We Should Stop Doing Autotransplants for Patients with Mantle Cell Lymphoma in First Remission

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Consultant to CRISPR and MorphoSys

Many Young Fit Patients with Mantle Cell NHL in a First CR Undergo a Consolidative Autotransplant (ASCT) Followed by Rituximab Maintenance

Why?

In fact, there has never been a single modern trial that has demonstrated that the transplant improves survival

And..only a single pre-rituximab era trial that showed such an improvement

Shouldn't THE endpoint of aggressive therapy like ASCT be to increase survival and lead to more cures?

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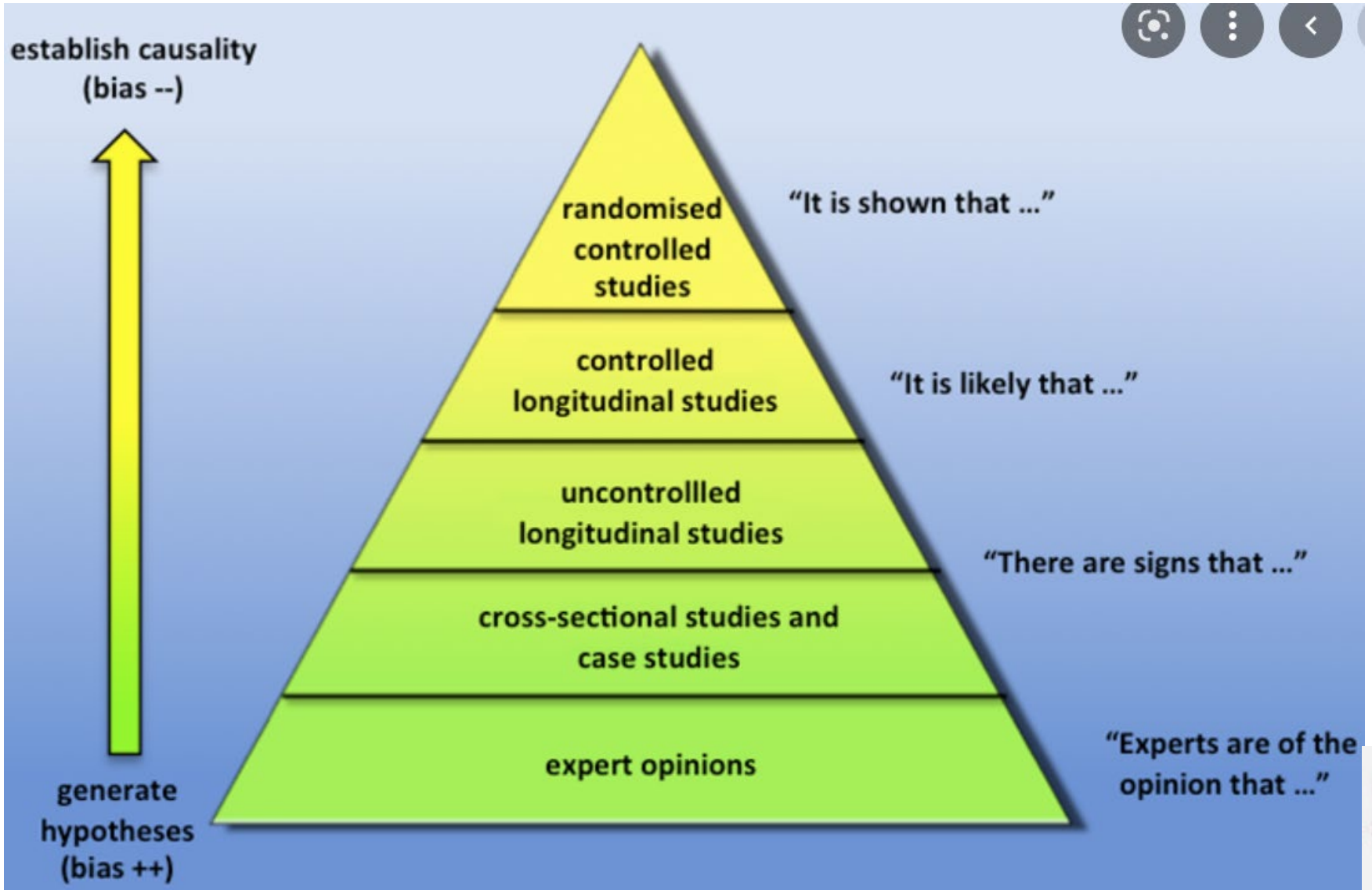
The Pinnacle of Proving One Treatment is Superior to Another is the Randomized Clinical Trial



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So….Why do we Continue to do ASCTs for MCL in First Remission?

- If they do not improve survival wouldn’t the toxicity, mortality risks and long term risks of MDS/AML demand that they stop?
- Until a trial is done to indicate benefit?...
- Because if they were indicated as the standard of care, wouldn’t a trial be unethical?

- The data…..

