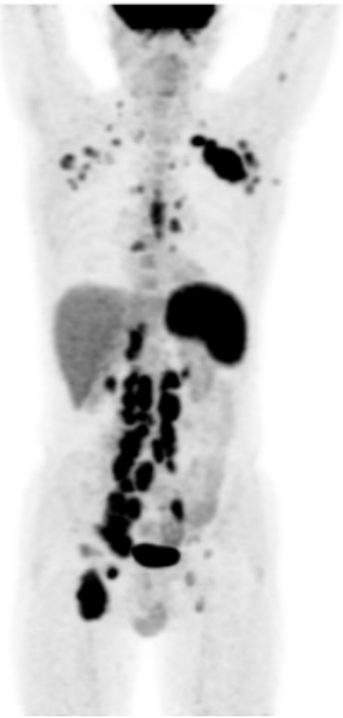


Blood exams: WBC 4000
Hb 14.2 PLTs 155.000
LDH increased

Nodal biopsy: classic mantle cell lymphoma
CCND1- CD5+ SOX11+ Ki67 30% *TP53* WT

AM: 30% MCL infiltration, t(11:14)+

MCL Stage IV,
MIPI IR MIPIc HR



PET scan: FDG uptake in supra and sub-diaphragmatic adenopathies (SUV Max 9) and spleen (SUV 6)

Best treatment option ?

- 6 R-CHOP/R-DHAP + ASCT + RITUXIMAB MAINTENANCE
- 6 R-CHOP+IBRUTINIB/R-DHAP (ARM I TRIANGLE) + IR MAINTENANCE
- 6 R-CHOP+IBRUTINIB/R-DHAP + ASCT (ARM A+I TRIANGLE) + IR MAINTENANCE
- 6 R-BAC

https://www.slido.com Codice: 3546 320

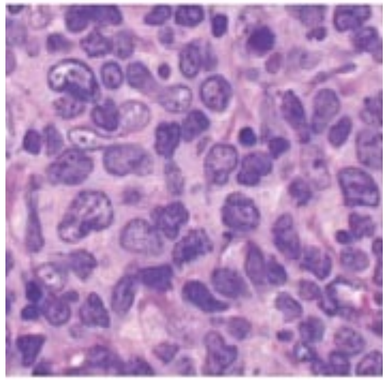
Male, 50 y.o.

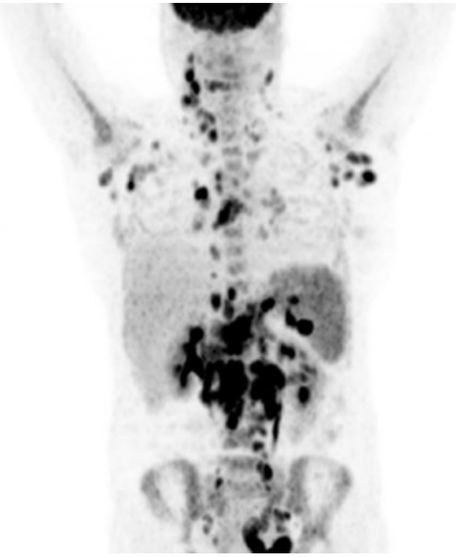
- Fit
- Engineer
- March 2024: onset of palpable adenopathies

Blood exams: WBC 7000 Hb 14 PLTs 200.000 cr 0.92 **LDH 2000**

Nodal biopsy: pleomorphic mantle cell lymphoma
CCND1+ CD5+ SOX11+
Ki67 50% p53 IHC 50%
***TP53* mut.**

MCL Stage IV, MIPIc HR





PET scan: multiple supra and sub-diaphragmatic adenopathies **(SUV Max 9)**

Best treatment option ? (clinical trial not available

- 6 R-CHOP/R-DHAP + ASCT + RITUXIMAB MAINTENANCE
- 6 R-CHOP+IBRUTINIB/R-DHAP (ARM I TRIANGLE) + IR MAINTENANCE
- 6 R-CHOP+IBRUTINIB/R-DHAP + ASCT (ARM A+I TRIANGLE) + IR MAINTENANCE
- 6 R-BAC

https://www.slido.com Codice: 3546 320

haematologica Vol. 101 No. 2 (2016): February, 2016

The role of targeted treatment in mantle cell lymphoma: is transplant dead or alive?

Martin Dreyling[1] and Simone Ferrero,[2] on behalf of European Mantle Cell Lymphoma Network

