19th International Ultmann Chicago Lymphoma Symposium

LIVE Symposium

APRIL 29-30
2022

19TH ULTMANN

THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

Debate:

Autologous HCT remains the preferred standard of care for first-line therapy of mantle cell lymphoma

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Medical Collage of Wisconsin

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Disclosures

- **Consulting and/or Speaking (past 24 months):** Adaptive Biotechnologies, AstraZeneca, Beigene, Bristol-Myers Squibb, CSL Therapeutics, Karyopharm, Kite, Morphosys, Pharmacyclics, Seattle Genetics, Sanofi, Servier Pharmaceuticals, TG Therapeutics
- I will mention **on-label** uses of ibrutinib (Pharmacyclics), acalabrutinib (Astrazeneca) and zanubrutinib (Beigene) in mantle cell lymphoma
- I will mention a trial looking at on **off-label** use of ibrutinib (Pharmacyclics) in mantle cell lymphoma

Outline

- Retrospective studies of transplant in MCL
- Prospective studies of transplant in MCL
- Comparison of transplant to non-transplant outcomes
- Importance of preventing MCL relapse
- Can we use a risk-adapted approach to select those most likely to benefit from auto-HCT?

History of Mantle Cell Lymphoma

- Initially decribed in 1982 by Weisenburger and in 1983 by Swerdlow
- Took several years to arrive consensus criteria for the diagnosis between U.S. and Europe: REAL Classification (1994)
- 1995-1997 at least 5 retrospective studies (each with n= 30-80) reporting **median OS in 3-5 yr range**
- 1998- present: successive prospective studies of different regimens

Mantle-Zone Lymphoma:

A Follicular Variant of Intermediate Lymphocytic Lymphoma

DENNIS D. WEISENBURGER, MD,* HUN KIM, MD,† AND HENRY RAPPAPORT, MD‡

***Cancer* 49:1429–1438, 1982.**

Centrocytic Lymphoma: A Distinct Clinicopathologic and Immunologic Entity

A Multiparameter Study of 18 Cases at Diagnosis and Relapse

S. H. SWERDLOW, MD, J. A. HABESHAW, MD, PhD, L. J. MURRAY, BA, H. S. DHALIWAL, MRCP, T. A. LISTER, FRCP, and A. G. STANSFELD, FRCPath

From the I.C.R.F. Department of Medical Oncology, St. Bartholomew's Hospital, West Smithfield, London, England

(Am J Pathol 1983, 113:181–197)

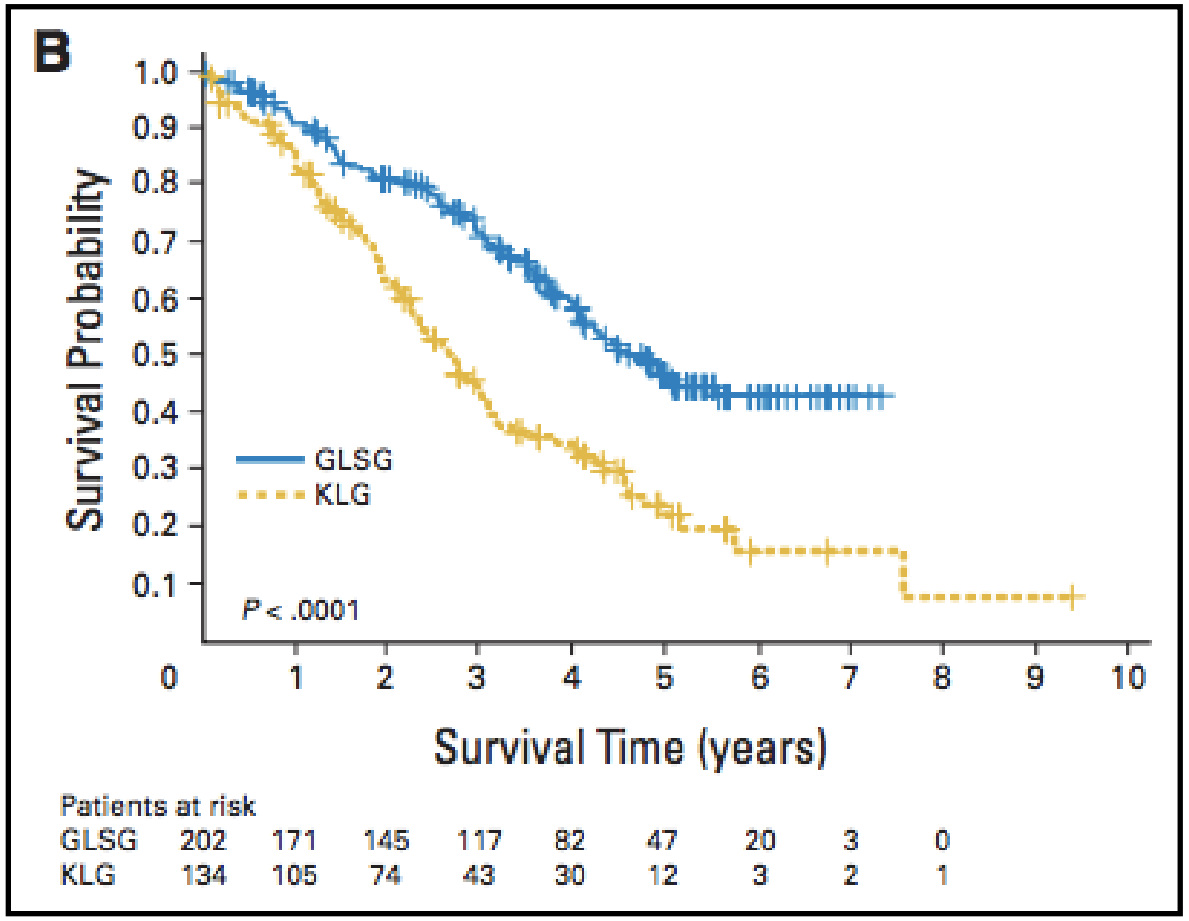
A Revised European-American Classification of Lymphoid Neoplasms: A Proposal From the International Lymphoma Study Group

By Nancy Lee Harris, Elaine S. Jaffe, Harald Stein, Peter M. Banks, John K.C. Chan, Michael L. Cleary, Georges Delsol, Christine De Wolf-Peeters, Brunangelo Falini, Kevin C. Gatter, Thomas M. Grogan, Peter G. Isaacson, Daniel M. Knowles, David Y. Mason, Hans-Konrad Muller-Hermelink, Stefano A. Pileri, Miguel A. Piris, Elisabeth Ralfkiaer, and Roger A. Warnke

Blood, Vol 84, No 5 (September 1), 1994: pp 1361-1392

Not an issue for debate: Outcomes in MCL have improved

- Hermann et al compared MCL outcomes from 2 different eras (1975-1986 vs 1996-2004)
  - Median OS 2.7 yrs → 4.8 yrs
  - But why?
- More recent retrospective and prospective trials have seen even better outcomes
  - median PFS 8-9 years
  - median OS >10 yrs in some studies



Herrmann et al, *J Clin Onc* (2009)