In the Pre-Rituximab Era, Autotransplants for MCL in 1st Remission Were Beneficial: First European Mantle Cell NHL Group Phase III Study

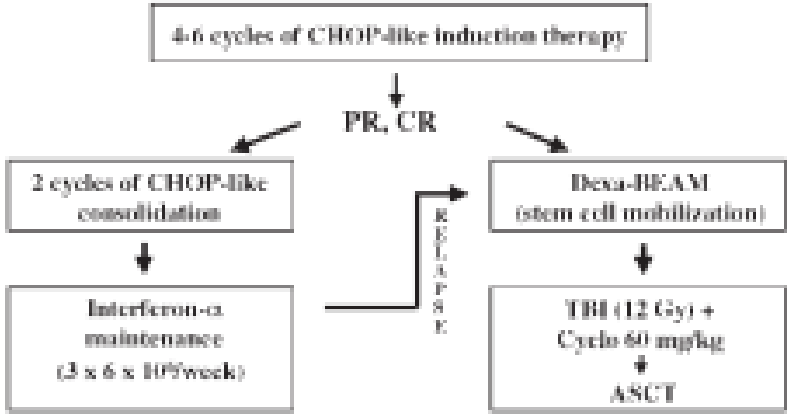

Figure 1. Design of the trial

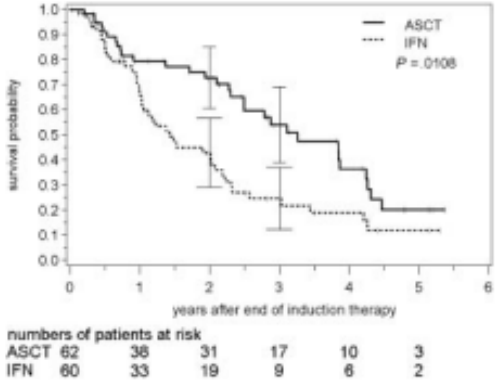

Figure 2. Progression-free survival after high-dose radiochemotherapy followed by autologous stem cell transplantation (ASCT) and interferon-α (IFN) maintenance in MCL. Patients assigned to stem cell transplantation experience significantly longer progression-free survival (log-rank test). Solid line indicates ASCT; broken line, IFN. Vertical bars indicate 95% confidence intervals for progression-free survival.

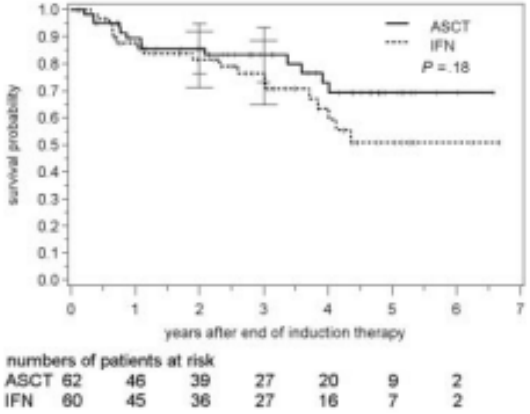

Figure 4. Overall survival following autologous stem cell transplantation and interferon-α maintenance, respectively. Bars indicate 95% confidence intervals.

Given the dismal outcome for chemotherapy alone, the suggestion that CRs to induction therapy were associated with a better outcome after ASCT, the follow-on studies attempted to improve the initial therapy and in all cases routinely added ASCT as consolidation. This continues to this day.

Dreyling et al Blood, 2005

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But Is Long Term Outcome Data Supportive in Ongoing European MCL Consortia Trials?

"Long-term survival of patients with mantle cell lymphoma after autologous haematopoietic stem-cell transplantation in first remission: a post-hoc analysis of an open-label, multicentre, randomised, phase 3 trial-European MCL Network "

On the surface, yes……

	Total (n=174)	Interferon alfa maintenance group (n=81)	Autologous HSCT group (n=93)
Age (years)	55 (47–60)	54 (49–60)	55 (47–60)
Sex			
Male	135 (78%)	60 (74%)	75 (81%)
Female	39 (22%)	21 (26%)	18 (19%)
Stage			
II	1 (1%)	0	1 (1%)
III	30 (17%)	14 (17%)	16 (17%)
IV	143 (82%)	67 (83%)	76 (82%)
Elevated serum LDH concentration*	51 (29%)	25 (31%)	26 (28%)
B symptoms present†	70/173 (40%)	36/81 (44%)	34/92 (37%)
Eastern Cooperative Oncology Group performance status			
0	72 (41%)	34 (42%)	38 (41%)
1	93 (53%)	41 (51%)	52 (56%)
2	9 (5%)	6 (7%)	3 (3%)
Mantle cell lymphoma international prognostic index			
Low risk	127 (73%)	55 (68%)	72 (77%)
Intermediate risk	35 (20%)	20 (25%)	15 (16%)
High risk	12 (7%)	6 (7%)	6 (6%)
Induction treatment			
CHOP	88 (51%)	43 (53%)	45 (48%)
R-CHOP	68 (39%)	27 (33%)	41 (44%)
CHOP-like chemotherapy regimen	18 (10%)	11 (14%)	7 (8%)
Quality of remission at end of induction			
Complete remission	51 (29%)	19 (23%)	32 (34%)
Partial remission	123 (71%)	62 (77%)	61 (66%)

Data are median (IQR), n (%), or n/N (%). HSCT=haematopoietic stem-cell transplantation. LDH=lactate dehydrogenase. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. R-CHOP=rituximab plus CHOP. *Greater than the upper limit of normal. †Information on B symptoms is missing in one patient because source data were not available.

