Mantle Cell Lymphoma: When to Choose Intensive Induction Therapy

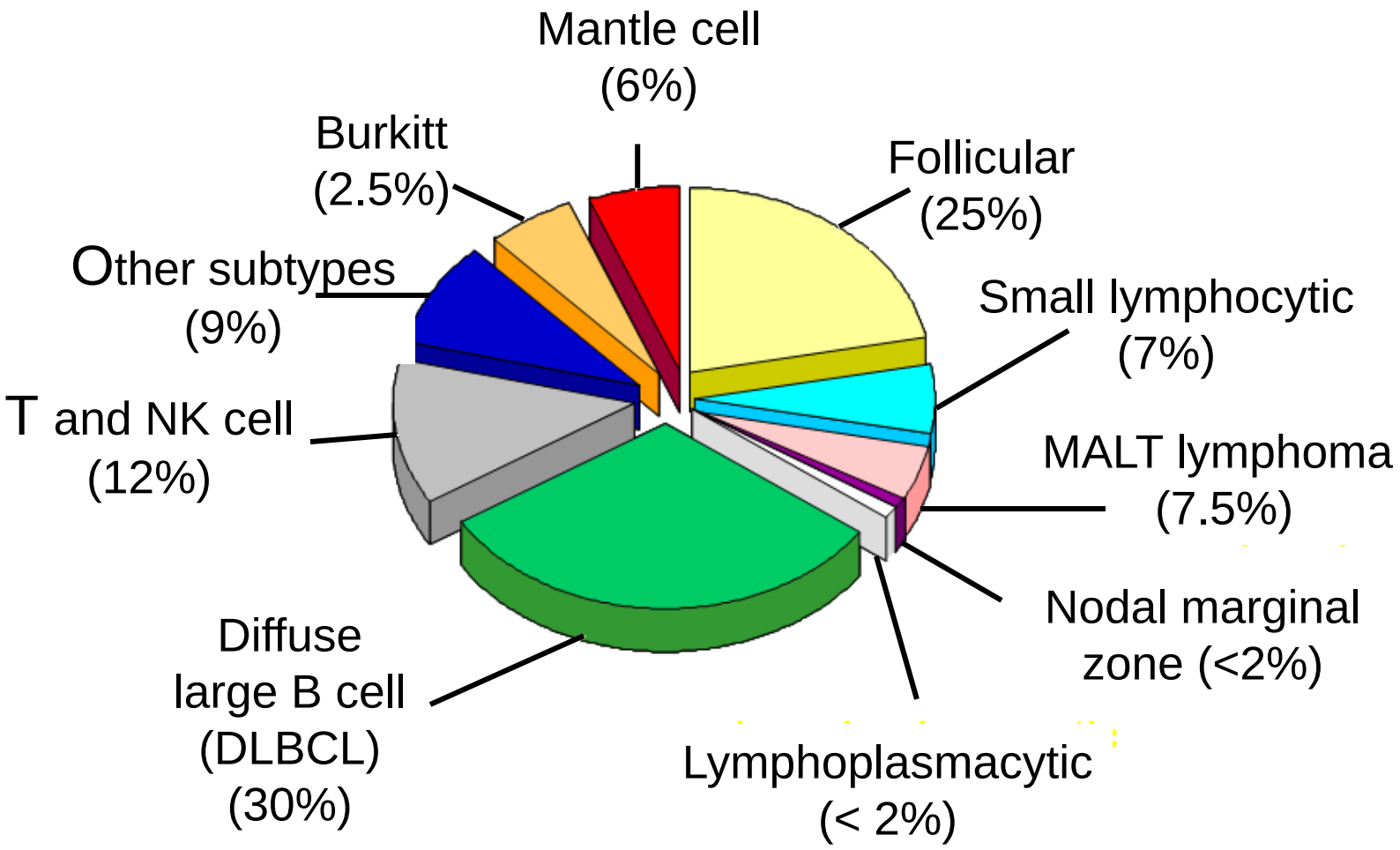
Brad Kahl, MD
Professor of Medicine

SITEMAN CANCER CENTER
BARNES-JEWISH Hospital BJC HealthCare | Washington University in St. Louis SCHOOL OF MEDICINE
NCCN National Comprehensive Cancer Network®
NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

Disclosures

- Consulting
  - Abbvie, Acerta, Astra Zeneca, ADCT, Celgene, Genentech, Juno, Kite, Morphosys, BeiGene, Pharmacyclics, Janssen,
- Research Funding
  - Genentech, ADCT, Acerta, Celgene, BeiGene