	Author	Study Features	Evaluable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (years)	Median OS (years)	Dropout rate	TRM	Secondary tumors rate
ASCT Based regimens	Dreyling *et al.*, 2005 [18]	Phase III, randomized	122	R-CHOP + TBI + ASCT *vs.* R-CHOP + TBI + interferon-α	98 (81) *vs.* 99 (37)	3,3 *vs.* 1,4	NR (83% 3-y OS) *vs.* NR (77% 3-y OS)	13% *vs.* na	5% *vs.* 0%	5%
	Hermine *et al.*, 2012 [34]	Phase III, randomized	455	R-CHOP + TBI + ASCT *vs.* R-CHOP/R-DHAP + HD-araC + ASCT	98 (63) *vs.* 99 (61)	3,8 *vs.* 7,3	6,8 *vs.* NR	na	4%	na
	Damon *et al.*, 2009 [26]	Phase II	77	R-CHOP + methotrexate + HD-araC/etoposide + ASCT	88 (69)	NR (56% 5-y PFS)	NR (64% 5-y OS)	13%	3%	na
	Van't Veer *et al.*, 2009 [27]	Phase II	87	R-CHOP + HD-araC + ASCT	70 (64)	NR (36% 4-y PFS)	NR (66% 4-y OS)	30%	5%	na
	Geisler *et al.*, 2012 [39]	Phase II	160	R-Maxi-CHOP + HD-araC+ ASCT	96 (54)	7,4	NR (64% 10-y OS)	9%	5%	4%
	Delarue *et al.*, 2013 [28]	Phase II	60	R-CHOP/R-DHAP + HD-araC + ASCT	100 (96)	6,9	NR (75% 5-y OS)	18%	1,5%	18%
	Touzeau *et al.*, 2013 [29]	Retrospective	396	Different ASCT-based schedules	83 (77)	NR (67% 3-y PFS)	NR (83% 3-y OS)	na	2,5%	6%
	Kolstad *et al.*, 2014 [40]	Phase II	160	R-Maxi-CHOP + HD-araC+/- Zevalin + ASCT	94 (82)	NR (71% 4-y PFS)	NR (78% 4-y OS)	9%	6%	3%
	Le Gouill *et al.*, 2014 [42]	Phase III, randomized	299	R-DHAP + ASCT +/- rituximab maintenance	na (92)	NR (74% 3-y PFS)	NR (83% 3-y OS)	14%	na	na
	Cortelazzo *et al.*, 2015* [99]	Phase III, randomized	260*	R-CHOP+R-CTX+HD-araC+ASCT +/- lenalidomide maintenance	86 (78)	NR (78% 2-y PFS)	NR (89% 2-y OS)	22%*	2%	na
Non-ASCT based regimens	Romaguera *et al.*, 2010 [6]	Phase II, monocentric	97	R-Hyper-CVAD	97 (87)	4,6	NR (64% 10-y OS)	29%	8%	5%
	Merli *et al.*, 2012 [31]	Phase II, multicentric	60	R-Hyper-CVAD	83 (72)	NR (73% 5-y PFS)	NR (61% 5-y OS)	63%	6,5%	1,5%
	Bernstein *et al.*, 2013 [32]	Phase II, multicentric	49	R-Hyper-CVAD	86 (55)	4,8	6,8	39%	2%	4%

- TRM up to 6%
- Major adverse events are infectious (neutropenic fever, pneumonia) and gastrointestinal (10%–15% of patients)

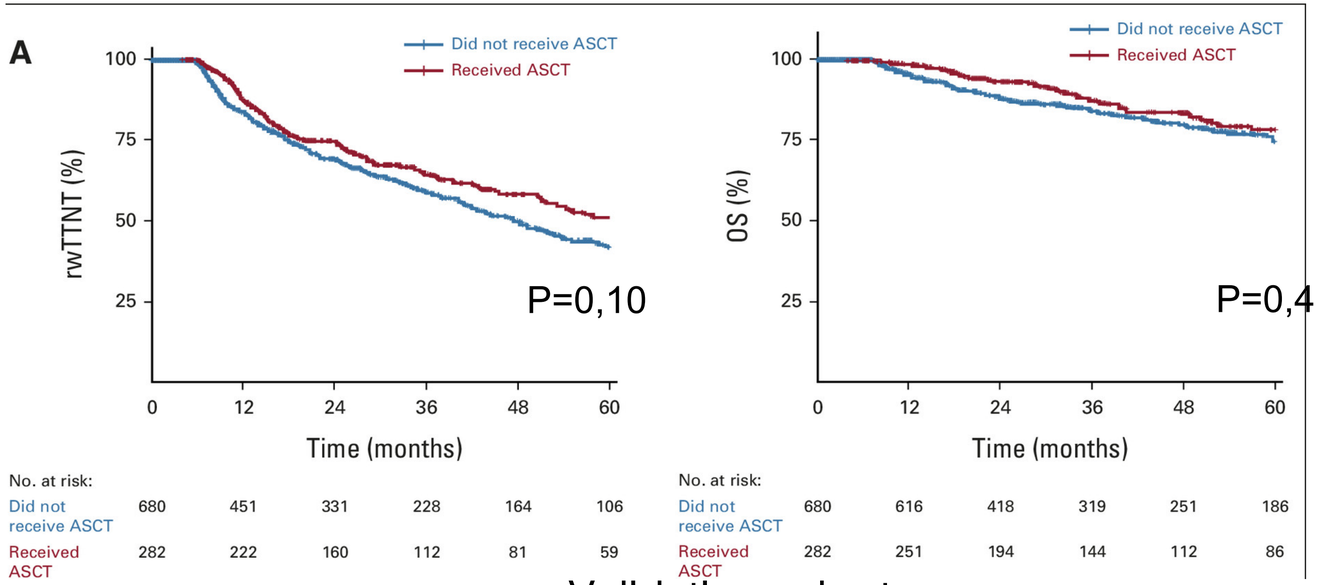
Treatment Outcomes and Roles of Transplantation and Maintenance Rituximab in Patients With Previously Untreated Mantle Cell Lymphoma: Results From Large Real-World Cohorts

Authors: Peter Martin, MD, Jonathon B. Cohen, MD, MS, Michael Wang, MD, Anita Kumar, MD, Brian Hill, MD, PhD, Diego Villa, MD, Jeffrey M. Switchenko, PhD, MS, ... SHOW ALL ... , and Gilles Salles, MD, PhD AUTHORS INFO & AFFILIATIONS