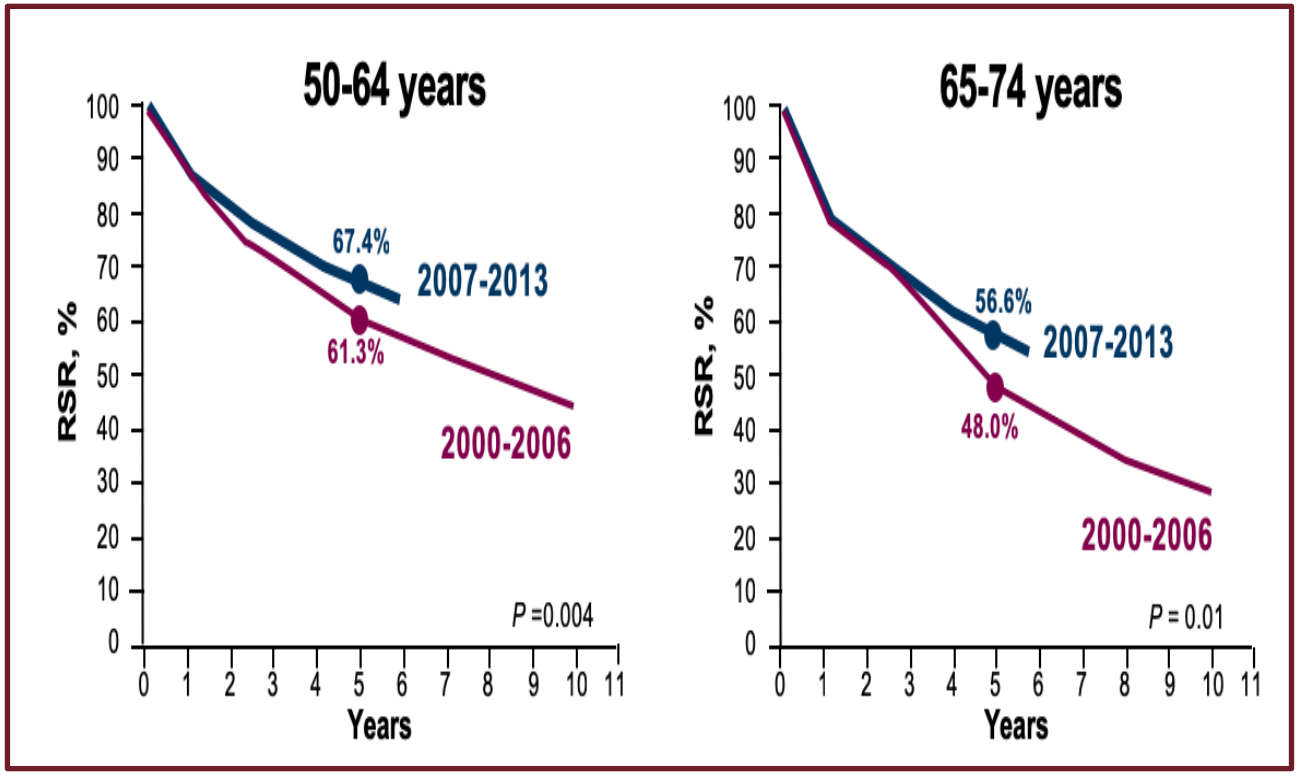
More recent retrospective series in MCL

- 395 patient series from 5 academic centers
- Median OS **11.6 yrs**
- 53% of them had auto-HCT
- Auto-HCT assoc with improved PFS (UVA) and OS (UVA and MVA)
- However there is always the issue of “selection bias” in retrospective trials: patients who are auto-HCT candidates have other favorable factors (lower age, fewer comorbidities, etc)

Calzada et al, Leuk Lym (2018)

MCL survival is improving in the U.S. (SEER)

- SEER database study
- N=8755 patients
- Broke into two 7 year eras:
  - 2000-2006: N=3799
  - 2007-2013: N=4956
- Patients <50 yrs, did well in both eras
- Significant improvement noted in patients aged 50-64 years and aged 65-74 yrs
- Again the question is why?
- Increased use of auto-HCT?



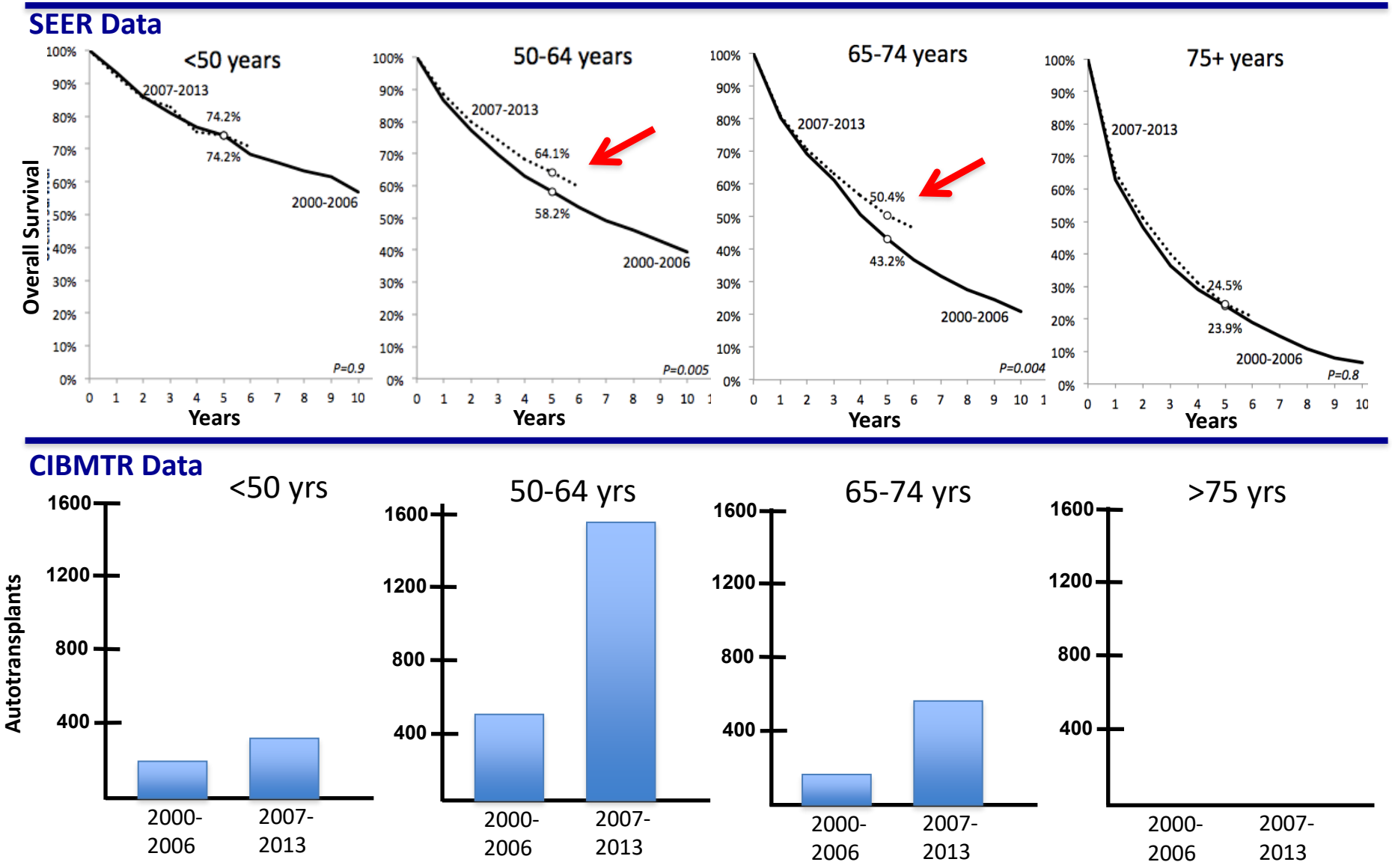
Incidence and survival trends in mantle cell lymphoma

19th International Ultmann Chicago Lymphoma Symposium

Narendranath Epperla[1]
Mehdi Hamadani[1]
Timothy S. Fenske[1]
Luciano J. Costa[2]