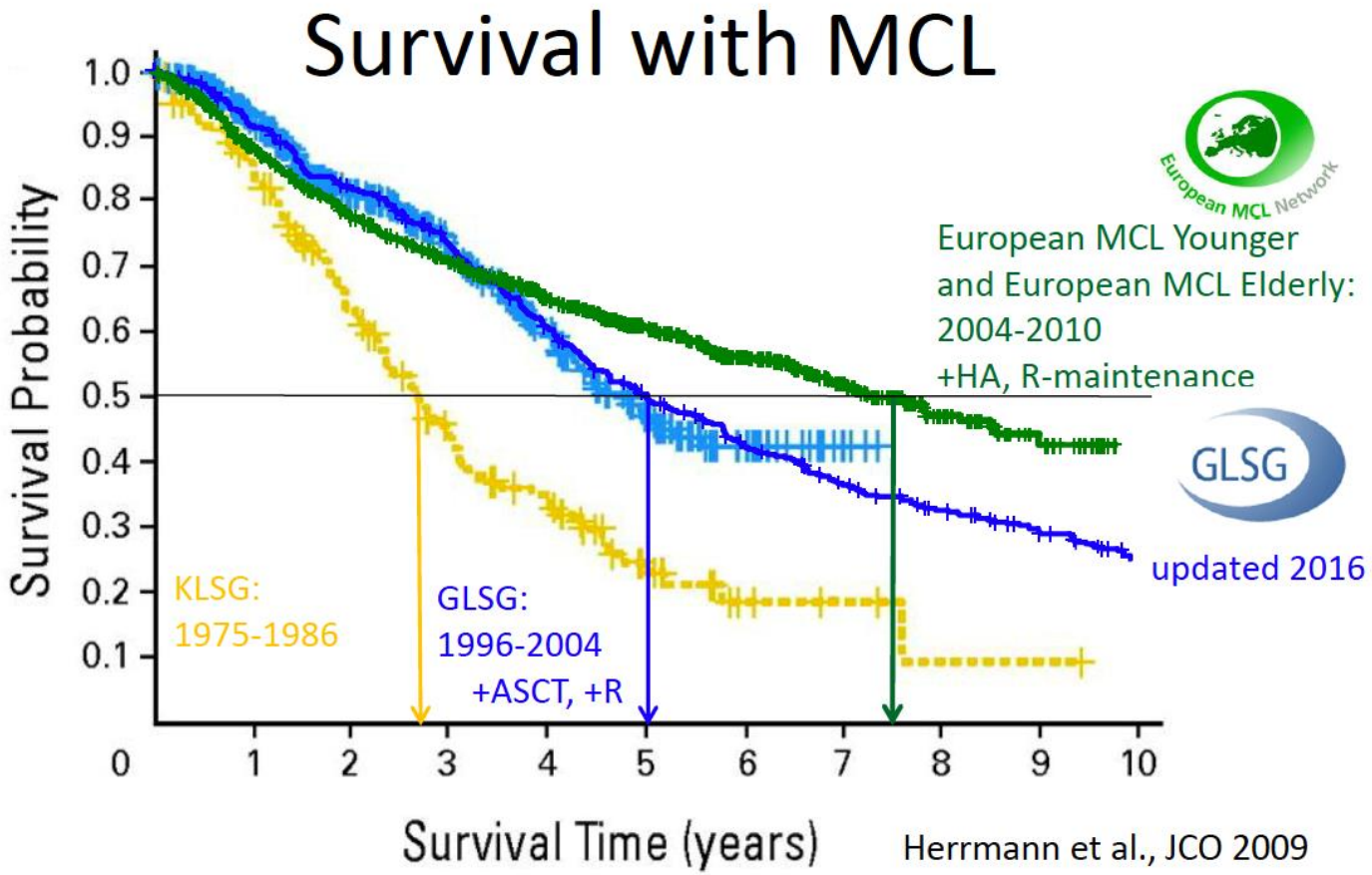
Mantle Cell Lymphoma ~ 6% of NHL Cases



MCL: Unique Clinical Features

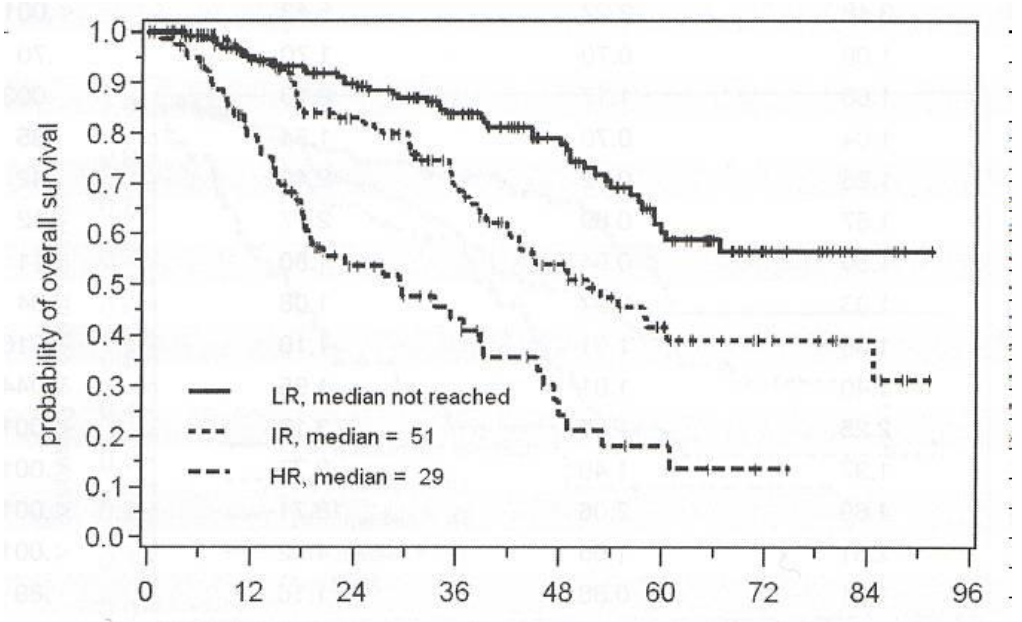
- 3:1 male predominance
- Median age ~ 65 years old
- 85-90% diagnosed with stage III/IV disease
  - Blood (lymphocytosis)
  - Bone marrow involvement
  - GI tract involvement detected in 80%
    - May manifest as lymphomatous polyposis
- 33% Elevated LDH
- 25% B symptoms
- CNS involvement rare (<1% at diagnosis)
  - Slightly more common in R/R MCL
- Generally regarded as “aggressive” and incurable
- Indolent presentation in ~ 20%

MCL: Natural History. Improving outcomes.



MCL: Clinical Prognostic Factors - MIPI

- 4 factors associated with OS
  - Age
  - ECOG PS
  - LDH
  - WBC
- Risk Distribution
  - Low 44% (<5.7)
  - Int 35%(5.7-6.1)
  - High 21% (≥6.2)



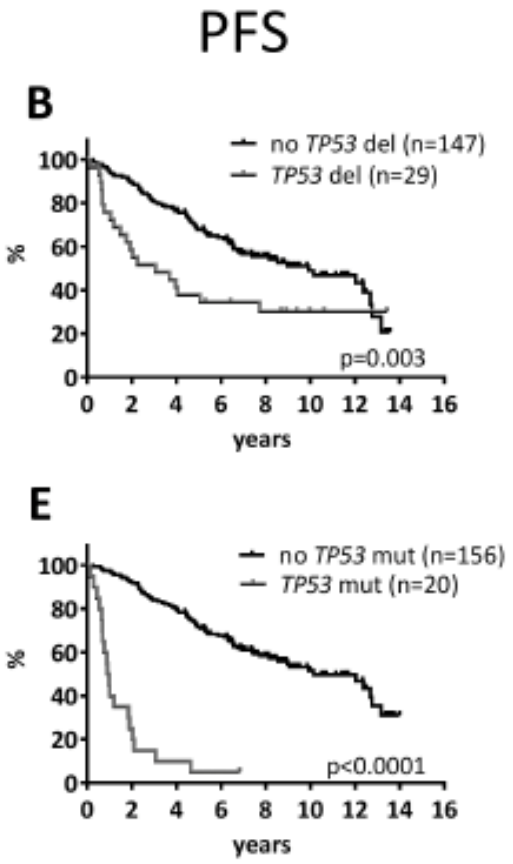
Formula for calculating MIPI:

[0.03535 x age (years)] + 0.6978 (if ECOG > 1) + [1.367 x log10(LDH/ULN)] + [log10(WBC count)]

Hoster et al, Blood 2008

Biologic prognostic factors

- Proliferation rate
  - Ki-67 > 30%
- Complex karyotype
  - ≥ 3 additional abnormalities
- Deletions or mutations in TP53
  - Time to start checking this at baseline



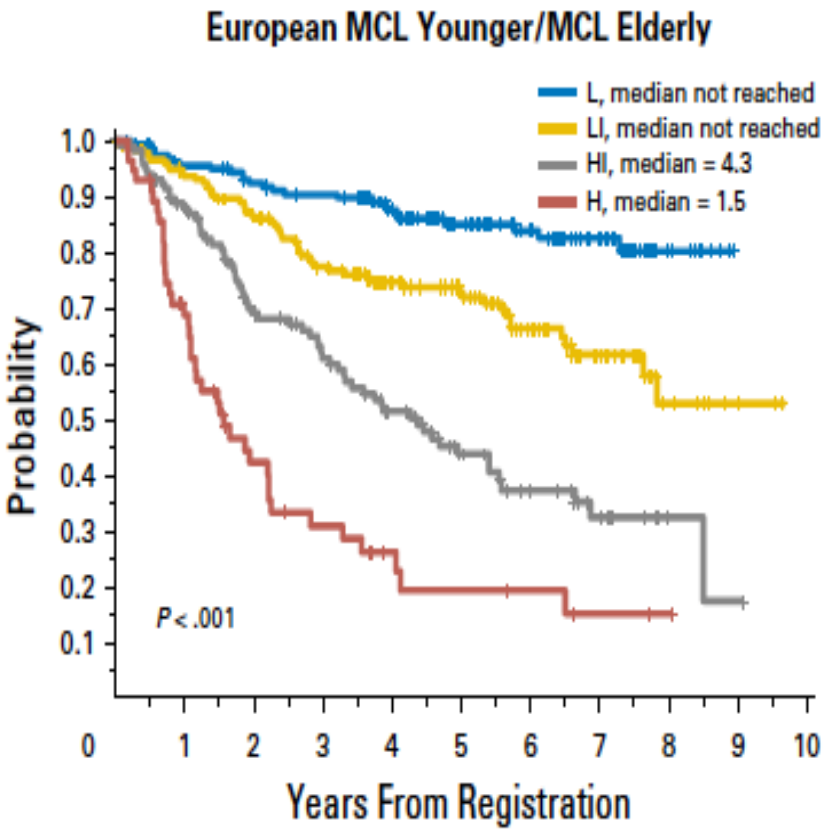
Eskelund et al, Blood online Aug 17, 2017

MIPI-c calculator
Integrating biologic and clinical risk predictors

- Ki-67 > 30% largely explains outcomes of blastoid and different growth patterns

- Integration of MIPI and Ki-67 > 30% generates 4 distinct risk groups

www.european-mcl.net/en/clinical_mipi.php



Hoster et al, JCO 2016

MIPI and MIPIc

- Very helpful for interpreting single arm studies
- Often not helpful for clinical decision making
  - Young patients typically have “low risk” disease
  - Older patient more likely to have “high risk”
- Can help me when I am on the fence regarding treatment options

MCL: My overarching treatment considerations

- Assume disease incurable
  - So need a strategy for long term disease management
  - Need to think about how you are going to sequence your therapies
- If patient is older and needing treatment –
  - I typically recommend a non-intensive strategy
- If patient is younger and needing treatment –
  - I typically recommend an intensive therapy
  - Generally produces longer first remissions. ? OS benefit.
  - Toxicity tradeoff
- For patients “on the fence”
  - Try to factor in MIPI score and biology (Ki-67)