Table 1: **Patient characteristics**

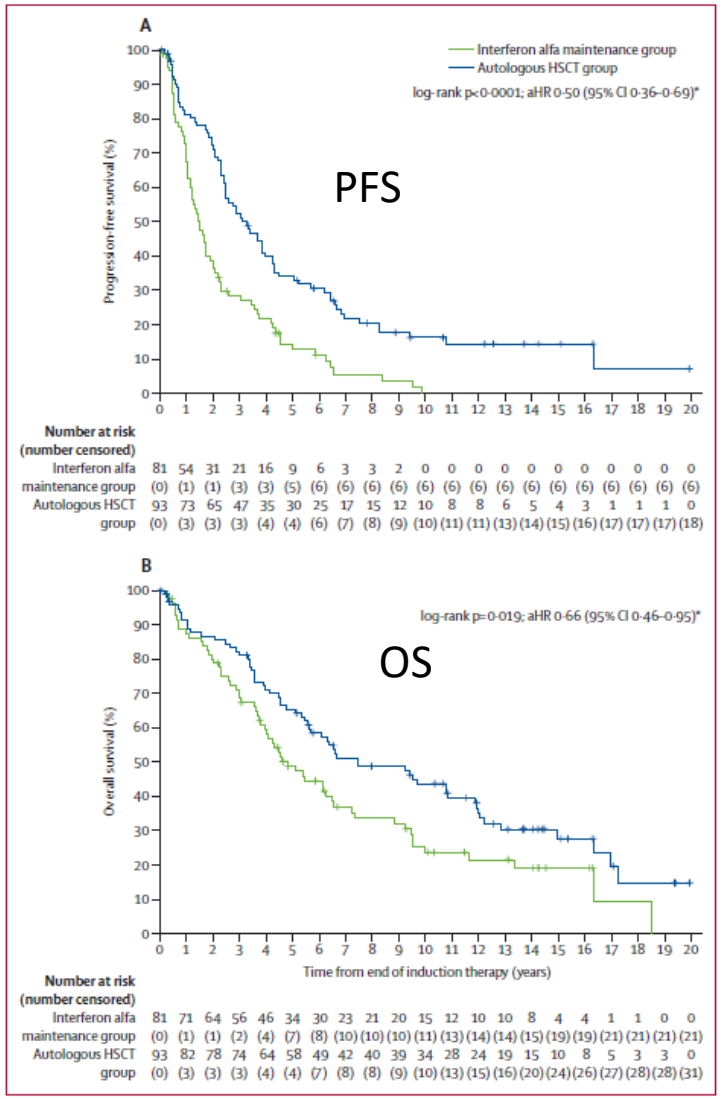

Figure 2: **Progression-free survival (A) and overall survival (B) of responding patients**
aHR=adjusted hazard ratio. HSCT=haematopoietic stem-cell transplantation. MIPI=mantle cell lymphoma international prognostic index. *The HR has been adjusted for MIPI score and rituximab use.

Zoellner, et al Lancet Hem, 2021

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Long-term survival of patients with mantle cell lymphoma after autologous haematopoietic stem-cell transplantation in first remission: a post-hoc analysis of an open-label, multicentre, randomised, phase 3 trial

However:

"For patients treated without rituximab, the progression-free survival adjusted HR for autologous HSCT versus interferon alfa was 0·40 (0·26–0·61), in comparison to 0·72 (0·42–1·24) for patients treated with rituximab (36%)"—i.e. not significant for Rituximab treated patients

"For overall survival, the adjusted hazard ratio for HSCT versus interferon alfa was 0·52 (0·33–0·82) without rituximab and again 1·05 (0·55–1·99) for patients who received rituximab….. "i.e. again not significant for Rituximab treated patients

"The reduced efficacy after immunochemotherapy supports the need for its re-evaluation now that antibody maintenance, high-dose cytarabine, and targeted treatments have changed the standard of care for patients with mantle cell lymphoma."