British Journal of Haematology, 2018, **181,** 682–711

Increasing use of autoHCT in CR1 correlates with improvement in MCL survival

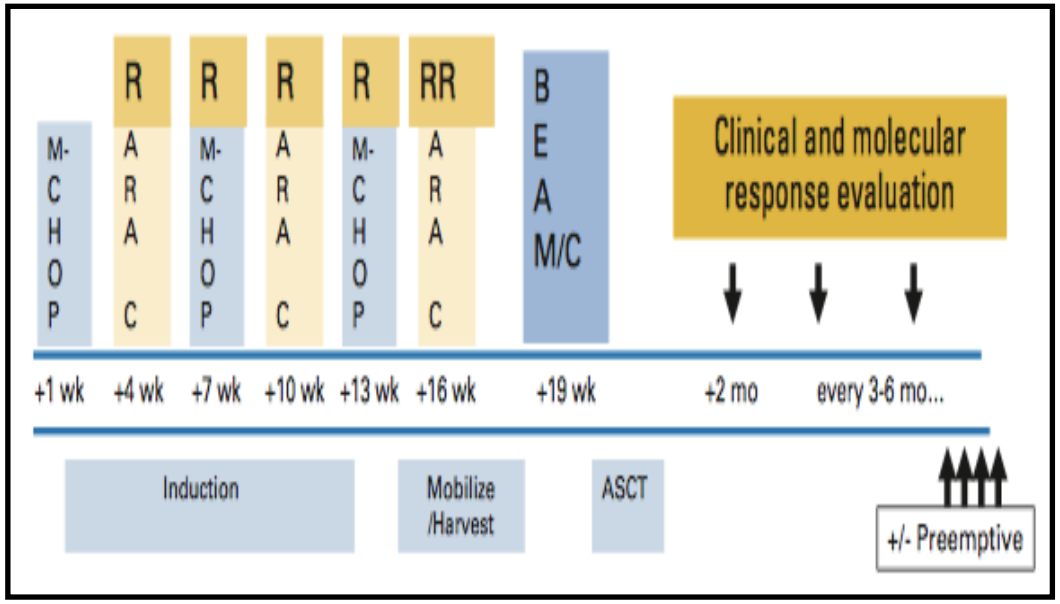


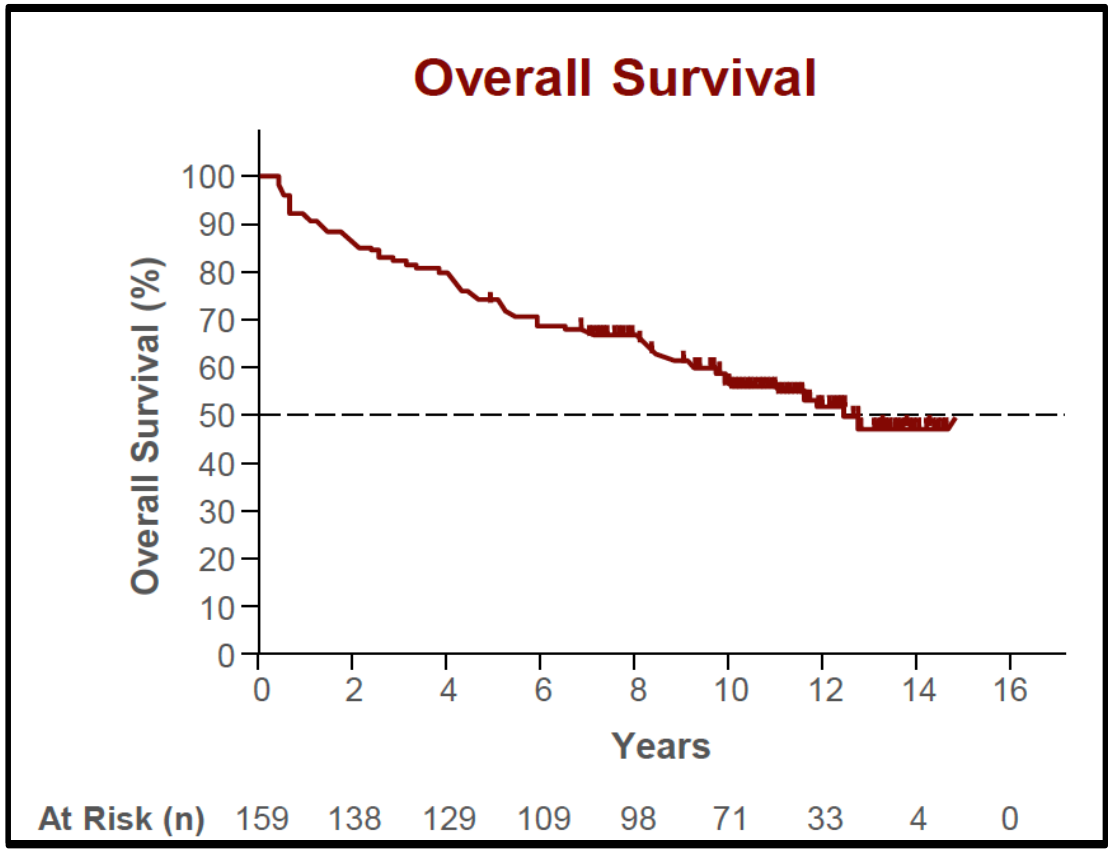
SEER Data: Epperla et al, Br J Haem (2018); CIBMTR data: M. Hamadani, personal communication (March 2017)

What about prospective trials?

Intensive 1L Rx for MCL: excellent results with hi-dose araC induction and autoHCT

- Nordic MCL-2 regimen as an example
- Low treatment-related mortality
- 8-9 yr median 1st remission (ITT); 11 yrs for those getting auto-HCT; median OS >10 yrs
- Feasible to give entirely outpatient
- Unclear how much benefit from the autoHCT component

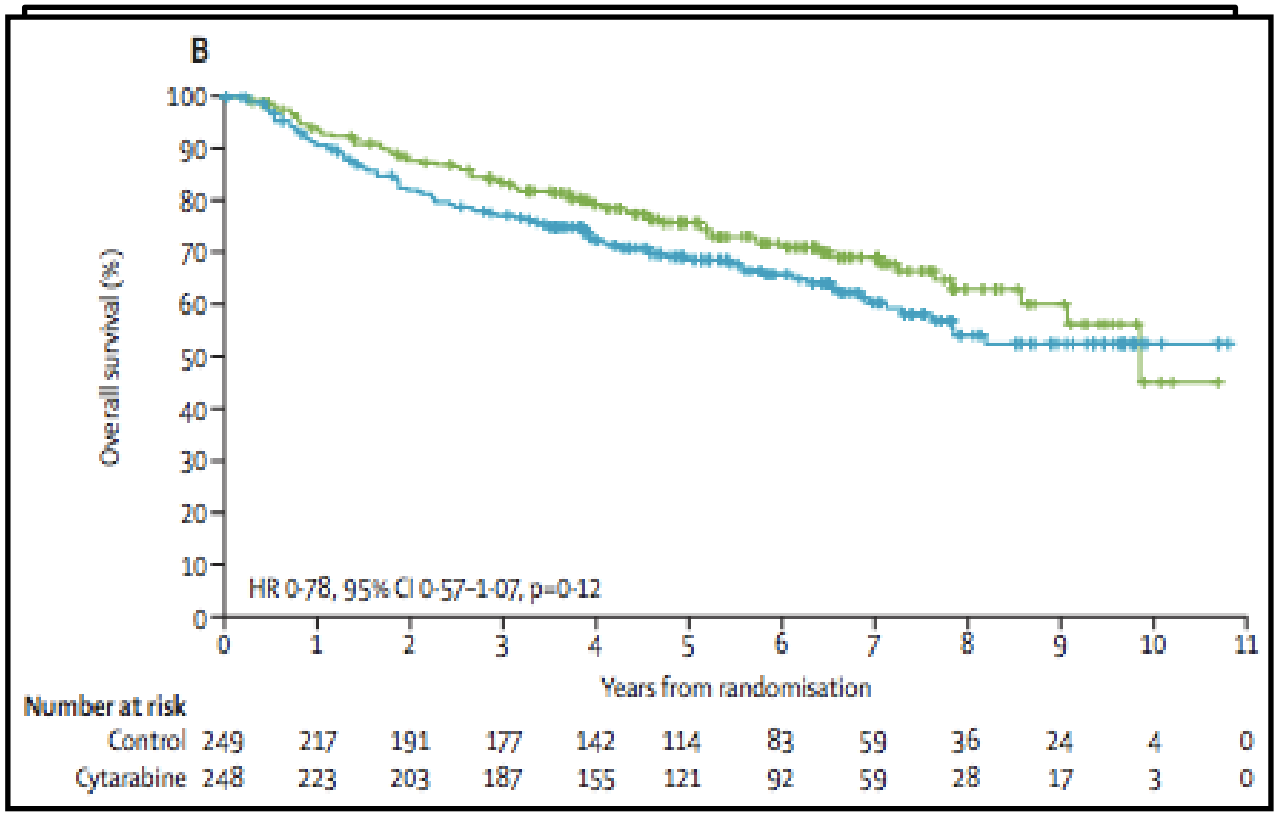




Geisler et al, Blood (2008)
Geisler et al, Br J Haem (2012)
Eskelund et al. Br J Hae (2016)