Its OK to watch and wait in MCL

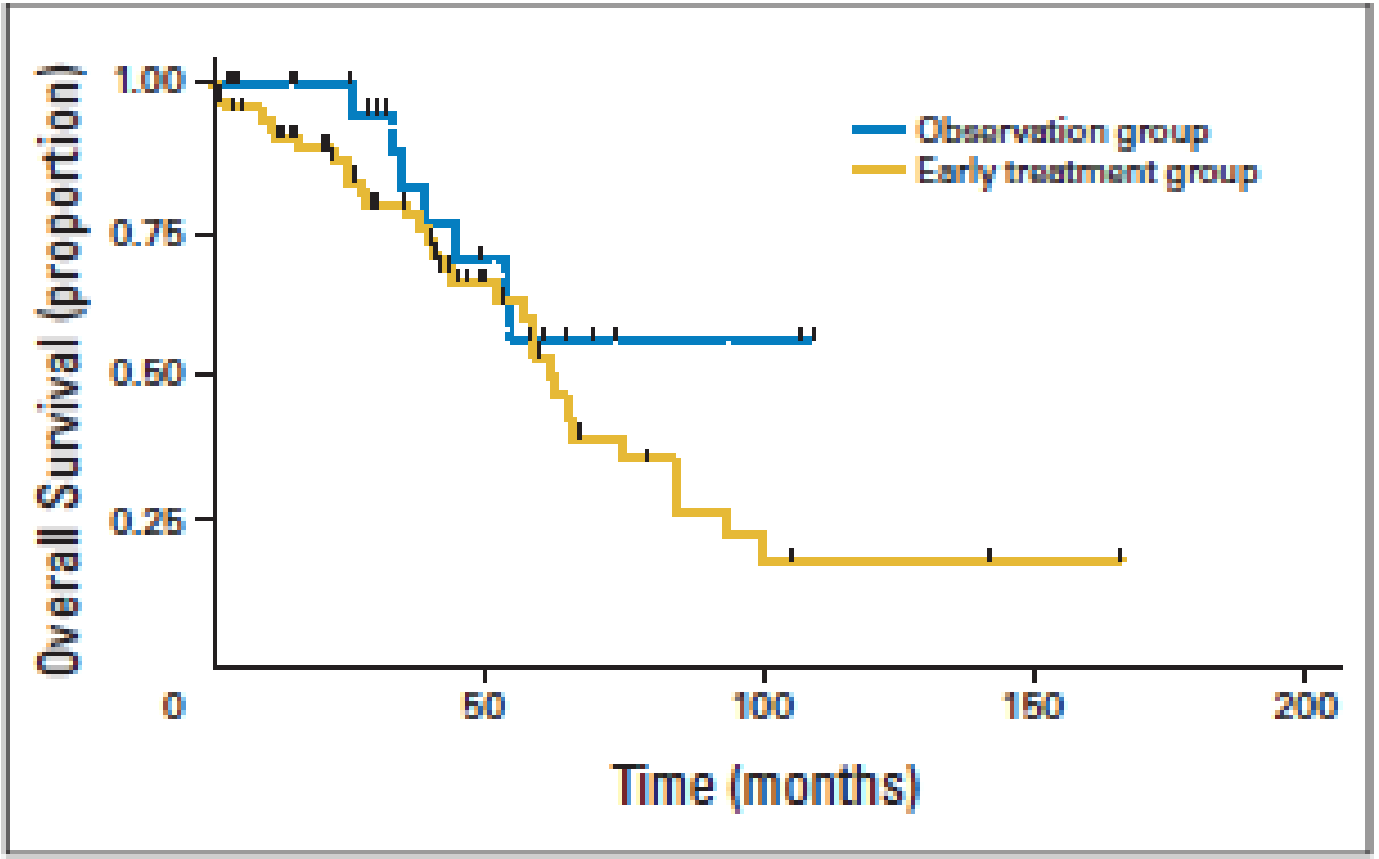


Fig 3. Overall survival of the observation versus early treatment groups from start of first systemic therapy.

Martin et al, JCO 2009

Some options for management of an older MCL patient:

1. R-CHOP
2. VR-CAP
3. BR (bendamustine-rituximab)
4. R-BAC
5. R^2 (lenalidomide-rituximab)
6. Any of the above followed by ASCT

Intensive strategies for older MCL patients

- MD Anderson experience (Fayad et al, Clin Lymph 2007)
  - Conventional R-hyperCVAD
    - ≤65 mPFS 5.5 years (N = 65)
    - > 65 mPFS 3.0 years (N = 32)
- U Penn experience (Frosch et al, Clin Lymph 2015)
  - Median age 65 (60-75)
  - R-CHOP plus ASCT or R-hyperCVAD
    - Median PFS 3.2 years
- Not my favorite strategy for older patients

Induction strategies for older MCL patients

- R-CHOP
  - N = 244. median age 66.
  - mPFS 14 months
- VR-CAP
  - Repeal vincristine and replace with bortezomib
  - N = 243. median age 65.
  - mPFS 24.7 months

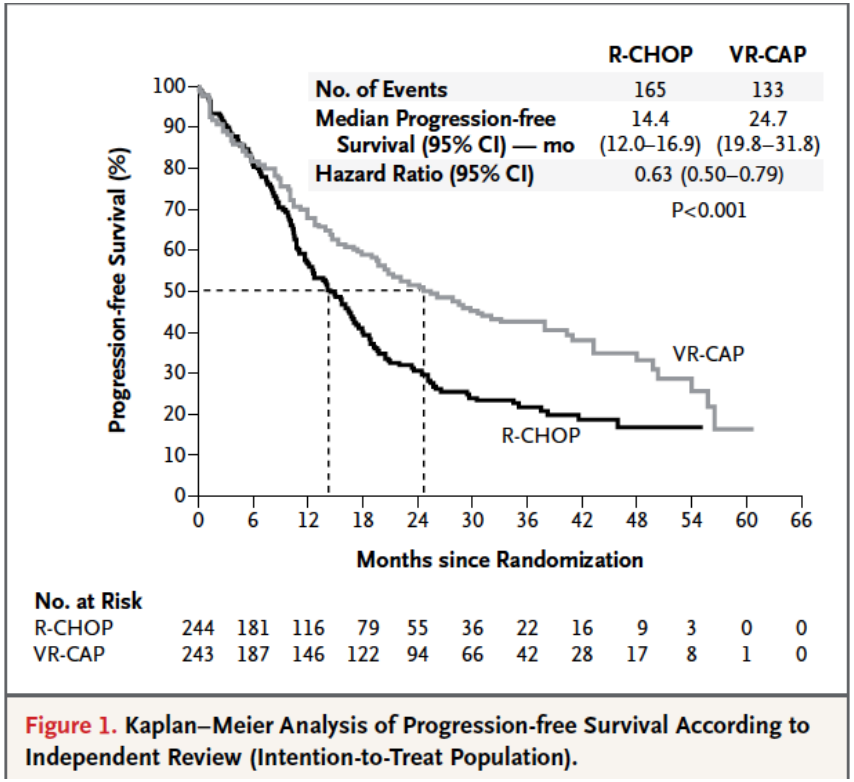
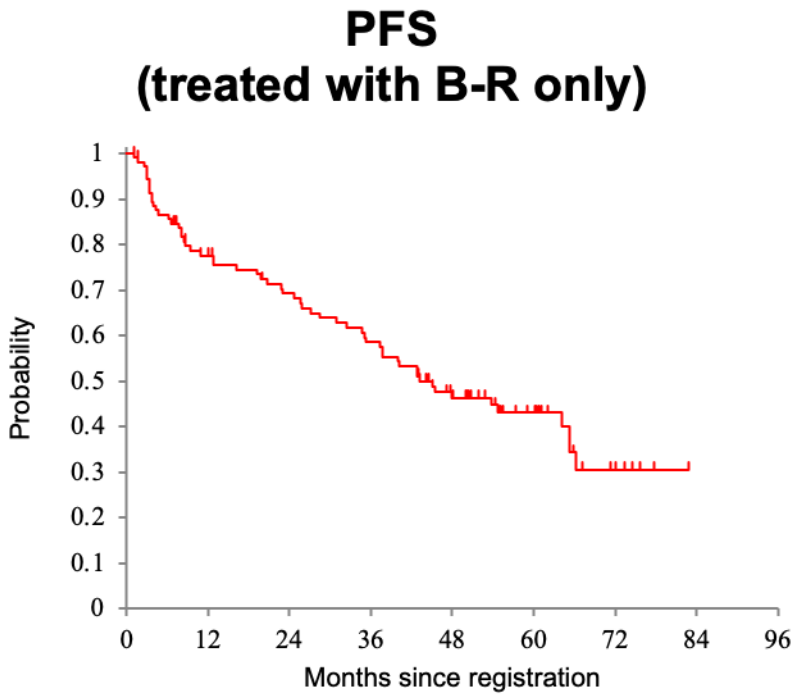


Figure 1. Kaplan–Meier Analysis of Progression-free Survival According to Independent Review (Intention-to-Treat Population).