Zoellner, et al Lancet Hem, 2021

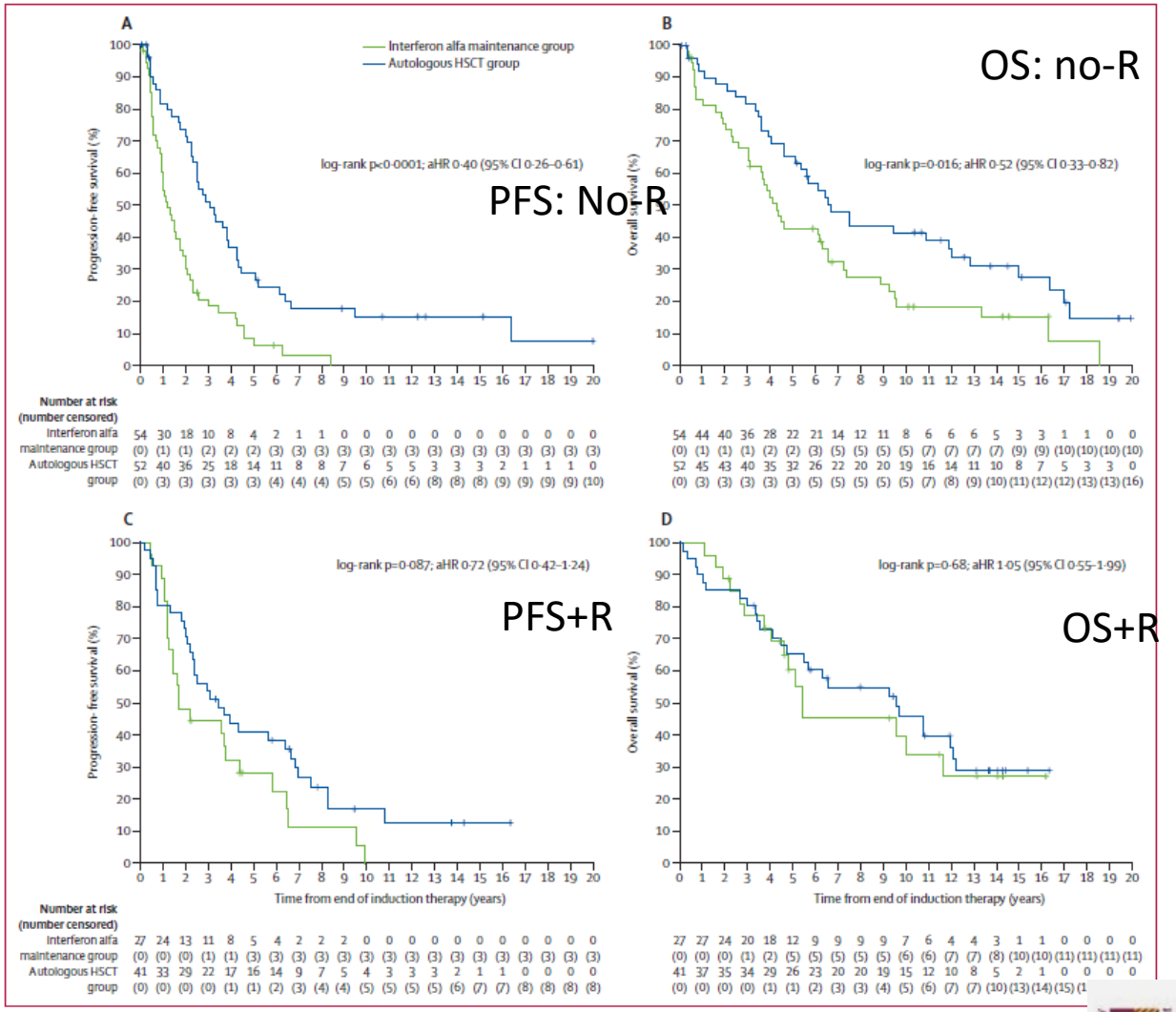

Figure 3: **Progression-free survival and overall survival of responding patients stratified by rituximab use in induction regimen**

(A) Progression-free survival with no rituximab in induction regimen. (B) Overall survival with no rituximab in induction regimen. (C) Progression-free survival with rituximab in induction r (D) Overall survival with rituximab in induction regimen. The HR has been adjusted for MIPI score. aHR=adjusted hazard ratio. HR=hazard ratio. HSCT=haematopoietic stem-cell transplanta MIPI=mantle cell lymphoma international prognostic index.

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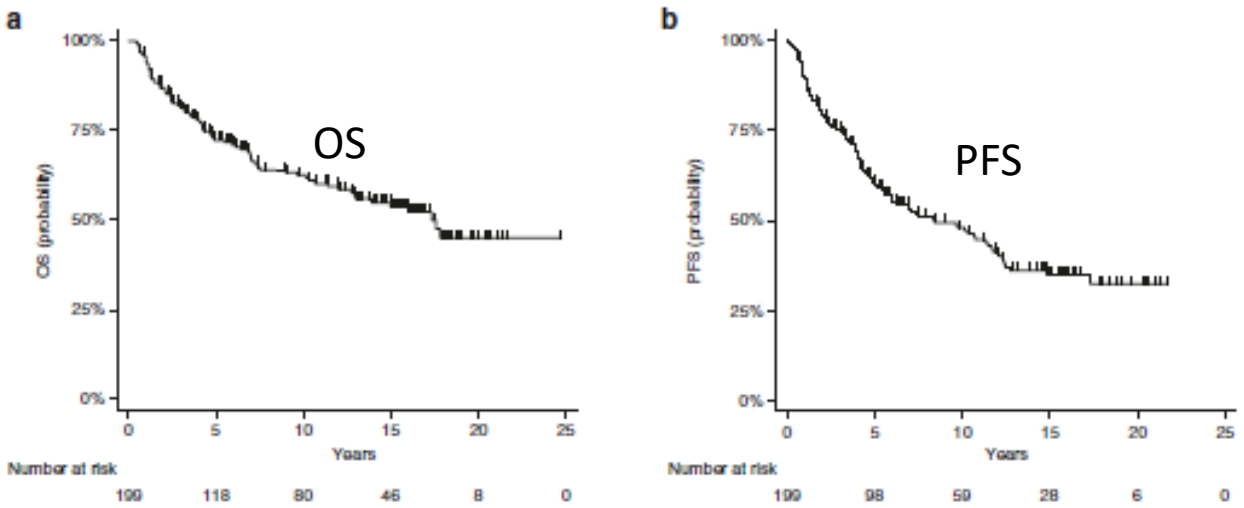
What About Other Long-Term Data?: Italian Multicenter Phase II Trial of Upfront Intensive Chemo-immunotherapy with ASCT in 199 Young Patients: 15+ Year Long Term f/u and Toxicities



Relapses or deaths still occurring out to 17+ years after ASCT!

The number of deaths not related to lymphoma was 28 (14%) of 199, mainly due to secondary malignancies, infections, or cardiac events; in this report, solid cancers occurred in 18 (9%), and haematological malignancies in 11 (6%).
{Chiapella and Ladettto; Lancet Hematology; 2021}

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What is the Data for No ASCT in MCL in First Remission?