Intensive 1L Rx for MCL: excellent results with hi-dose araC induction and autoHCT

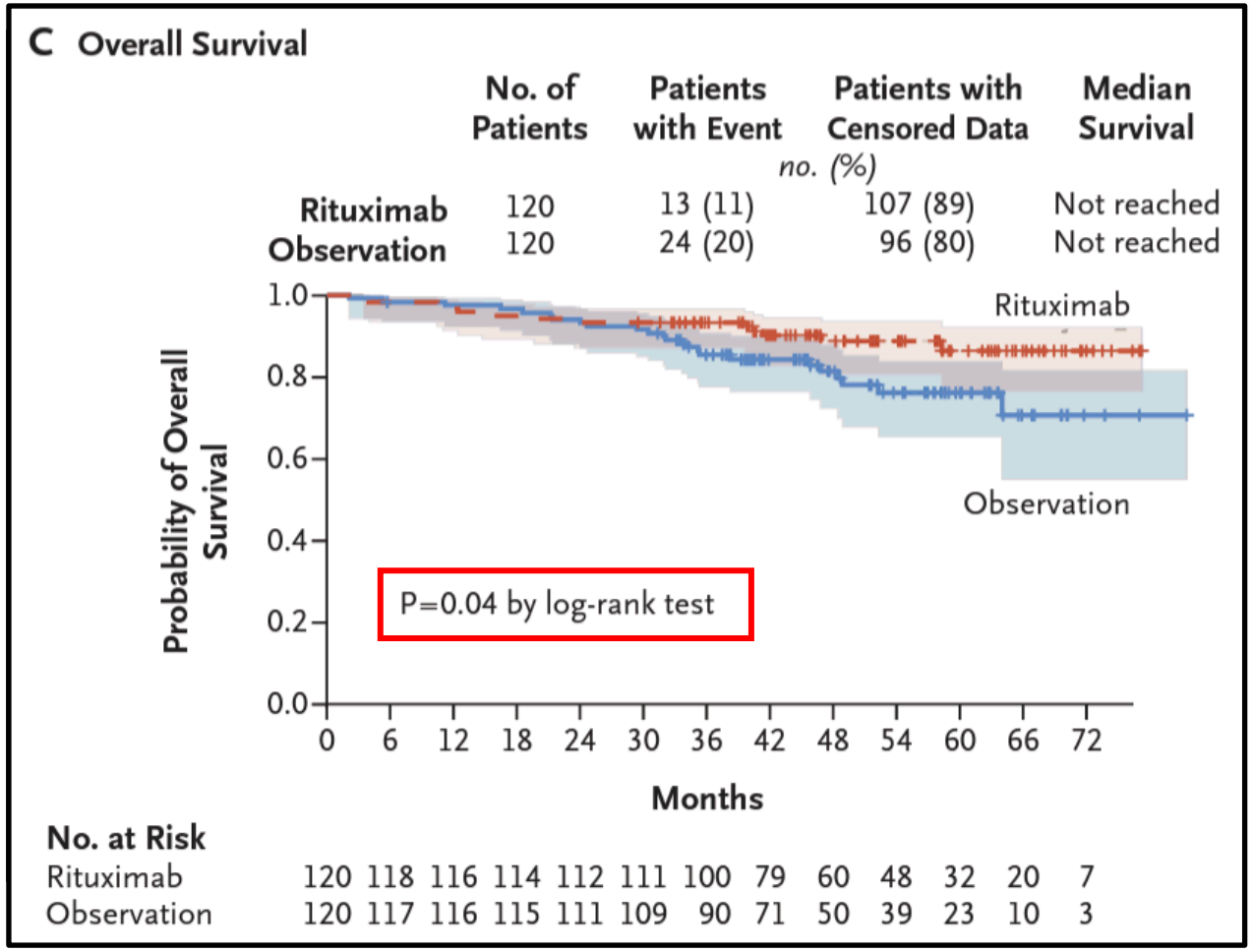
- Compared RCHOPx6 vs RCHOP alt with RDHAP as induction
- RCHOP/ RDHAP arm had superior outcomes
  - 9.1 yr med TTTF
  - Med OS 9.8 yrs
  - Outcomes even better in subgroup that actually got to transplant
- All patients underwent auto-HCT



Hermine et al, Lancet (2016)

LyMa/ LYSA trial: maintenance rituximab post auto-HCT

- N=299 enrolled
- Induction: R-DHAP x 4
- 257 (86%) underwent AutoHCT
- 238 (80%) randomized to no maint vs 3 yrs R maint
- OS at 4 years: 89% vs 80%
- Extrapolation of OS curve: 8-10 years med OS ?
- All patients were planned to undergo auto-HCT



Le Gouill et al, NEJM (2017)

So, outcomes for MCL have definitely improved. But why?

- Earlier diagnosis? (lead time bias)
- Better treatment
- Identifying the subset who can defer therapy, and leaving them alone
- Rituximab
- Intensive induction (including high dose araC)
- More widespread use of autoHCT?
- Newer ”non-chemotherapy” drugs
  - Proteasome inhibitors, BTK inhibitors, lenalidomide, bcl-2 inhibitors
- CAR-T cell therapy (too new to explain improvements in 2010-2019)

How do non-transplant approaches compare?
Outcomes with non-intensive induction (>30 pts)

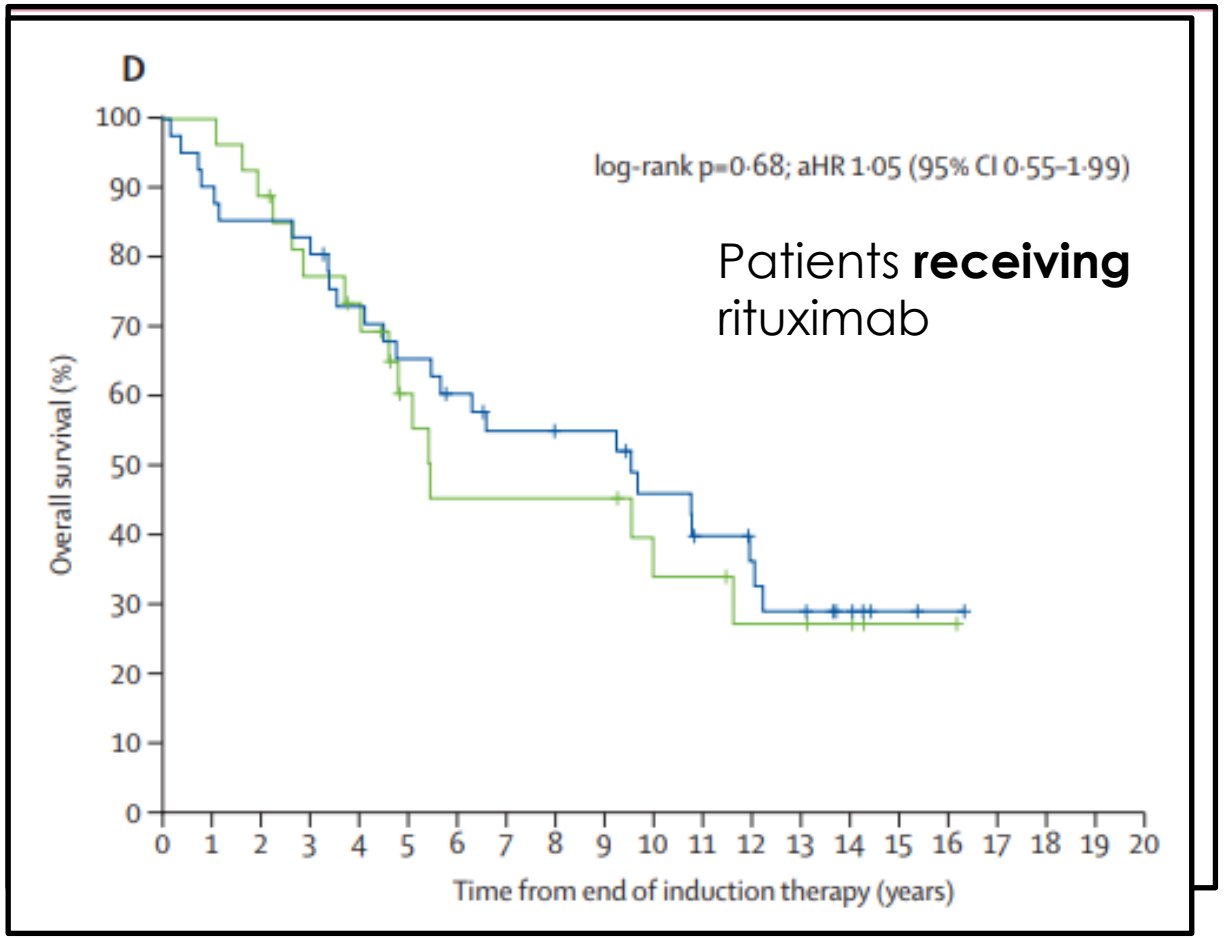
Regimen	# pts	Median PFS	Ref
CHOP vs R-CHOP	112	14-21 months	1
MCP vs R-MCP	90	18-20 months	2
RCHOP → R	560 (subset)	5-6 years	3
RCHOP vs BR	94	21 months vs 35 months	4
RCHOP vs VRCAP	487	14 vs 25 months	5
BR vs BR → R	120	4.6 yrs	6
R^2	38	>4 yrs (7.8% secondary malignancy)	7
OVERALL		**1-6 years (2-4 on average)**	