Robak et al, NEJM 2014

BR induction in older MCL patients

- N = 106
- Median age 70
- Median PFS
  - 43.2 months



Rummel et al, ASCO 2016

Summary of non intensive induction regimens*

	N	Age	ORR	CR	mPFS
R-CHOP	244	66	89%	42% (CT)	14.4 mo
VR-CAP	243	65	92%	53% (CT)	24.7 mo
BR**	188	70	~90%	~45% (CT)	35-48 mo
RBAC500	57	71	91%	91% (PET)	Not reached

*no maintenance therapy
**pooled data from 3 trials

REGULAR ARTICLE

blood advances

Bendamustine and rituximab as induction therapy in both transplant-eligible and -ineligible patients with mantle cell lymphoma

Diego Villa,[1,2] Laurie H. Sehn,[1,2] Kerry J. Savage,[1,2] Cynthia L. Toze,[3,4] Kevin Song,[3,4] Wendie D. den Brok,[5] Ciara L. Freeman,[1,2] David W. Scott,[1,2] and Alina S. Gerrie[1-4]

[1]Centre for Lymphoid Cancer, BC Cancer Research Centre, Vancouver, BC, Canada; [2]Division of Medical Oncology, University of British Columbia, Vancouver, BC, Canada; [3]Leukemia/Bone Marrow Transplant Program of BC, Vancouver Coastal Health/University of British Columbia/BC Cancer Agency, Vancouver, BC, Canada; [4]Division of Hematology, Vancouver General Hospital, Vancouver Coastal Health/University of British Columbia, Vancouver, BC, Canada; and [5]Division of Medical Oncology, Fraser Valley Centre, BC Cancer Agency, Surrey, BC, Canada

Population based analysis from BC Canada

- June 2013 changed from R-CHOP to BR for MCL
- 190 MCL patients
- 248 R-CHOP patients from prior 10 year era
- Populations comparable

BR performed better than R-CHOP

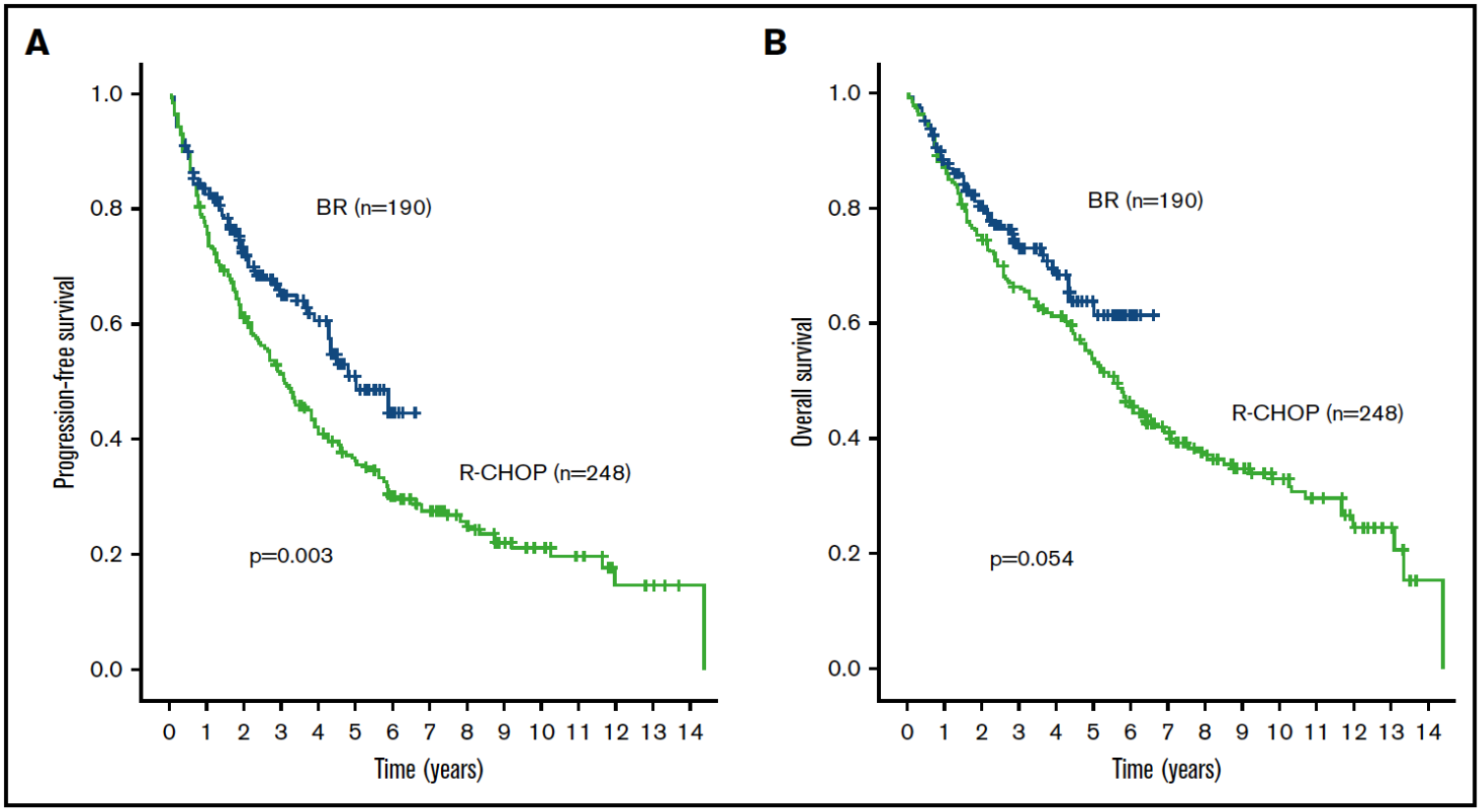


Figure 2. Outcome comparisons between the entire BR (blue line) and R-CHOP (green line) cohorts. (A) PFS. (B) OS.

3 yr PFS: 66% for BR vs. 51% for R-CHOP

More detailed look

Panel A:

PFS in patients under 65

3 yr PFS 76% vs. 64%

Panel C:

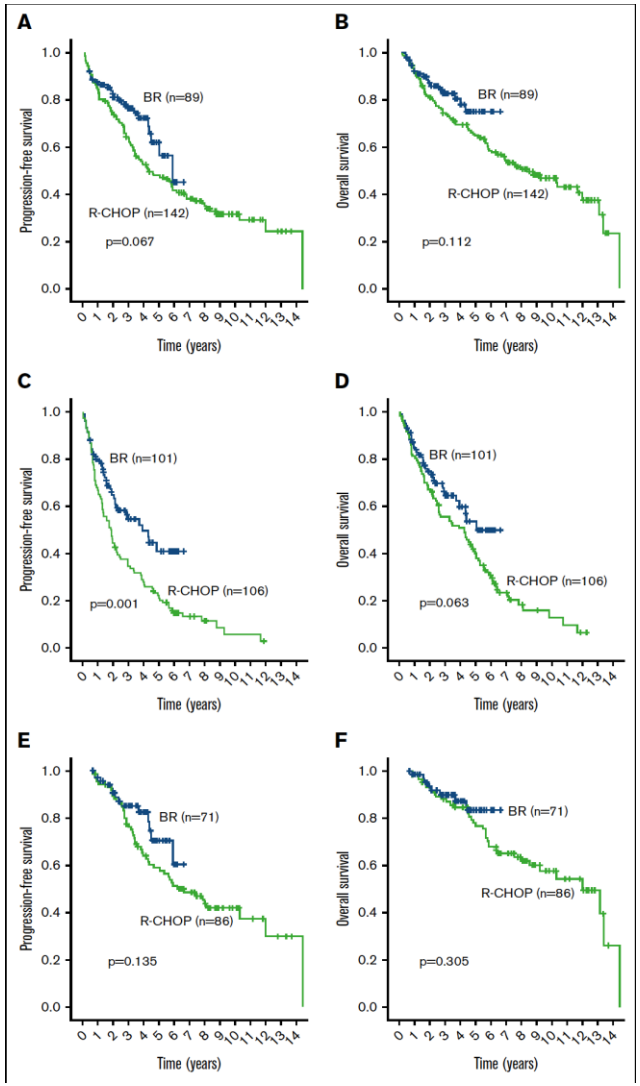
PFS in patient over 65

3 yr PFS 56% vs. 35%

Panel E:

PFS in patients receiving ASCT

3 yr PFS 85% vs 76%

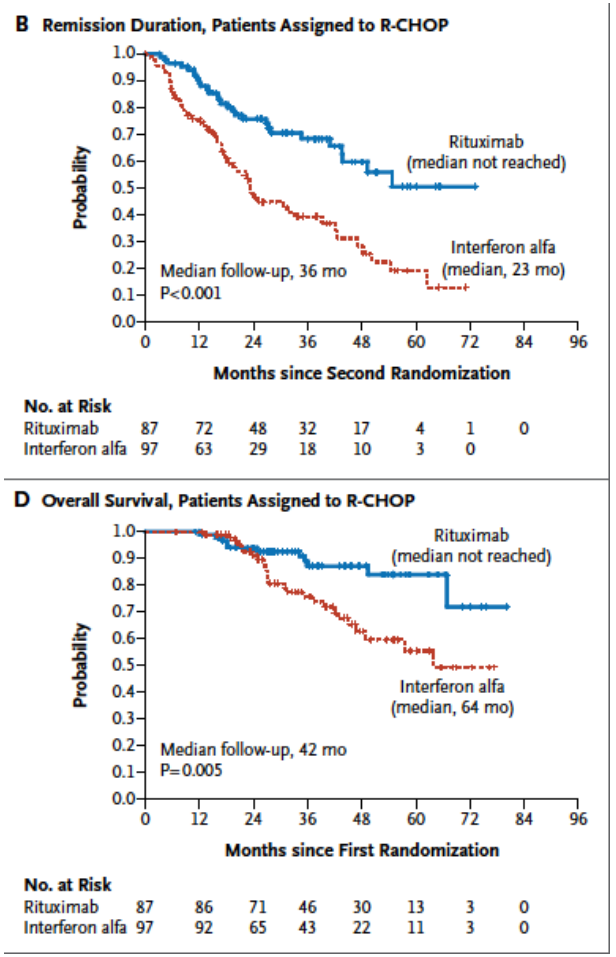


MCL older: Induction strategies

- BR appears to be a solid platform
  - See little reason to use R-CHOP
  - VR-CAP reasonable if bendamustine not an option
- Can BR induction be improved?
  - RBAC500 interesting. Worry about myelosuppression.
  - BR ± bortezomib (E1411)
  - BR ± BTKi being tested (SHINE, ACE 308)
  - BR plus venetoclax (PrE0405)
- R^2 looks good
  - Patient selection?
  - How much durability is due to indefinite therapy?
- Other "chemo-free" strategies
  - BTK plus antiCD20 (MD Anderson)

Maintenance Rituximab

- European MCL Network Study
- N = 532. Median age 70.
- R-CHOP > FCR as induction strategy
- Responding patients randomized to interferon alfa vs. MR given indefinitely
- MR not beneficial after FCR



Kluin-Nelemans et al, NEJM, 2012

What about MR after intensive therapy?

The NEW ENGLAND JOURNAL of MEDICINE

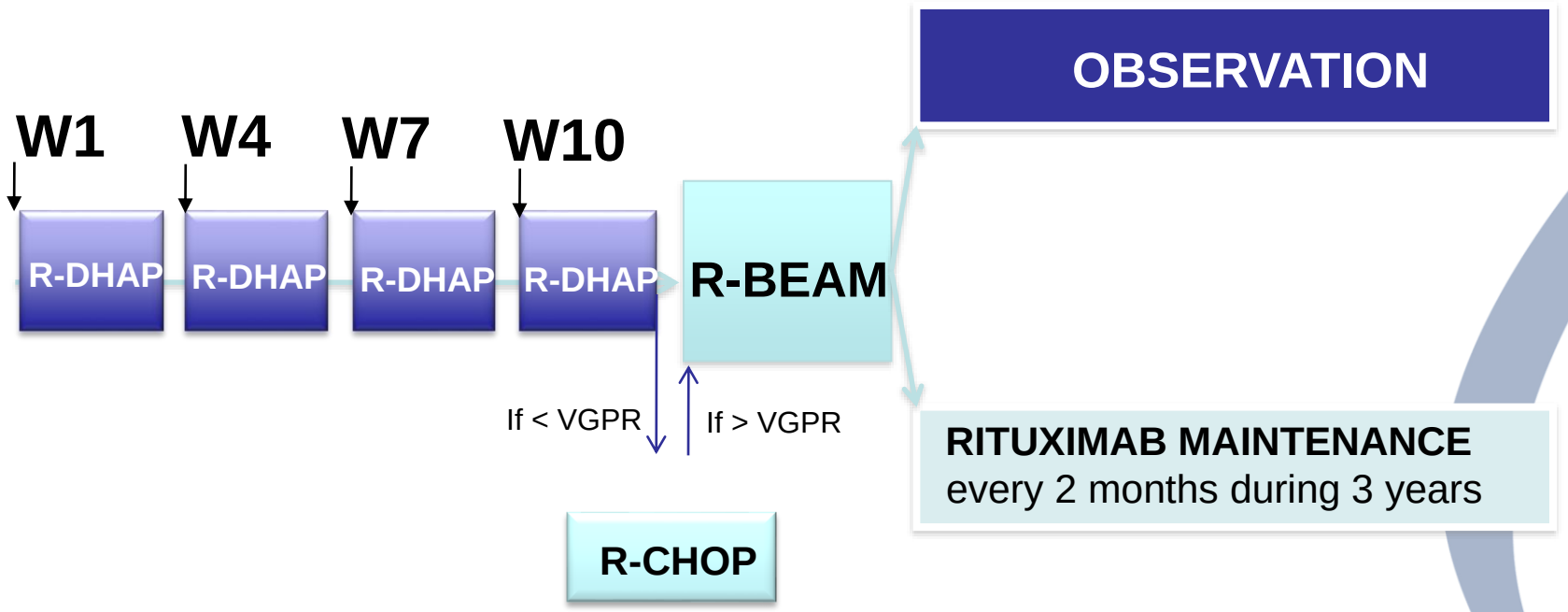
ORIGINAL ARTICLE

Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma

S. Le Gouill, C. Thieblemont, L. Oberic, A. Moreau, K. Bouabdallah, C. Dartigeas, G. Damaj, T. Gastinne, V. Ribrag, P. Feugier, O. Casasnovas, H. Zerazhi, C. Haioun, H. Maisonneuve, R. Houot, F. Jardin, E. Van Den Neste, O. Tournilhac, K. Le Dû, F. Morschhauser, G. Cartron, L.-M. Fornecker, D. Canioni, M. Callanan, M.C. Béné, G. Salles, H. Tilly, T. Lamy, R. Gressin, and O. Hermine, for the LYSA Group*