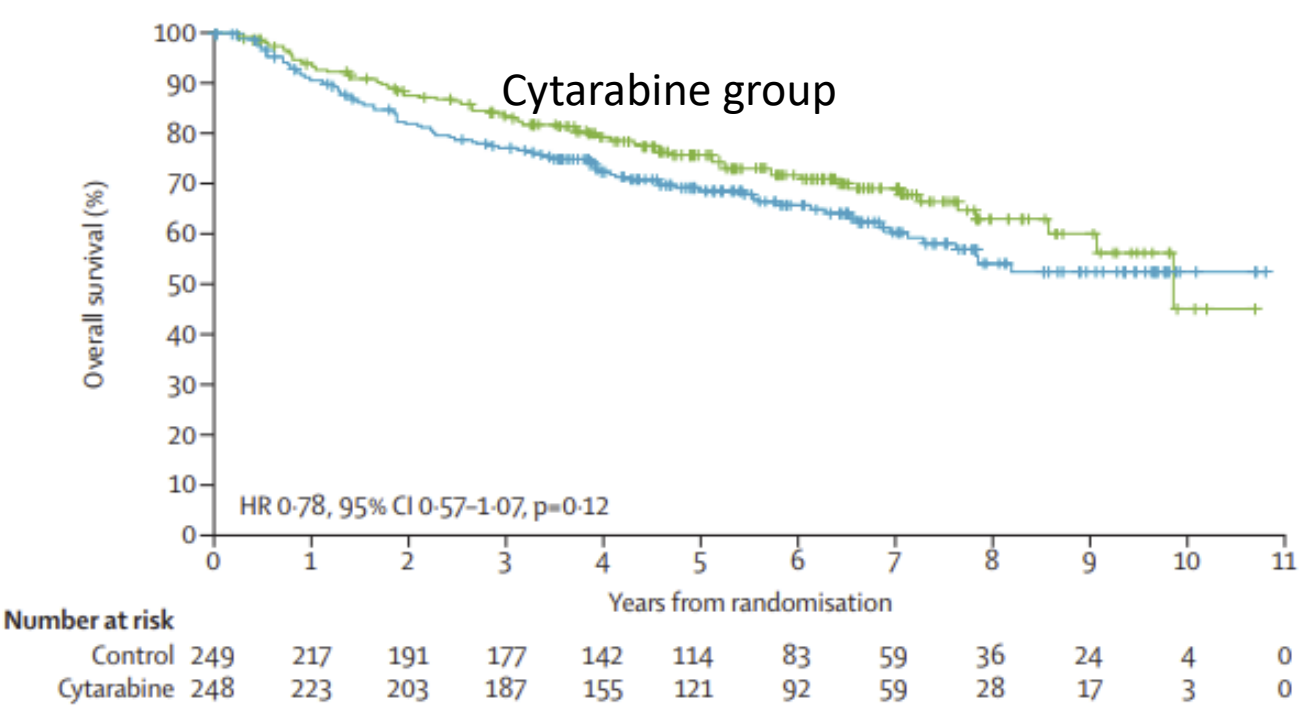
Pretty much all trials over the last 10 years for ‘young, fit’ patients have included ASCT in all arms of any Phase III trials—so none

But…elderly patients or ‘un-fit’ patients typically do not undergo ASCT
So how do they do?? Can we infer the value of ASCT in this typically higher risk group?

Let’s look at some of the best data for young fit patients undergoing ASCT and compare to older un-fit patients who do not get transplant…

Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network

-Phase 3 trial was done in 128 centers
-Patients aged 65 years or younger with untreated stage II–IV mantle cell lymphoma were centrally randomised (1:1), to 6 courses of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by myeloablative radiochemotherapy and ASCT (control group), or 6 courses of alternating R-CHOP or R-DHAP (rituximab plus dexamethasone, high-dose cytarabine, and cisplatin) followed by a high-dose cytarabine-containing conditioning regimen and ASCT (cytarabine group).



Hermine; Lancet 2016

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The NEW ENGLAND JOURNAL of MEDICINE