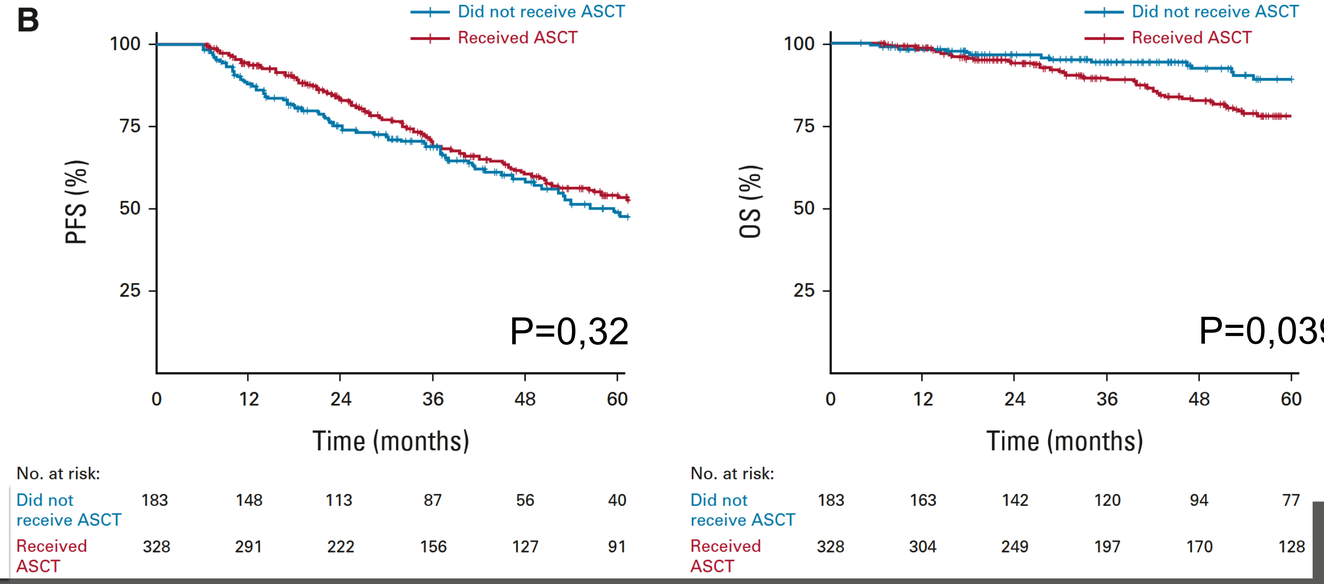
Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal
June 28, 2022

- Retrospective data from 4,216 patients with mantle cell lymphoma in the Flatiron Health electronic record-derived deidentified database diagnosed between 2011 and 2021, mostly in US
- Validation in an independent cohort of 1,168 patients from 12 academic centers.
- rwTTNT and OS in the ASCT-eligible cohort by ASCT status (yes *v* no) in the Flatiron cohort;