[1]Lenz (2005); [2]Hermine et al, Lancet (2016); [3]Kluin-Nelemans (2012); [4]Rummel (2013); [5]Robak (2015); [6]Rummel (2016); [7]Ruan (2018)

Getting back to the question of whether auto-HCT in first remission actually improves survival ?

Prospective RCT of auto-HCT for MCL: Does it improve OS?

- Dreyling et al: CHOP followed by autoHCT vs IFN
  - PFS benefit but no OS benefit
  - Outdated induction
  - Outdated transplant (Cy/TBI)
  - Trial started in 1996; original pub 2005
- Follow up publication in 2021
  - PFS benefit persisted
  - OS benefit emerged (7.5 y vs 4.8 y)
  - However PFS and OS benefit only seen in patients who did NOT receive rituximab
  - So… better induction may reduce benefit of auto-HCT



Dreyling M, et al. *Blood* (2005); Zoellner AK, et al. *Lancet Haem* (2021)

First-line therapy for MCL: Does it improve OS?

- Dreyling et al: CHOP followed by autoHCT vs IFN
  - PFS benefit and OS benefit
  - Outdated induction and transplant
  - PFS and OS benefit limited to those **not** receiving rituximab
- **No published prospective trials of auto-HCT vs no auto-HCT using modern induction regimens**
  - TRIANGLE study and ECOG-ACRIN 4151 are ongoing
- Are there any recent retrospective studies that specifically address the auto-HCT question ?
- (Can't use CIBMTR database for this question)

Dreyling M, et al. Blood. 2005;

original report

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

James N. Gerson, MD[1]; Elizabeth Handorf, PhD[1]; Diego Villa, MD[2]; Alina S. Gerrie, MD[2]; Parv Chapani[2]; Shaoying Li, MD[3]; L. Jeffrey Medeiros, MD[3]; Michael I. Wang, MD[3]; Jonathon B. Cohen, MD[4]; Oscar Calzada[4]; Michael C. Churnetski[4]; Brian T. Hill, MD, PhD[5]; Yazeed Sawalha, MD[5]; Francisco J. Hernandez-Ilizaliturri, MD[6]; Shalin Kothari, MD[6]; Julie M. Vose, MD[7]; Martin A. Bast[7]; Timothy S. Fenske, MD[8]; Swapna Narayana Rao Gari, MD[8]; Kami J. Maddocks, MD[9]; David Bond, MD[9]; Veronika Bachanova, MD, PhD[10]; Bhaskar Kolla, MD[10]; Julio Chavez, MD[11]; Bijal Shah, MD[11]; Frederick Lansigan, MD[12]; Timothy F. Burns, MD[12]; Alexandra M. Donovan, MD[12]; Nina Wagner-Johnston, MD[13]; Marcus Messmer, MD[13]; Amitkumar Mehta, MD[14]; Jennifer K. Anderson, MD[14]; Nishitha Reddy, MD[15]; Alexandra E. Kovach, MD[15]; Daniel J. Landsburg, MD[16]; Martha Glenn, MD[17]; David J. Inwards, MD[18]; Reem Karmali, MD[19]; Jason B. Kaplan, MD[19]; Paolo F. Caimi, MD[20]; Saurabh Rajguru, MD[21]; Andrew Evens, DO[22]; Andreas Klein, MD[22]; Elvira Umyarova, MD[23]; Bhargavi Pulluri, MD[23]; Jennifer E. Amengual, MD[24]; Jennifer K. Lue, MD[24]; Catherine Diefenbach, MD[25]; Richard I. Fisher, MD[1]; and Stefan K. Barta, MD[1]

Journal of Clinical Oncology®
Volume 37, Issue 6 471

- Retrospective study from 25 centers
- Patients were considered *transplant-eligible* based on age and co-morbidities
- Compared outcomes of those who had autoHCT in first remission vs those who did not
- 1,029 patients total
- 657 underwent autoHCT; 372 did not

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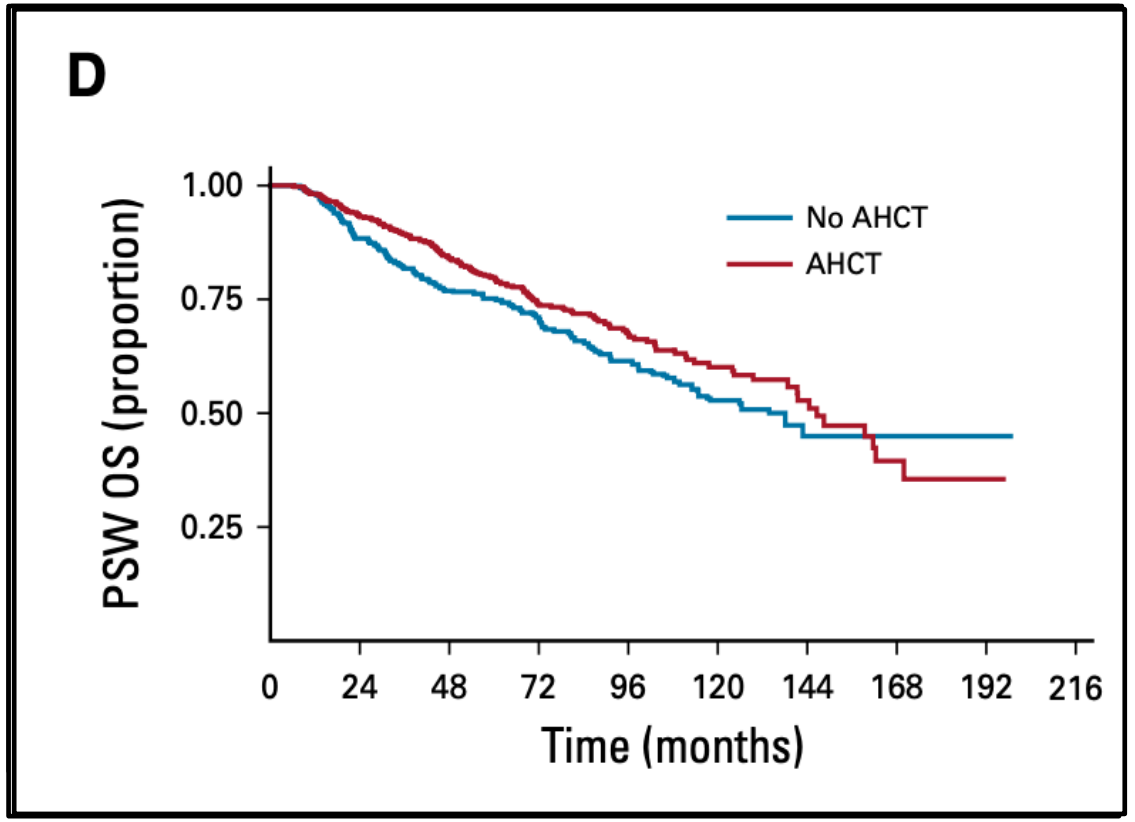
Journal of Clinical Oncology®
Volume 37, Issue 6 **471**