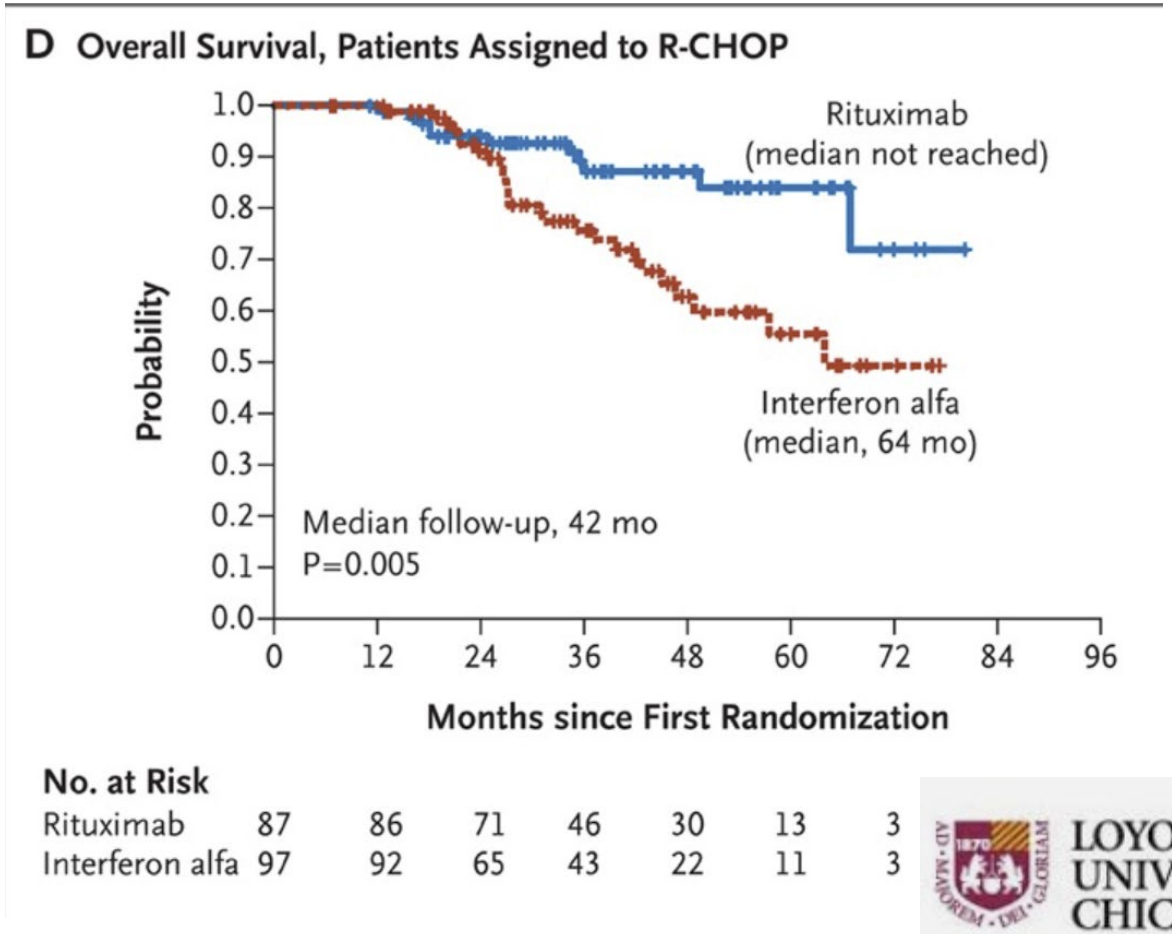
ORIGINAL ARTICLE

Treatment of Older Patients with Mantle-Cell Lymphoma

-Enrolled patients 60 years of age or older (adverse risk factor for MCL) with mantle-cell lymphoma, stage II to IV, who were not eligible for high-dose therapy were randomized to six cycles of rituximab, fludarabine, and cyclophosphamide (R-FC) every 28 days or to eight cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 21 days.

-Patients who had a response underwent a second randomization to maintenance therapy with rituximab or interferon alfa, each given until progression.