NEJM, Sept 2017

LyMa trial

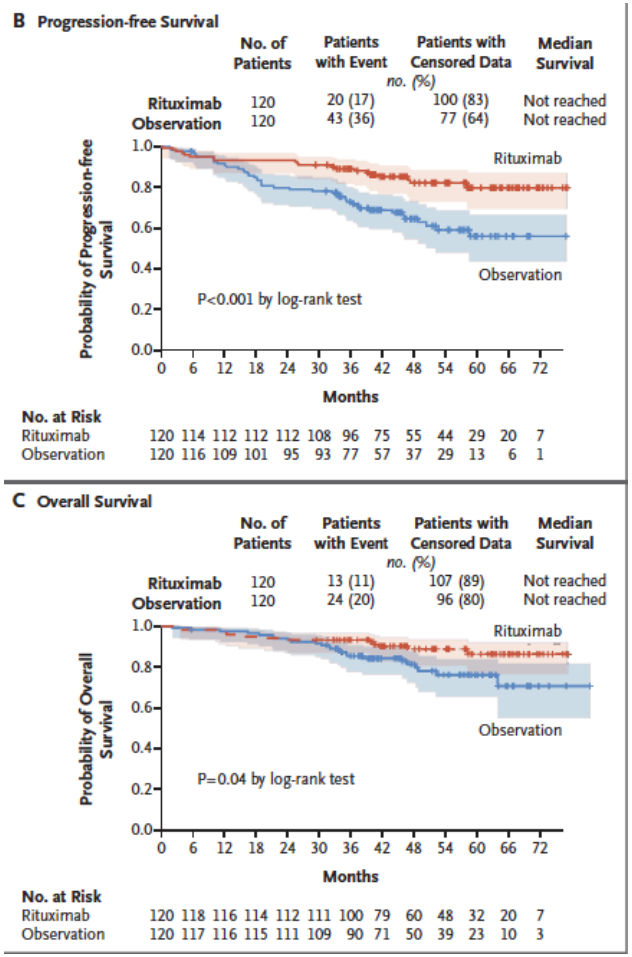


R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or oxaliplatin or carboplatin)

R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

MR after ASCT in MCL

	TOTAL N=299 (%)
Age, median (range), yrs	57 (27-65)
Male sex-no (%)	236 (79)
Ann Arbor Stage-no.(%)	
II	18 (6)
III	31 (10.5)
IV	249 (83.5)
B symptoms-no.(%)	89 (29.8)
PS ECOG-no.(%) <2	282 (94.3)
BM involvement-no.(%)	192 (64.5)
LDH elevation-no.(%)	115 (38.5)
MIPI score-no.(%)	
low risk	159 (53)
intermediate risk	82 (27.5)
high risk	58 (19.5)



Thoughts on MR for MCL

- MR appears beneficial in MCL
  - Optimal duration?
    - 2 yrs vs. 3 yrs vs. 5 yrs vs. until PD
  - Does induction therapy matter?
    - Controversial to give after BR
    - One underpowered RCT says no benefit
    - Analysis for ASH 2019 suggests benefit (Hill et al)
  - More study needed

How about MR after bendamustine-rituximab?

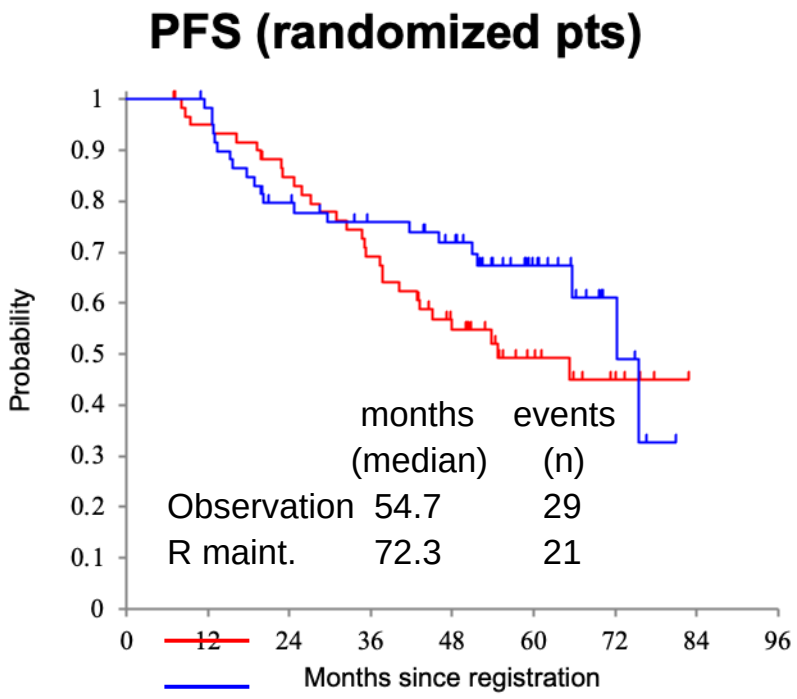
Patients: n = 168

Patients randomized: n = 122 *

R maintenance
n = 60

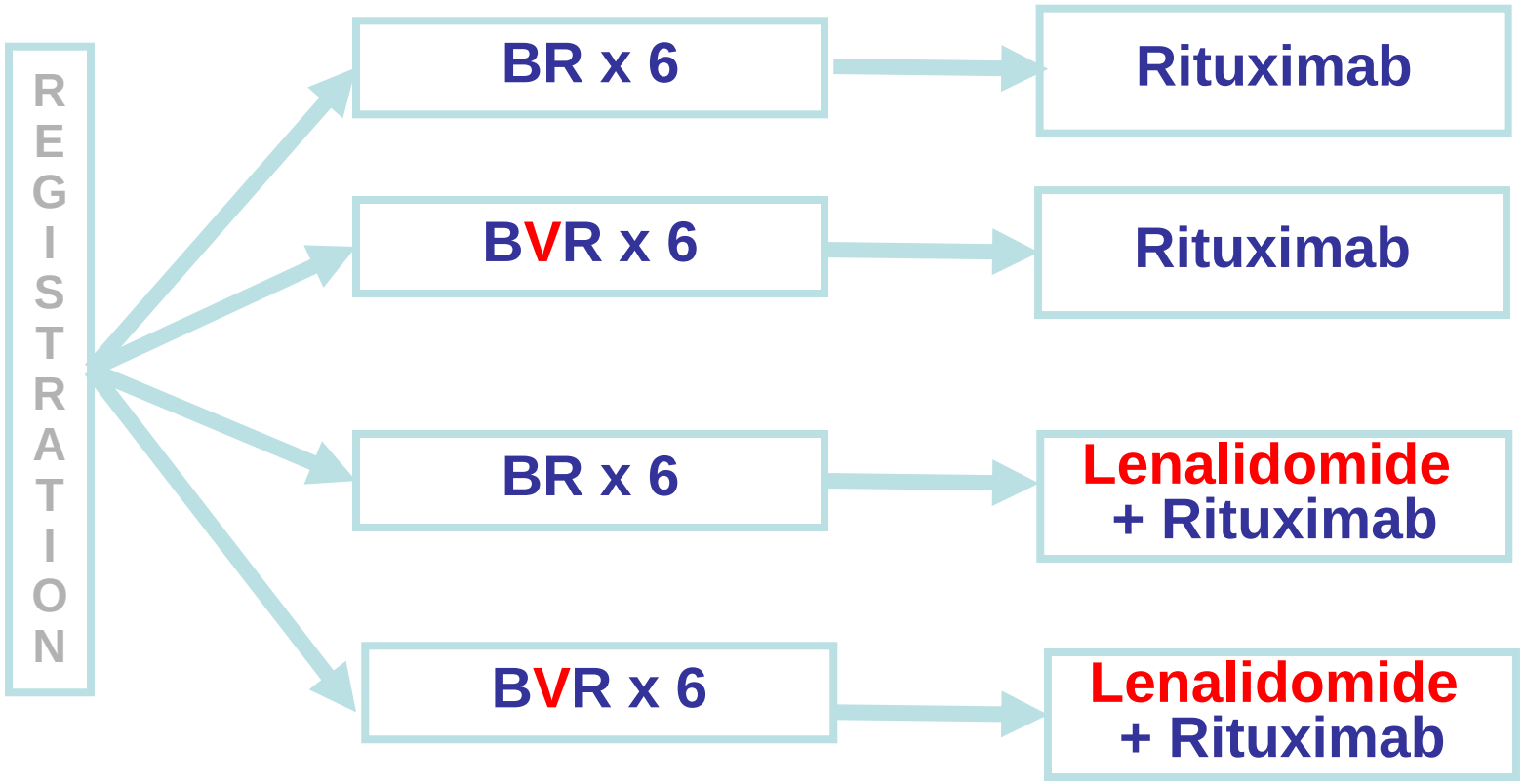
Observation
n = 62

Patients analyzed (n = 122)



Rummel et al, ASCO 2016

E1411: Randomized Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma



N = 372

Management of young/fit MCL patients

- What is younger?
  - I am declaring young as age 65 and under
  - Many trials have used this age cut point for eligibility purposes
  - Patient obviously need to be “fit” enough to receive intensive therapy
- What constitutes intensive treatment?
  - any treatment that includes autologous stem cell transplantation as a consolidation or intensive chemotherapy such as conventional R-hyperCVAD with alternating R-M/A

MCL Younger: Intensive frontline results

- Conventional R-hyperCVAD (Fayad et al, Clin Lymph 2007)
  - ≤65 mPFS 5.5 years (N = 65)
- RM-CHOP (CALGB regimen) (Damon et al, JCO 2009)
  - N = 78, Median age 57
  - mPFS ~ 5 yrs.
- R-CHOP x 6 plus ASCT (Hermine et al, Lancet 2016)
  - N = 234, Median age 56
  - mPFS ~ 5 years.