- On unadjusted analysis, autoHCT was associated with improved me PFS (75 vs 44 mo, P<0.01) and OS (147 mo vs 115 mo, p<0.05).
- On MVA, autoHCT was assoc with improved PFS (HR 0.54, p <0.01) and a trend toward improved OS (HR 0.77, p=0.06).
- After propensity-score weighted analysis, auto-HCT remained assoc with improved PFS (HR 0.70, p<0.05) but not OS (HR 0.87, p = .2).
- Suggests selection bias still present, despite effort to only include transplant-eligible pts



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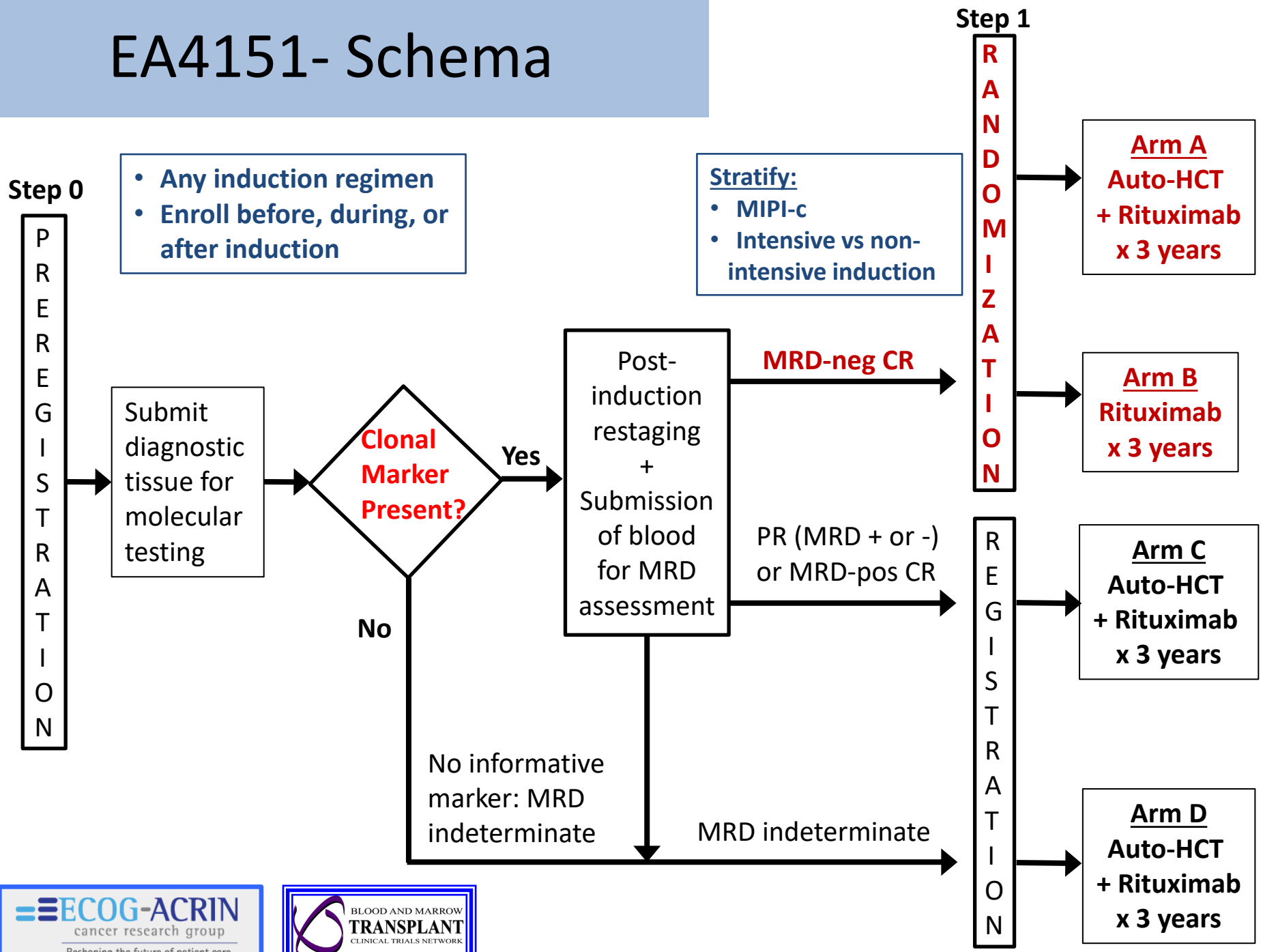
- "Prospective, randomized trials are urgently needed to determine the true benefit of consolidative auto-HCT. It is likely that some subgroups derive minimal benefit from auto-HCT consolidation, such as patients with certain genetic abnormalities (e.g. TP53 mutations) and those who achieve minimal residual disease negativity after induction."

EA4151- Schema



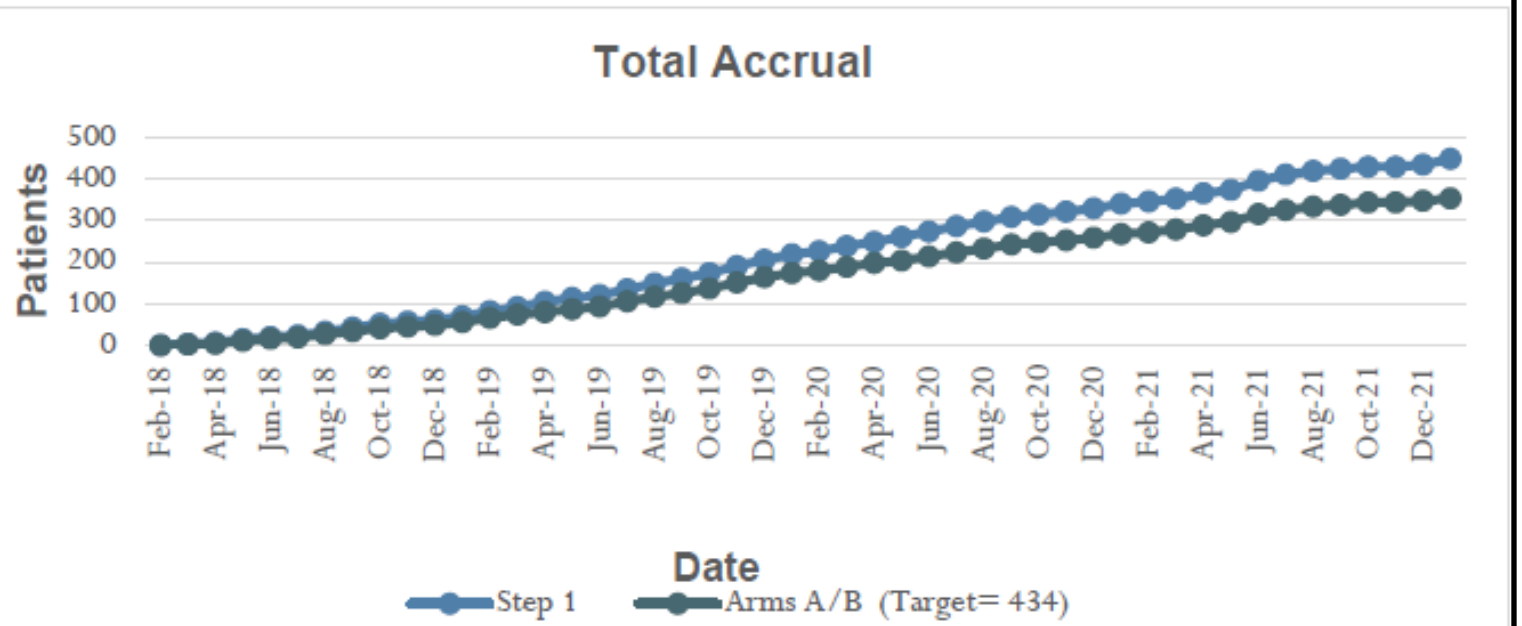
- Target 434 pts randomized (217 per arm)
- Activated 8/30/17
- On track to complete accrual Dec 2022 with current design