Kluin-Nelemans; NEJM, 2012



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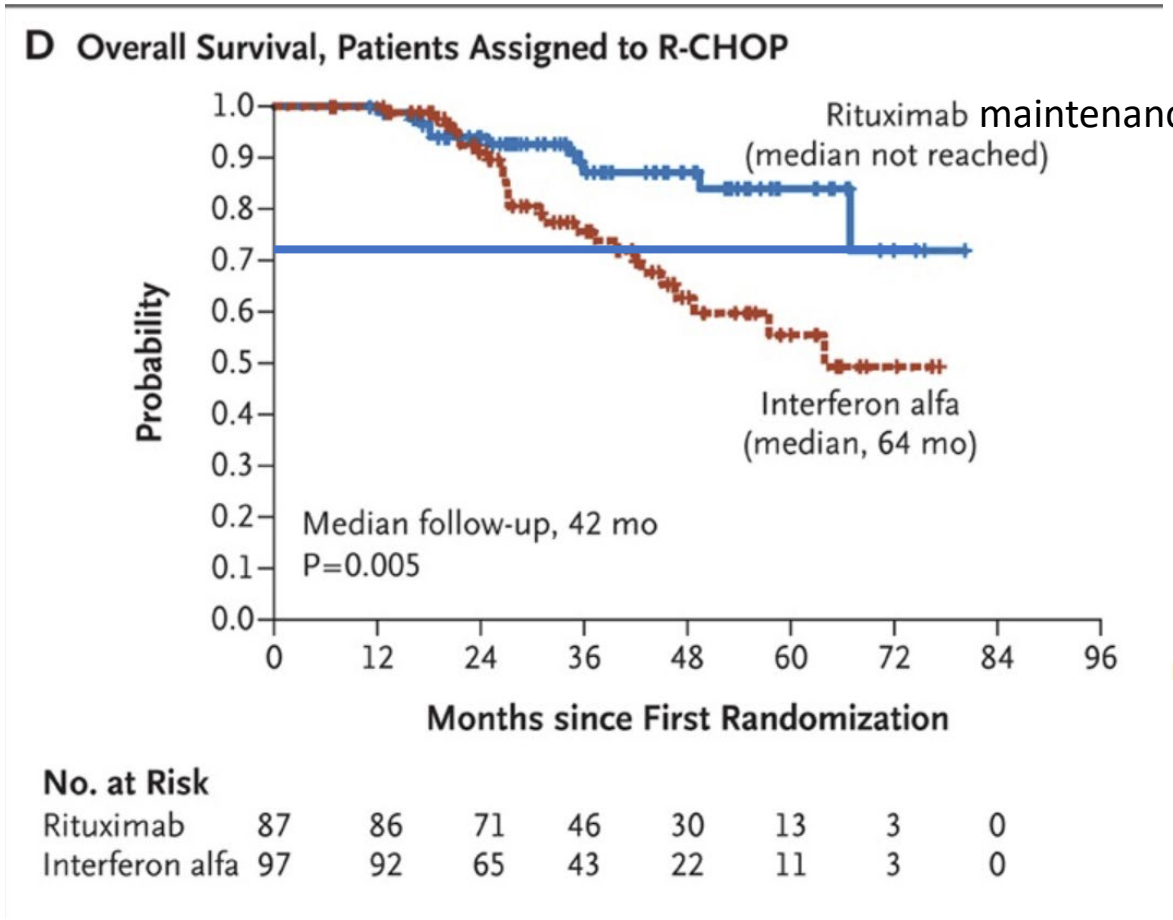
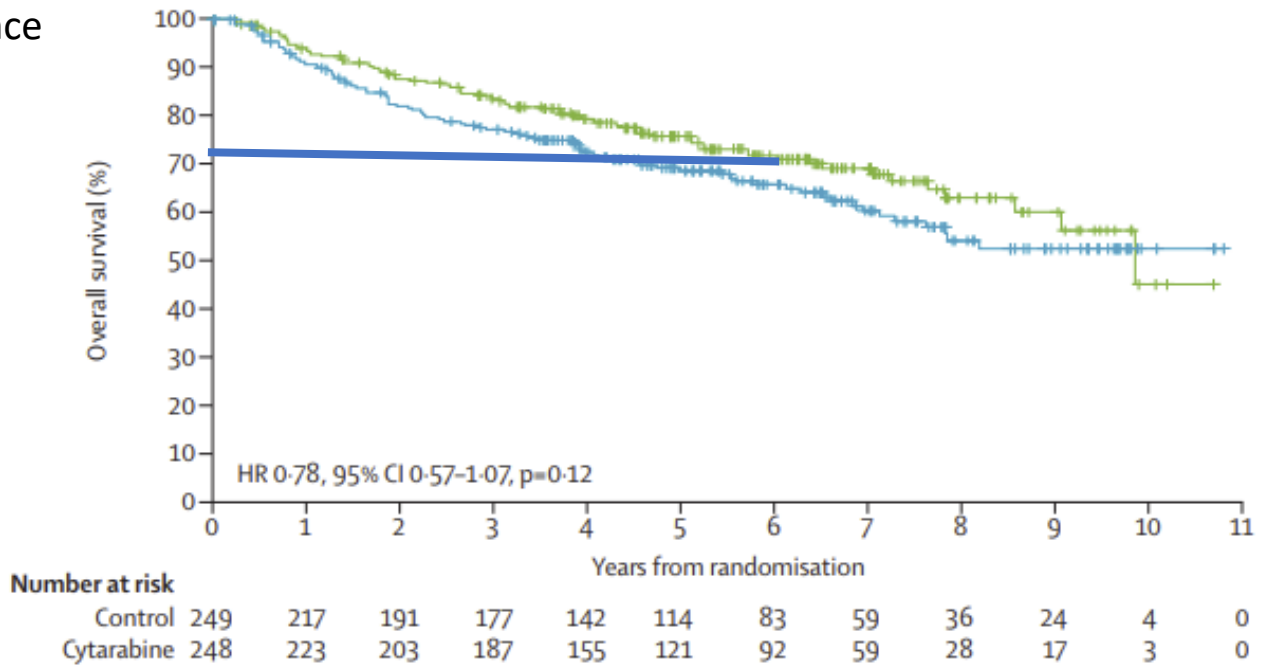
So Let's Compare an Older MCL Group Without Transplant (NEJM) to Arguably the Best Current Approach for Younger Patients With Transplant (Lancet), Focusing on the Most Important Endpoint: Survival for a Disease that has a Low Probability of Cure with any Best Conventional Therapy





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What about long-term data without transplant for the most aggressive regimen used to treat this disease: Hyper-CVAD/HDMtx/Ara-C?

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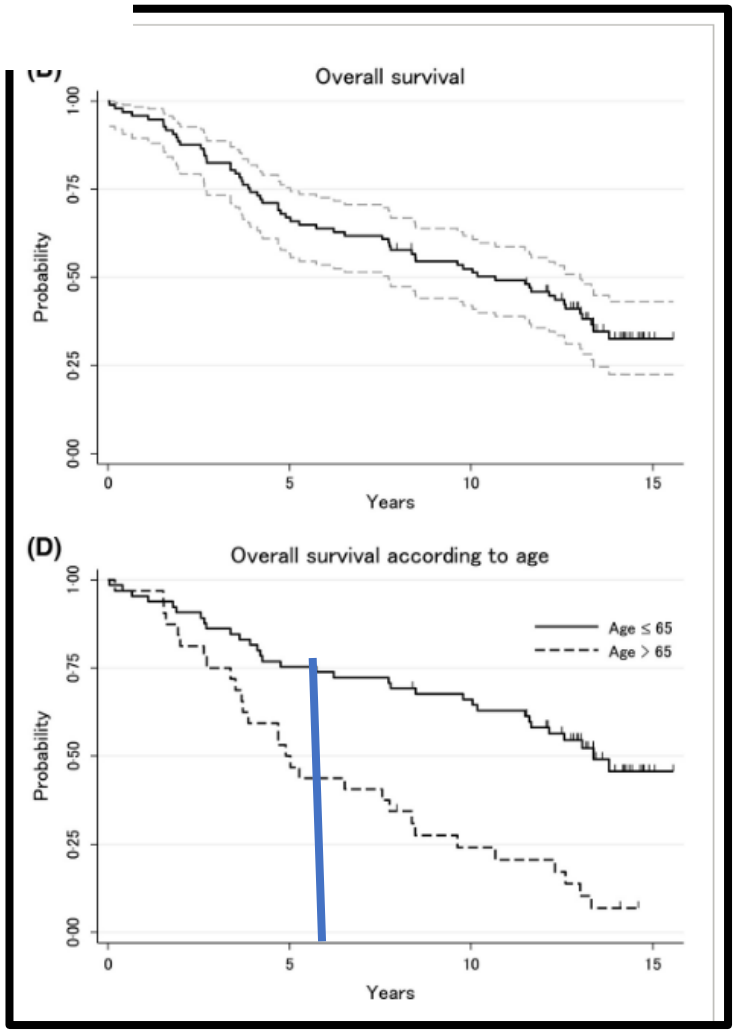
BJHaem
BRITISH JOURNAL OF HAEMATOLOGY
British Society for Haematology
Research Paper | Free Access