Flatiron cohort



Validation cohort

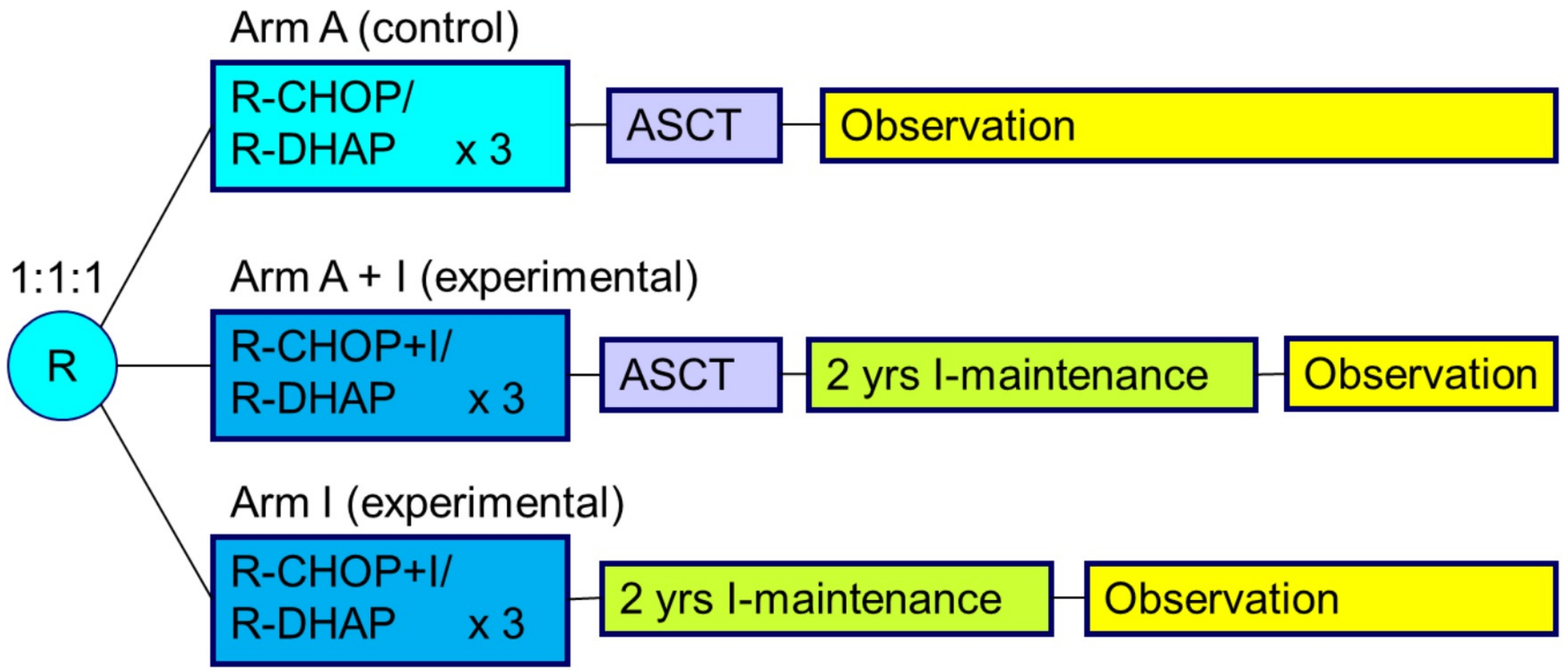


TRIANGLE: Trial Design

- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

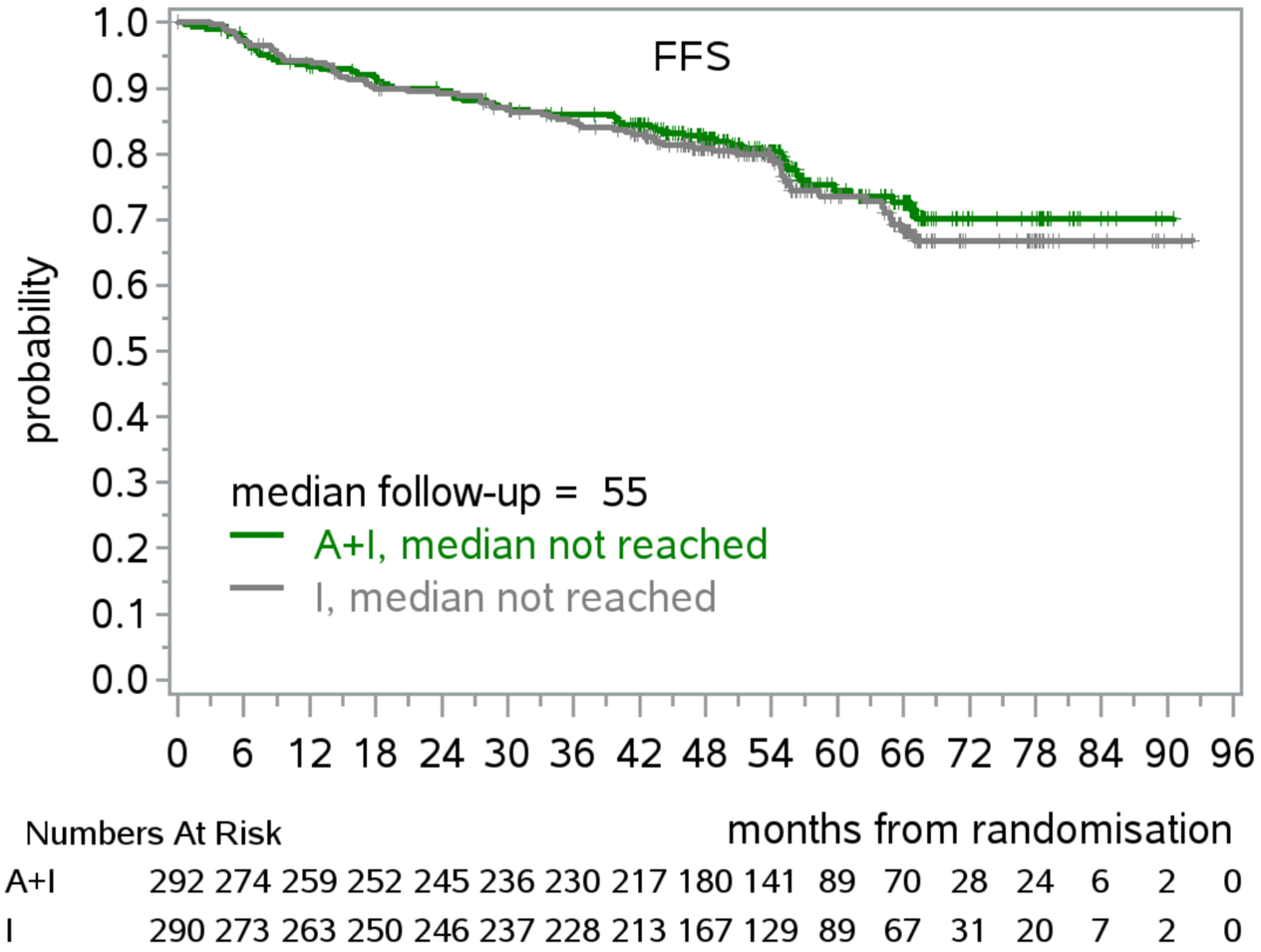
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety



- 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

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



- 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

What is the optimal **age cut-off** for the new intensive induction therapy that omits ASCT in MCL?

267 | EVALUATION OF ESTABLISHED PROGNOSTIC MARKERS IN YOUNGER MANTLE CELL LYMPHOMA PATIENTS UNDER IBRUTINIB CONTAINING REGIMENS—AN ANALYSIS EMBEDDED IN THE MULTIPLY PROJECT

K. Gutmair, S. Reinke, S. Beà, E. Campo, M. Ladetto, J. Doorduijn, E. Giné, M. Jerkeman, J. Walewski, M. Hutchings, U. Mey, J. Riise, M. Trneny, V. Vergote, O. Shpilberg, M. Gomes da Silva ... See all authors