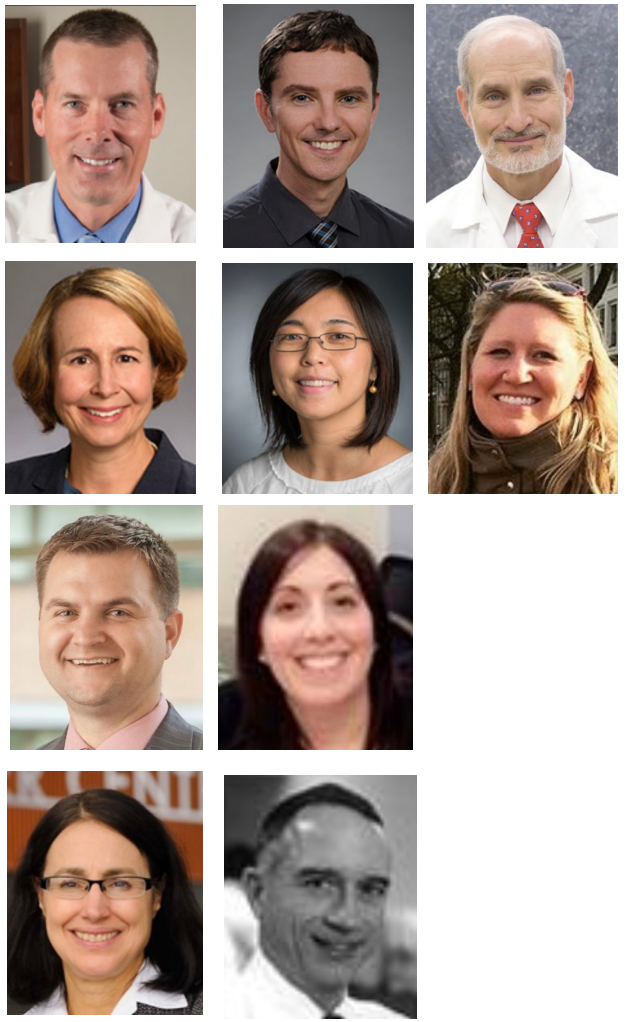
ECOG-ACRIN cancer research group
Reshaping the future of patient care

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

EA4151 monthly pre-registrations, as of 2/10/22

- Patients assigned to a treatment arm = **449** (plus ~25 pending), Arm A=175, Arm B=184, Arm C=34, Arm D=56
- **83% of target of 359/434 patients randomized to Arms A & B**