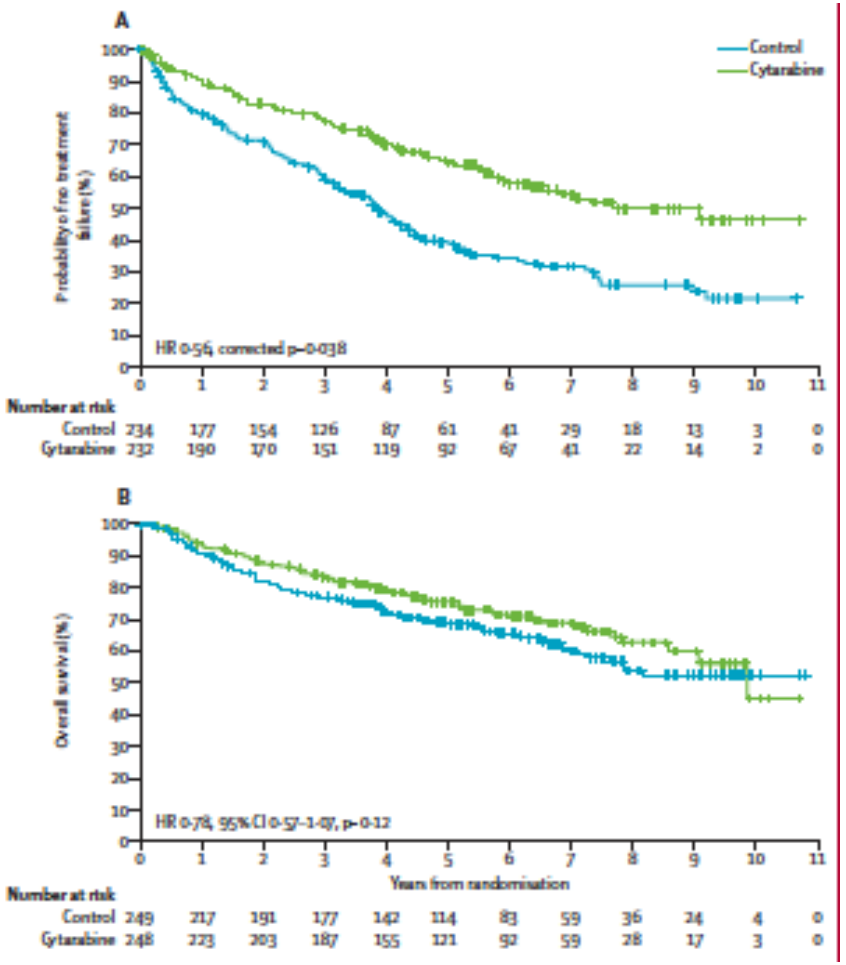
MCL Younger: Intensive frontline results

- R-CHOP with R-DHAP plus ASCT (Hermine et al, Lancet 2016)
  - N = 232, Median age 56
  - Median PFS 9.1 years.
- R-CHOP with R-DHAP plus ASCT (Delarue et al, Blood 2013)
  - N = 60, Median age 57
  - mPFS 7.0 years
- Nordic (Geisler et al, BJH 2012, Eskelund Br. J Haem 2016)
  - N = 166, Median age 56
  - mPFS 8.5 years

Role of high dose cytarabine

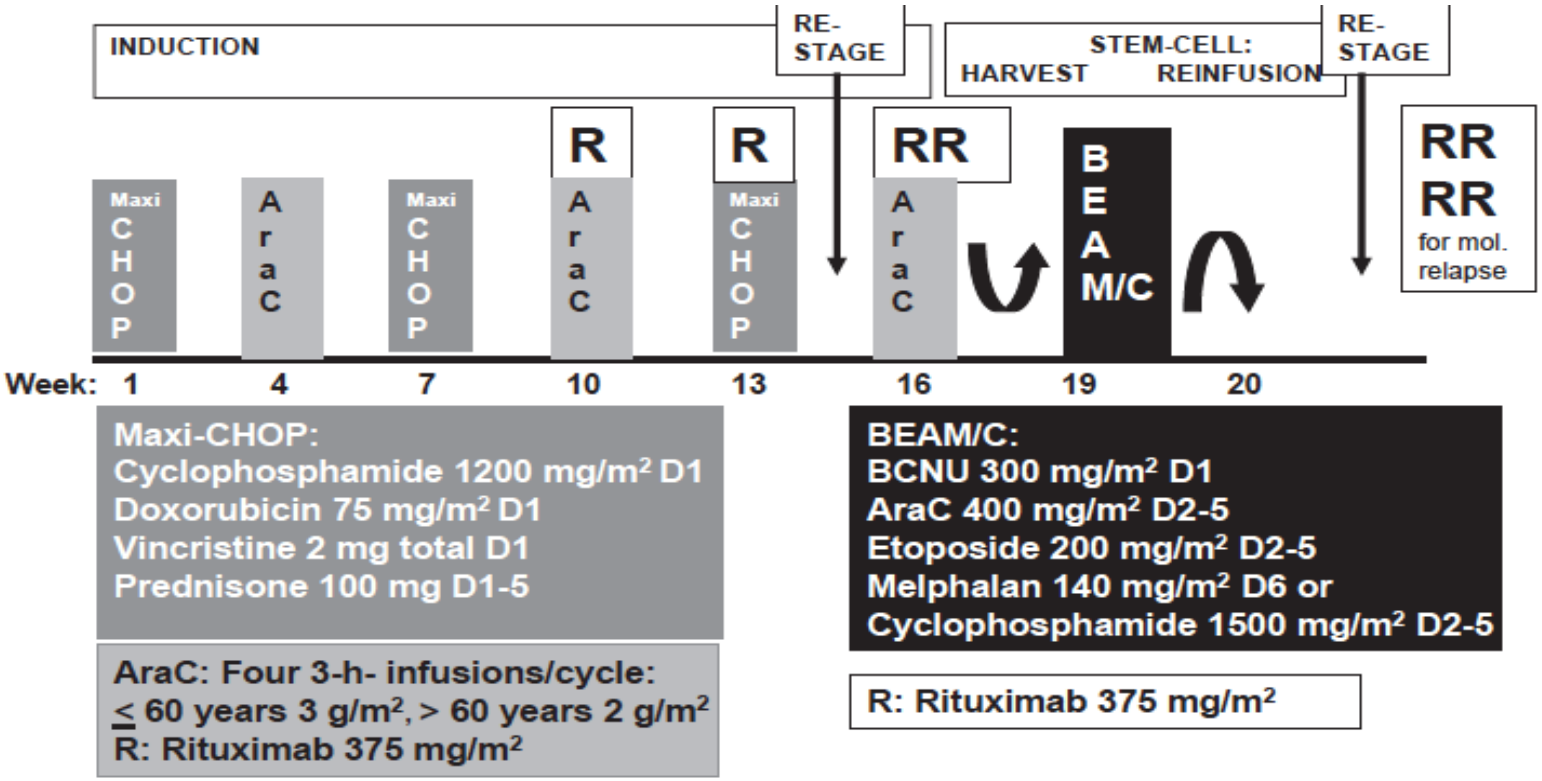
- Inclusion of HD cytarabine improves PFS
- Not OS
- More toxicity

- If going "intensive" my recommendation is to include HD cytarabine
- Does it need to be in the form of R-DHAP?



Hermine et al, Lancet 2016

Nordic Regimen



Geisler et al, Blood 2008. Geisler et al, BJH 2012.

Does ASCT in 1st remission improve OS?