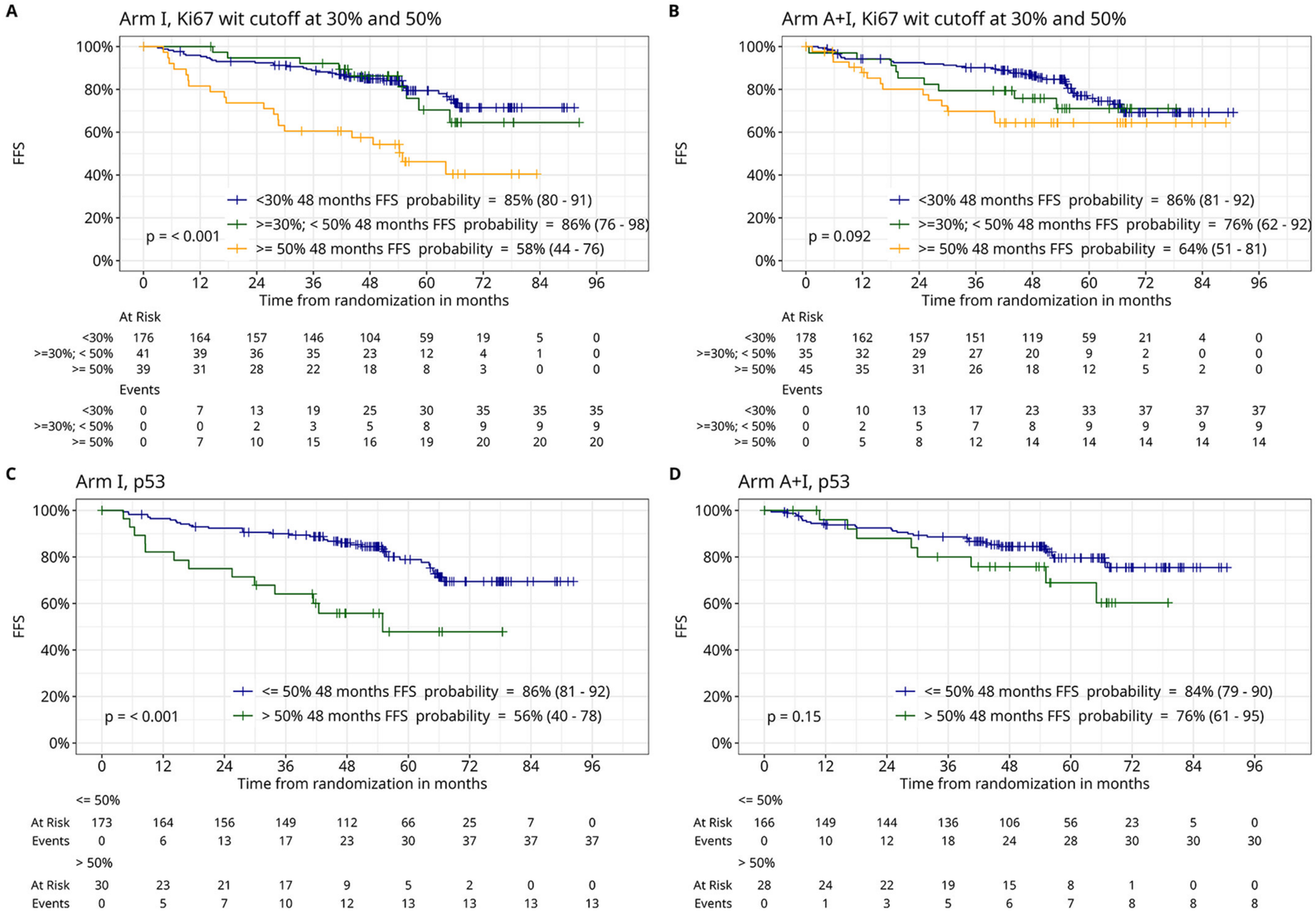
Hematological ONCOLOGY

Poster @ICML 2025 –
First published: 16 June 2025

EUROPEAN mCL NETWORK

muTIPLY

- After adjusting p53 for MIPI, Ki67 and cytology, the discrimination remained significant in arm I (> 50% vs. ≤ 50% I: HR: 2.18, $p = 0.026$), but not in A+I (HR: 1.64, $p = 0.2$).
- The prognostic value of established biological factors (high Ki-67, p53 alterations) seems to be partly overcome by ASCT and ibrutinib, suggesting a synergistic potential of this combination in high-risk patients.



137 | IBRUTINIB ADDED TO MCL TREATMENT HAS STRONG IMPACT ON MRD RESPONSE AND DISEASE KINETICS: RESULTS FROM THE TRIANGLE TRIAL

Hematological ONCOLOGY

June 2025

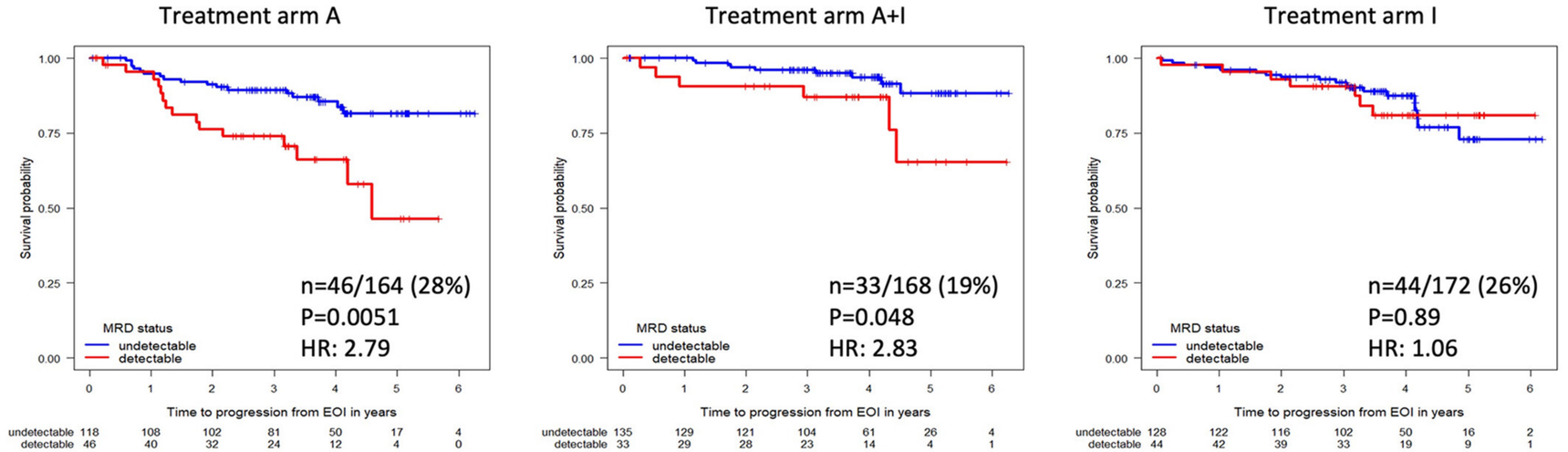
M. Khouja, V. Jurinovic, S. Ferrero, E. Genuardi, B. Kehden, A. M. Civita, C. U. Niemann, R. García Sanz, A. M. Herrera, C. Homburg, O. J. Verhagen, V. H. van der Velden, S. Kubetzko ... See all authors