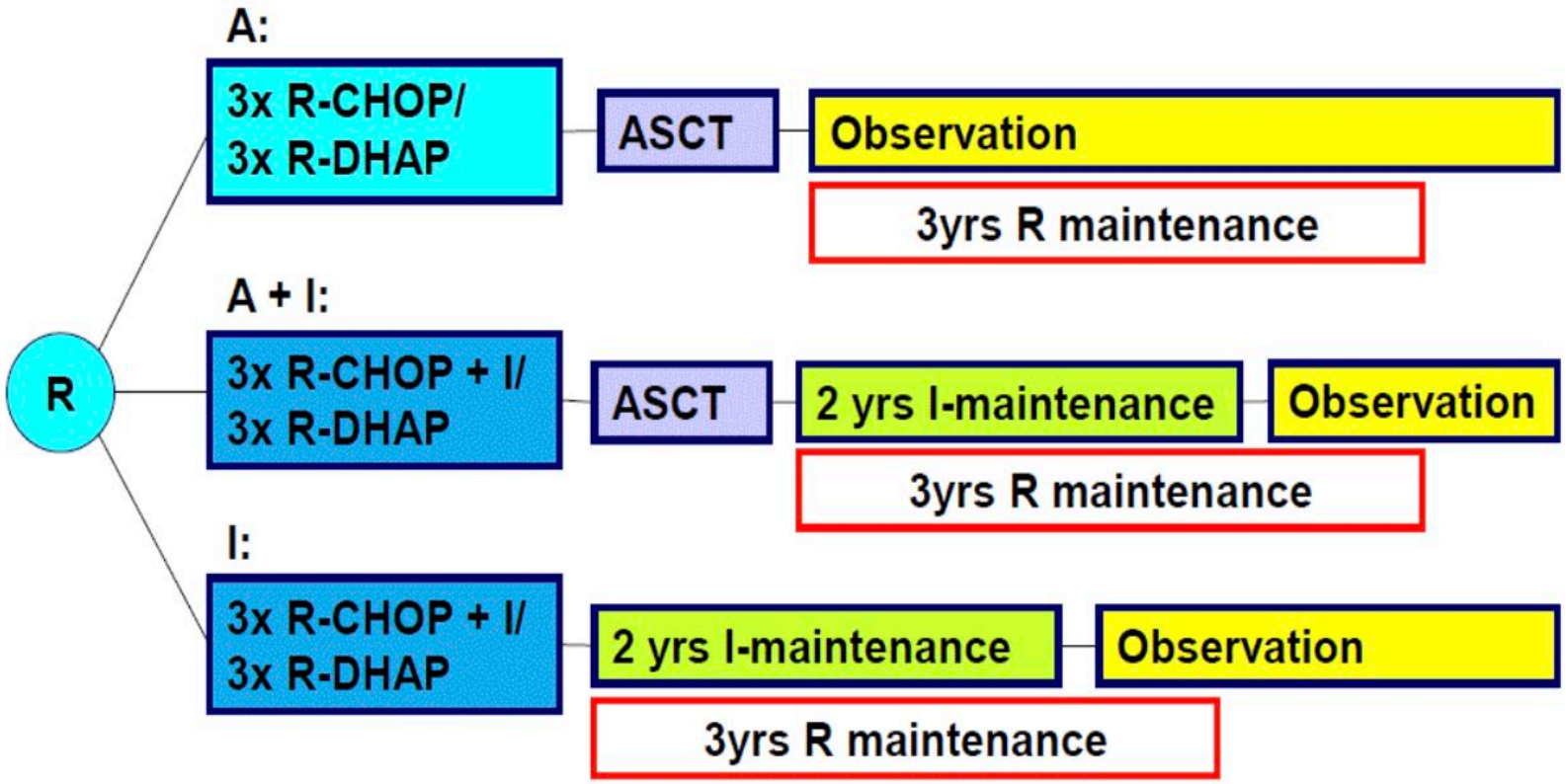


ECOG-ACRIN cancer research group
Reshaping the future of patient care

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

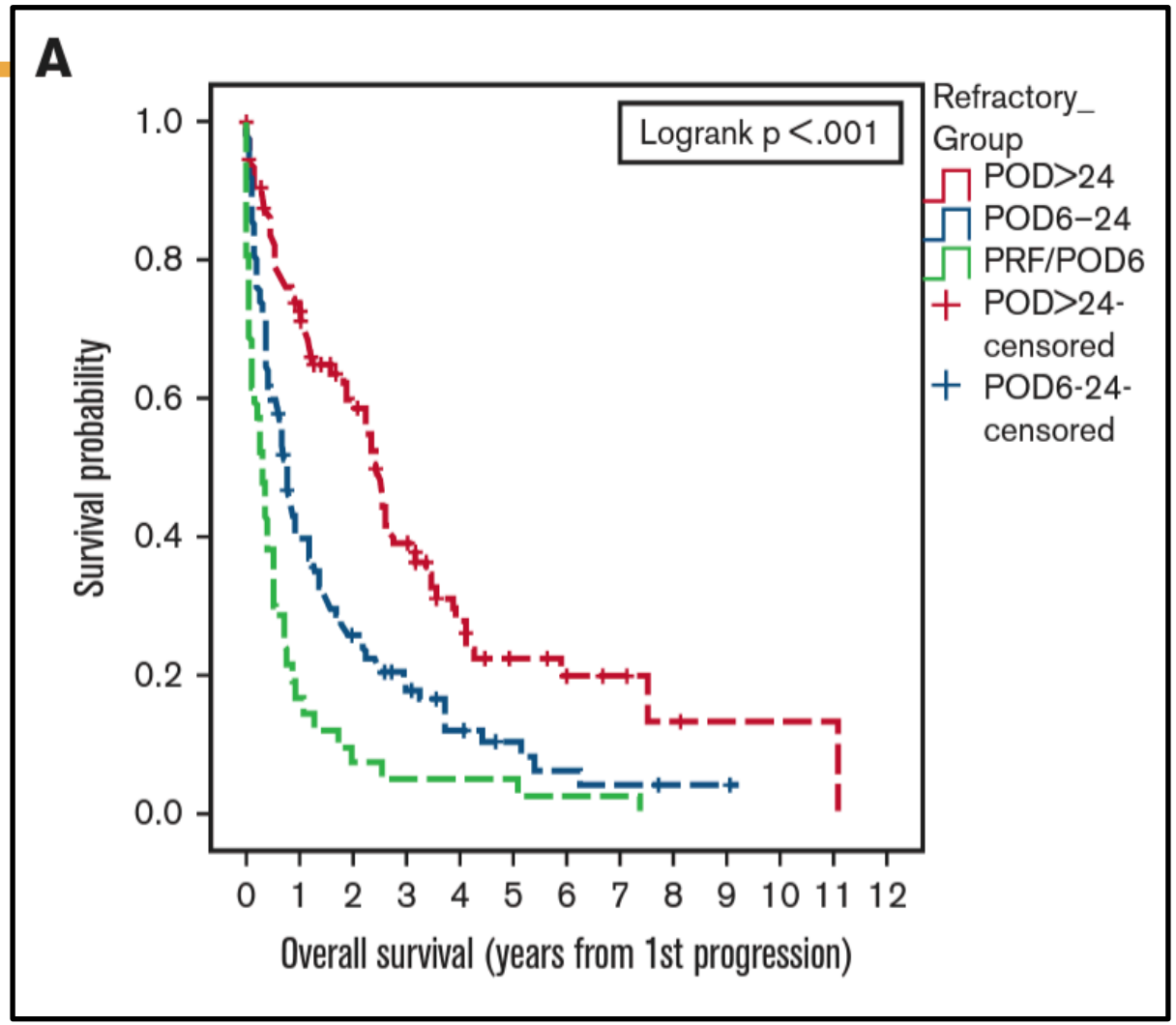
TRIANGLE Trial (Europe)

- Target 870 pts (290 per arm)
- Activated Oct 2017
- Completed accrual Dec 2020
- Endpoint eval May 2024 (?)



Relapse of MCL is no picnic

- Recent cohort of >1000 MCL pts from 12 U.S. centers (2000-2017)
- 465 had a relapse
- Outcomes poor esp if POD<24 mo.
- Confirmed in BCCA validation set
  - median OS <3 yrs even in the group with POD > 24 mo



Bond et al, Blood Adv (2021)

Non-transplant/ CAR options for rel-refr MCL

Published studies with n>30, only MCL

Regimen	# pts	ORR	Median PFS	Median OS	Ref
Bortezomib*	141	32%	7 mo	23 mo	1
Temsirolimus	162	22%	3-7 months	13 mo (T); 10 mo (IC)	2
Temsir+ ritux	71	59%	10 months	29 months	3
Lenalidomide* (prior bortez)	134	28%	4 months	19 months	4
Len*+Ritux (R^2)	44	57%	11 months	24 months	5
Ibrutinib*	111	67%	13 months	22.5 months	8,9
Idelalisib	40	40%	4 months 8 mo if <6 prior reg	Not reported	10
Acalabrutinib*	124	81%	20 months	>24 months (72% at 2 yrs)	11,12
Zanubrutinib*	112	85% (62% CR)	26 months	38 months	13
OVERALL		**20-80%**	**Approx 1-2 years**	**Approx 2-3 (maybe 4) years**	

*FDA Approved Agent for R/R MCL

[1]Goy et al, Ann Oncol (2009); [2]Hess et al, JCO (2009); [3]Ansell et al, Lancet Oncol (2011); [4]Goy et al, JCO (2013); [5]Wang et al, Lancet Oncol (2012); [6]Kouroukis et al, Leuk Lym (2011); [7]Visco et al, JCO (2013); [8]Wang et al, NEJM (2013); [9]Wang et al, Blood (2015); [10]Kahl et al, Blood (2014); [11]Wang et al, Lancet (2017); [12]Wang et al, ASH (2018); [13]Zhou et al, J Hem Onc (2021)

EUPHORIA


ibrutinib
140 mg
120 capsules


acalabrutinib
100 mg
60 capsules


zanubrutinib
80 mg
120 capsules

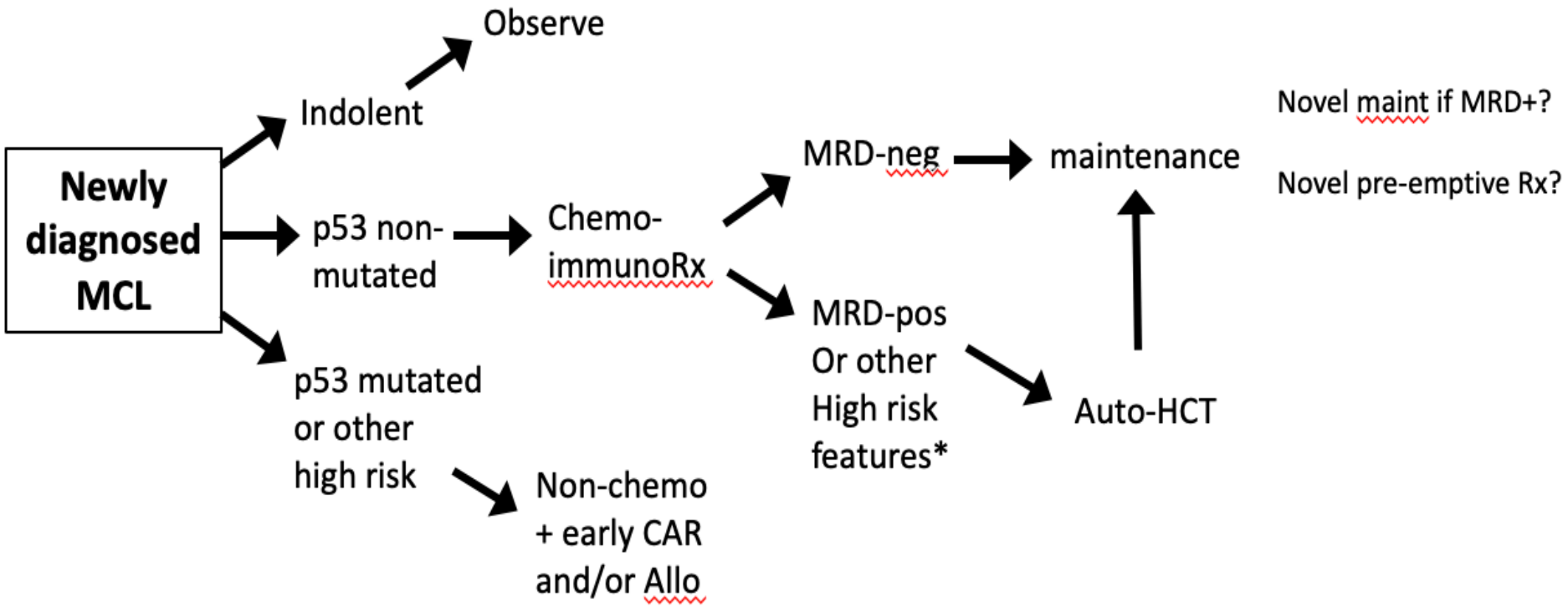
Once MCL relapses, the clock is ticking

- So. . . Goal should be LONGEST POSSIBLE FIRST RESMISSION

MCL is not a “one size fits all” disease

First-line Rx of MCL in 2022 and beyond:

Hybrid of big guns and magic bullets?



*MIPI-c, complex karyotype, high risk genomic alterations (KMT2D, CDKN2A, MCL-35(?), mIR-18b(?), others?

Summary

- For younger MCL patients, when combined with induction that includes rituximab and araC, auto-HCT consolidation:
- Leads to longer PFS vs non-auto-HCT approaches
- Can avoid additional therapy for **8-10 yrs or longer**
- Has modest late toxicities
- Avoids the need for continuous or repeated therapies
- Avoids/ defers need for continuous BTK-i , CAR-T, allo-HCT