Survival Outcomes of Younger Patients With Mantle Cell Lymphoma Treated in the Rituximab Era

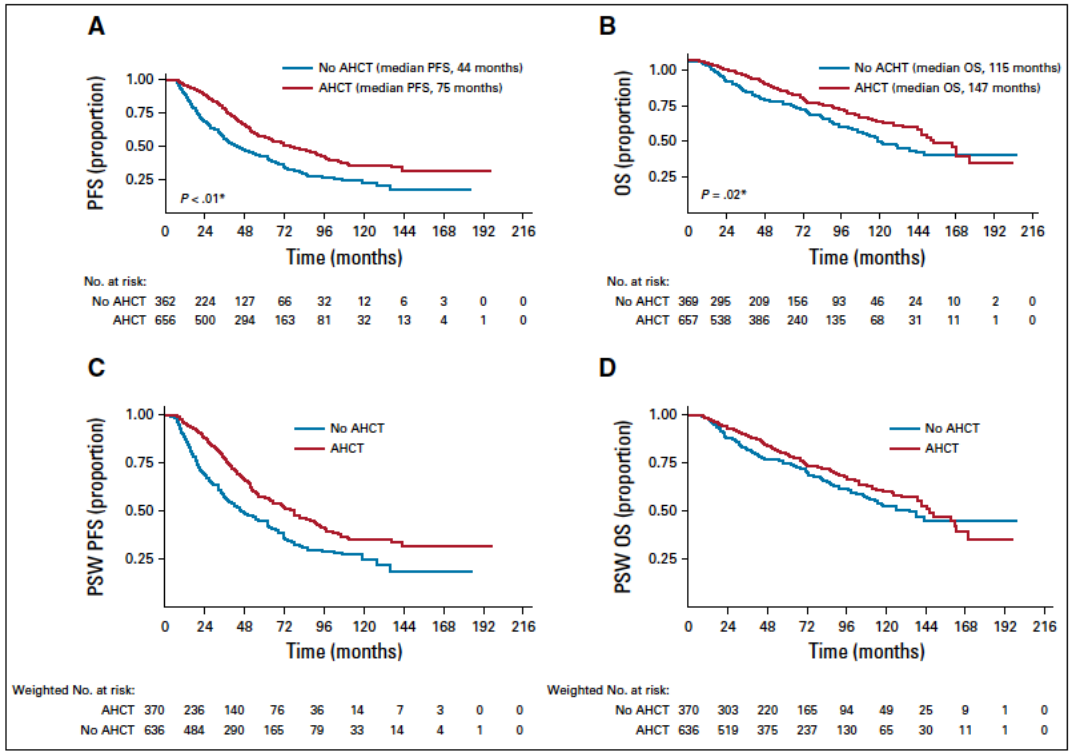


FIG 2. Kaplan-Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS) at 6 months and for (C) propensity score–weighted (PSW) PFS and (D) PSW OS at 6 months. AHCT, autologous hematopoietic cell transplantation. (*) Log-rank test.

Gerson et al, JCO 2019

Younger MCL patient summary

- When time to treat, I will recommend an intensive strategy to maximize length of 1st remission
  - Median now over 7 years
  - Gives your patient several years free of any treatment
  - Gives you several years to find better ways to treat R/R MCL
  - Had you saved your intensive option for later, your patient would be older and less fit at the time of application
- Now recommending maintenance rituximab

- Given lack of proven OS benefit with intensive therapy, OK to recommend a non-intensive strategy

MCL Treatment: The Horizon

- Older MCL patients
  1. SHINE trial: BR ± ibrutinib until PD
  2. Acerta 308: BR ± acalabrutinib until PD
  3. E1411: BR ± bortezomib. R maintenance ± lenalidomide
  4. PrE0405: BR + venetoclax

We are anxious to develop next intergroup trial

- Younger MCL patients
  1. EA4151: US intergroup
     - MRD based treatment assignment. ASCT + MR vs. MR.
  2. EA4181
     - Induction trial testing acalabrutinib with “standard” therapy
  3. TRIANGLE trial: European MCL consortium

Intergroup Induction Concept

- Randomized phase II trial comparing three induction strategies (EA4181)

ARM 1: BR with sequential R-HiDAC (BR/CR)

» Vs

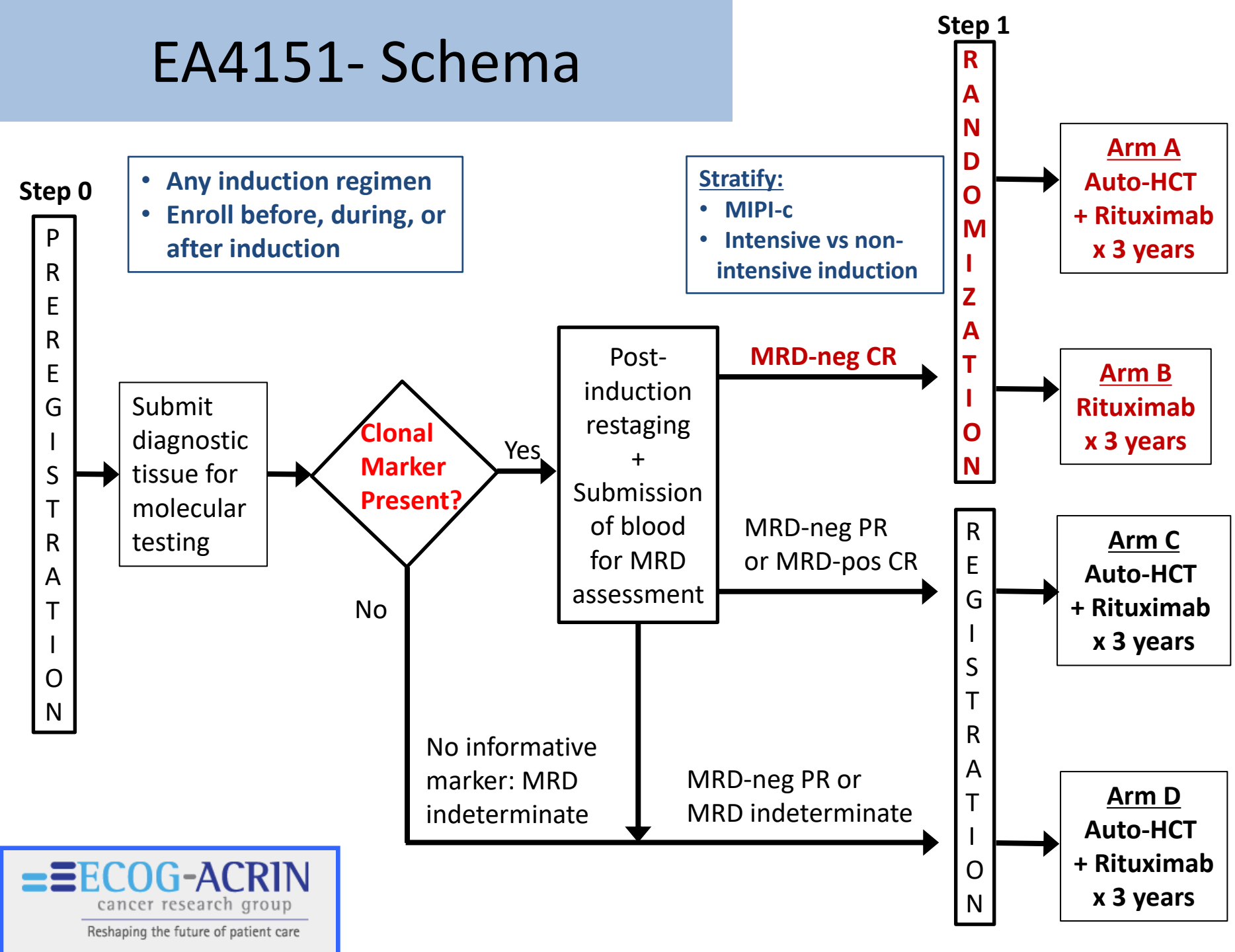
ARM 2: Acalabrutinib plus BR/CR

» Vs

ARM 3: Acalabrutinib plus BR

- Primary endpoint: MRD neg CR rate

EA4151- Schema



ECOG-ACRIN cancer research group
Reshaping the future of patient care

Conclusions

- Outcomes appear to be improving in MCL
  - rituximab, bendamustine, HiDAC, maintenance, ASCT, novel agents
- Older patients can be managed reasonably well with non-intensive strategies
  - 1st remission should last well over 3 years nowadays
- Younger patients get longer remissions with intensive strategies
  - MRD assessments may allow more personalized approaches
- Encouraging novel agents
  - Ibrutininb, acalabrutinib, venetoclax
  - Need to figure out how to use them in combination

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