EUROPEAN MCL NETWORK

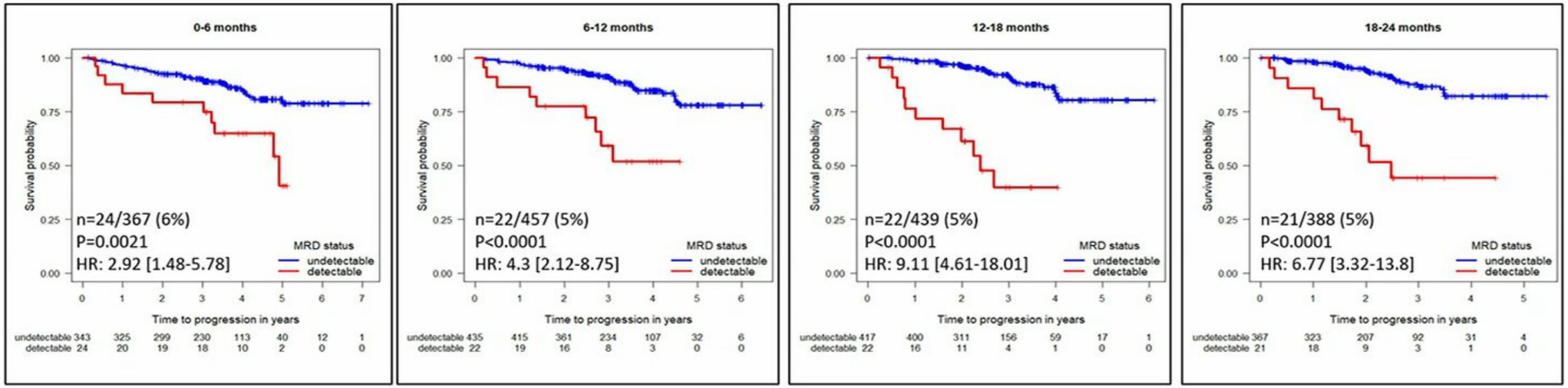
MUTIPLY

- MRD at EOI also significantly correlated with time to progression (TTP) in arms A and A+I, but not in arm I
- Landmark analysis confirmed the prognostic value of MRD during maintenance, peaking at 12–18 months.

MRD at EOI



Landmark analysis during maintenance therapy

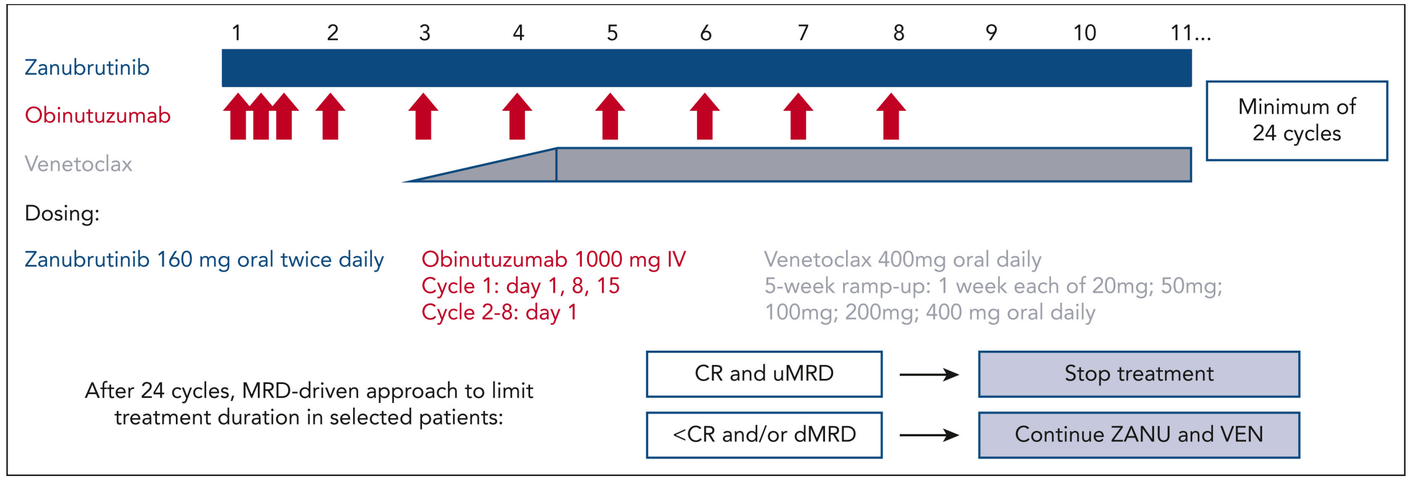


CLINICAL TRIALS AND OBSERVATIONS | JANUARY 30, 2025

Zanubrutinib, obinutuzumab, and venetoclax for first-line treatment of mantle cell lymphoma with a *TP53* mutation

Clinical Trials & Observations

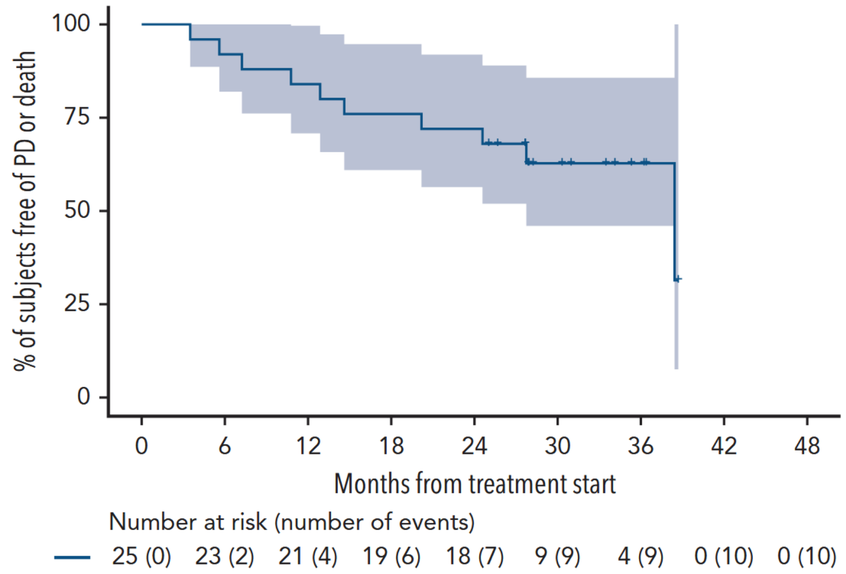
Anita Kumar, Jacob Soumerai, Jeremy S. Abramson, Jeffrey A. Barnes, Philip Caron, Shalini Chhabra, Maria Chabowska, Ahmet Dogan, Lorenzo Falchi, Clare Grieve, J. Erika Haydu, Patrick Connor Johnson, Ashlee Joseph, Hailey E. Kelly, Alyssa Labarre, Jennifer Kimberly Lue, Rosalba Martignetti, Joanna Mi, Alison Moskowitz, Colette Owens, Sean Plummer, Madeline Puccio, Gilles Salles, Venkatraman Seshan, Elizabeth Simkins, Natalie Slupe, Honglei Zhang, Andrew D. Zelenetz

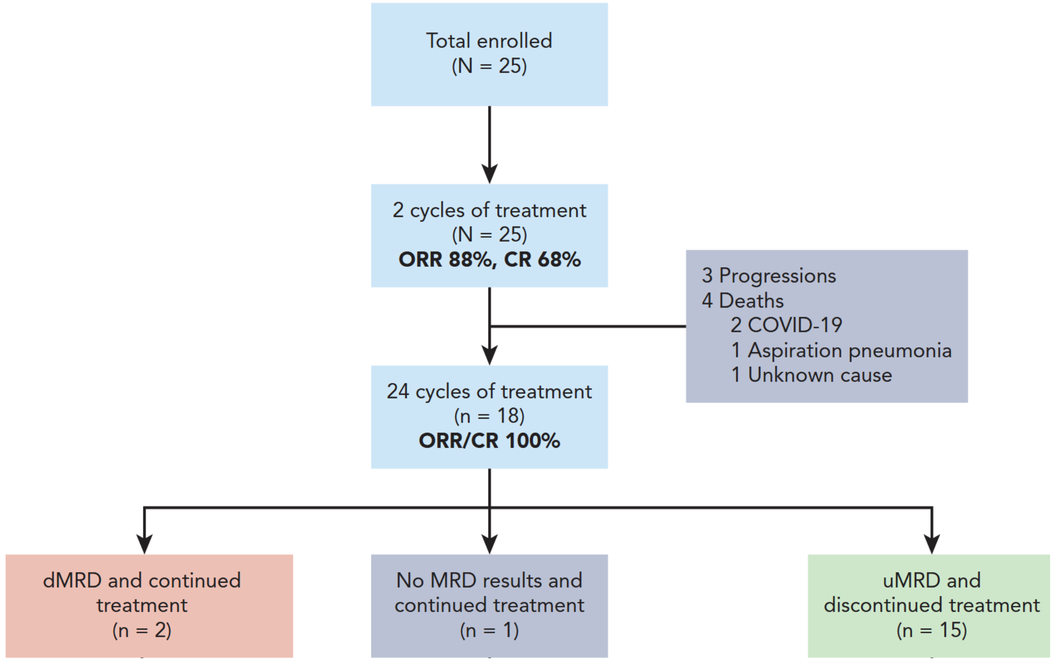


- Median age was 68 (29-82) years
- 2-year progression-free 72%
- 2-year overall survival 76%

- Common Aes low grade and included diarrhea (64%), neutropenia (32%), and infusion-related reactions (24%).

Median follow-up of 28.2 months





Your chemo is no good here: management of high-risk MCL

Hematology 2024 | ASH Education Program

Yazeed Sawalha and Kami Maddocks

Department of Internal Medicine, Division of Hematology, Arthur G. James Comprehensive Cancer Center, The Ohio State University Wexner Medical Center, Columbus, OH

Study name (identifier)	Phase	Treatment(s)	Key inclusion criteria
CARMAN (EuCT 2022–502405–15–00)	2	Ibrutinib + rituximab → ibrutinib + R-CHOP or ibrutinib monotherapy → brexucabtagene → ibrutinib maintenace vs ibrutinib + R-CHOP/R-DHAP → ASCT (≤65 y) or ibrutinib + R-CHOP or BR (>65 y)→ ibrutinib and RM	Age ≤75y High intermediate or high MIPI-c and/or *TP53* mutation or p53 expression >50%
NCT05861050	1/2	Glofitamab (with obinutuzumab pretreatment), venetoclax, and lenalidomide	≥1 high-risk feature: blastoid/pleomorphic, Ki-67 ≥ 50%, *TP53* aberration or p53 overexpression, complex karyotype, high MIPI, bulky disease, other high-risk mutations
MCL Elderly III (Eudra CT 2020–002935–30)	2	Ibrutinib + venetoclax + rituximab vs BR + ibrutinib	≥60 and transplant ineligible
ALTAMIRA (NCT05214183)	2	Acalabrutinib + rituximab	≥60 and transplant ineligible
WINDOW-3 (NCT05495464)	1	Acalabrutinib + rituximab → brexucabtagene	High-risk including high MIPI-c, blastoid, Ki-67 ≥ 50%, *TP53* aberrations or other high-risk mutations, or bulky disease

3 **RTX ODHA alternating 3 RTX CHOP** → PMR
(March 2022)

How is going our young MCL patient ?

Ibrutinib → CMR
(Aug 2022)

MCL relapse with palpable abdominal mass (Jan 2024)

Radiotherapy + CAR-T (PMR)

R-BAC (PMR)

Glofitamab (SD)

Pirtobrutinib (SD)
Venetoclax (SD)

Allo-HSCT

Take-home messages

- In **standard-risk younger patients** with MCL, frontline treatment should follow **arm I of the TRIANGLE trial** (optimal age cut-off for intensive chemotherapy?)

- **High-risk MCL younger patients might still benefit from ASCT**, but ongoing trials of **chemo-free regimens** (potentially including CAR-T cell therapy) are likely to define the most effective options in the near future.

- **Rituximab maintenance remains effective even after ibrutinib** has been used in the frontline setting.

- Although currently not yet applied routinely, **MRD assessment remains a valuable predictor of MCL progression**, and **MRD+ patients may benefit from additional therapeutic interventions**.

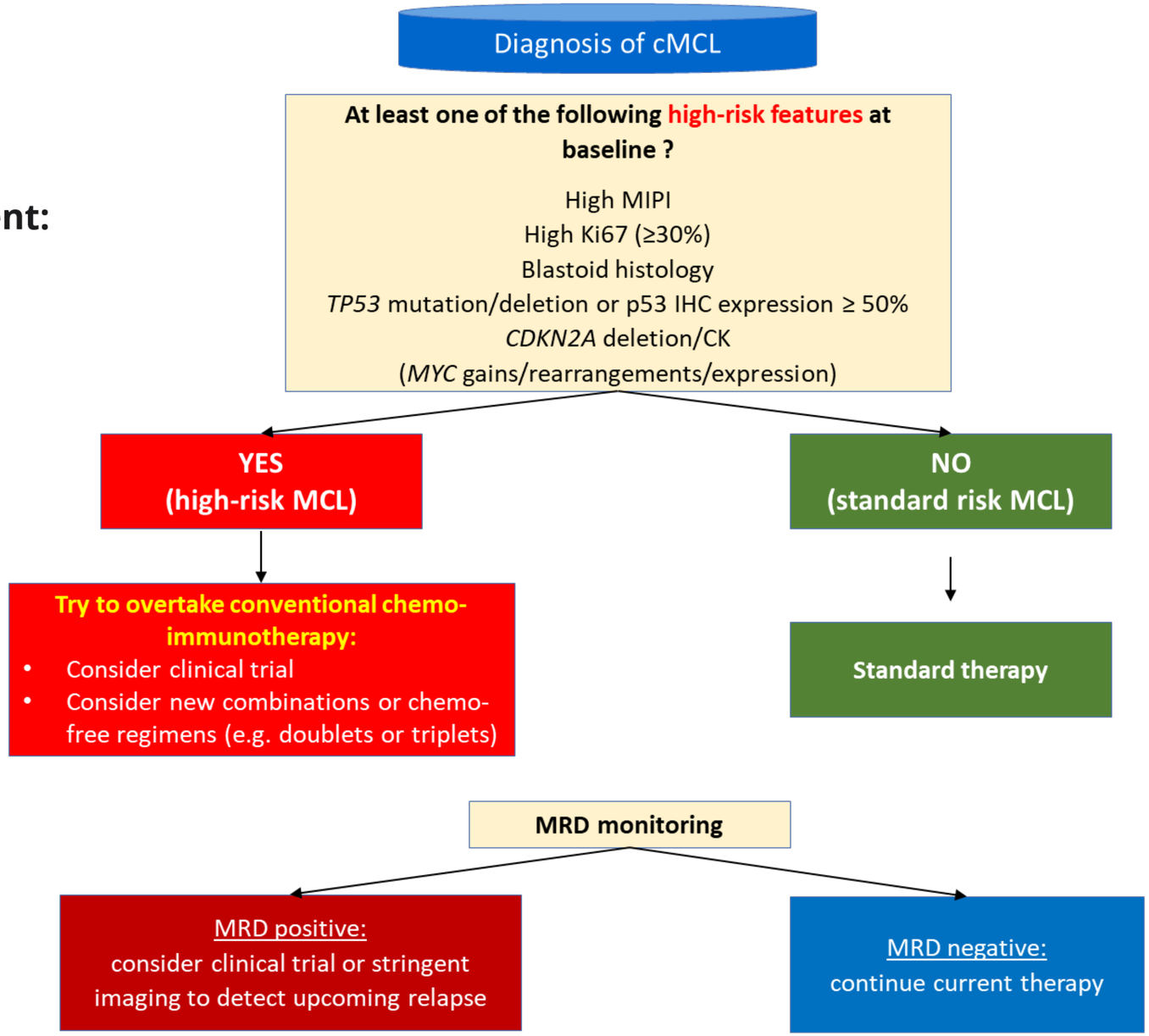
Hematological ONCOLOGY

SUPPLEMENT ARTICLE | Open Access

Advancing Mantle Cell Lymphoma Risk Assessment: Navigating a Moving Target

Simone Ferrero, Simone Ragaini

First published: 15 June 2025 | https://doi.org/10.1002/hon.70072



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FIL-MCL Clinical Trials