Rituximab plus hyper-CVAD alternating with MTX/Ara-C in patients with newly diagnosed mantle cell lymphoma: 15-year follow-up of a phase II study from the MD Anderson Cancer Center Without Transplant

-Long-term survival outcomes from a pivotal phase II trial of rituximab, hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine (R-HCVAD/MA).
- 97 consecutive patients with newly diagnosed MCL were enrolled in the prospective phase II trial between March 1999 and March 2002
-Response was assessed every 2 cycles (one cycle of R-HCVAD and one cycle of R-MA) by computerized tomography (CT) scan
-CR was defined by negative CT scan, negative upper and lower endoscopy with random biopsies and negative bone marrow biopsy with no lymphoma cells by flow cytometry.
-Patients who achieved CR after 2 cycles received up to 6 cycles in total; patients not in CR after 2 cycles were given up to 8 cycles (four cycles of R-HCVAD and four cycles of R-MA).



Chihara et al; Br J Haem, 2015

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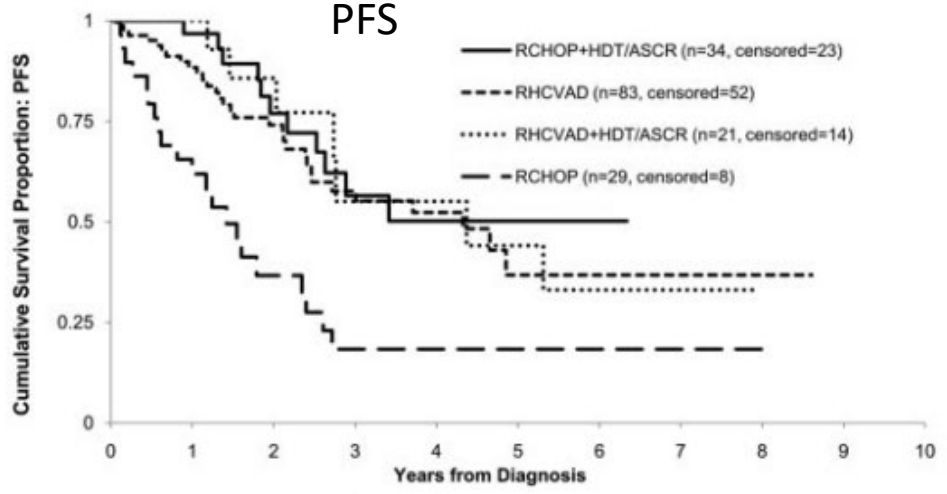
Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: an analysis from the NCCN NHL Database

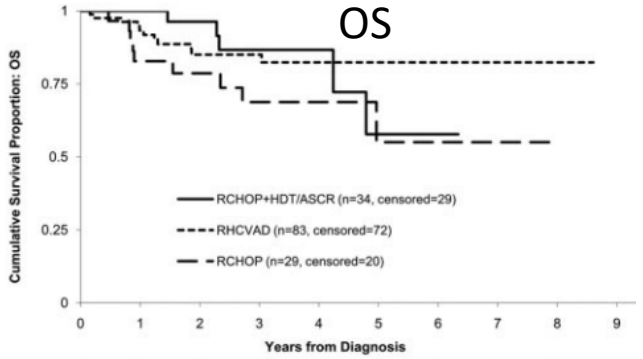
- The National Comprehensive Cancer Network (NCCN) conducted a prospective cohort study collecting clinical, treatment, and outcome data at 7 NCCN centers to compare the effectiveness of initial therapies in MCL.
- Patients younger than 65 diagnosed between 2000 and 2008 were included if they received R-HyperCVAD, R-CHOP + ASCT, R-HyperCVAD+ ASCT, or R-CHOP alone.
- N = 167
- While ASCT improved PFS for R-CHOP only treated patients (not a new outcome and not used in 2022 as induction therapy), ASCT did not improve PFS for HyperCVAD and in no group was OS superior, confirming the previous data

PFS



RCHOP	29	17	8	3	3	1	1	1	1
RCHOP+HDT/ASCR	34	28	18	9	3	2	1	0	0
RHCVAD	83	59	40	24	17	5	1	1	1
RHCVAD+HDT/ASCR	21	19	11	5	5	4	3	2	0

OS



RCHOP	29	23	18	11	8	4	4	3	1
RCHOP+HDT/ASCR	34	29	23	15	7	3	1	0	0
RHCVAD	83	63	45	33	22	12	4	1	1

LaCasce et al, Blood, 2012

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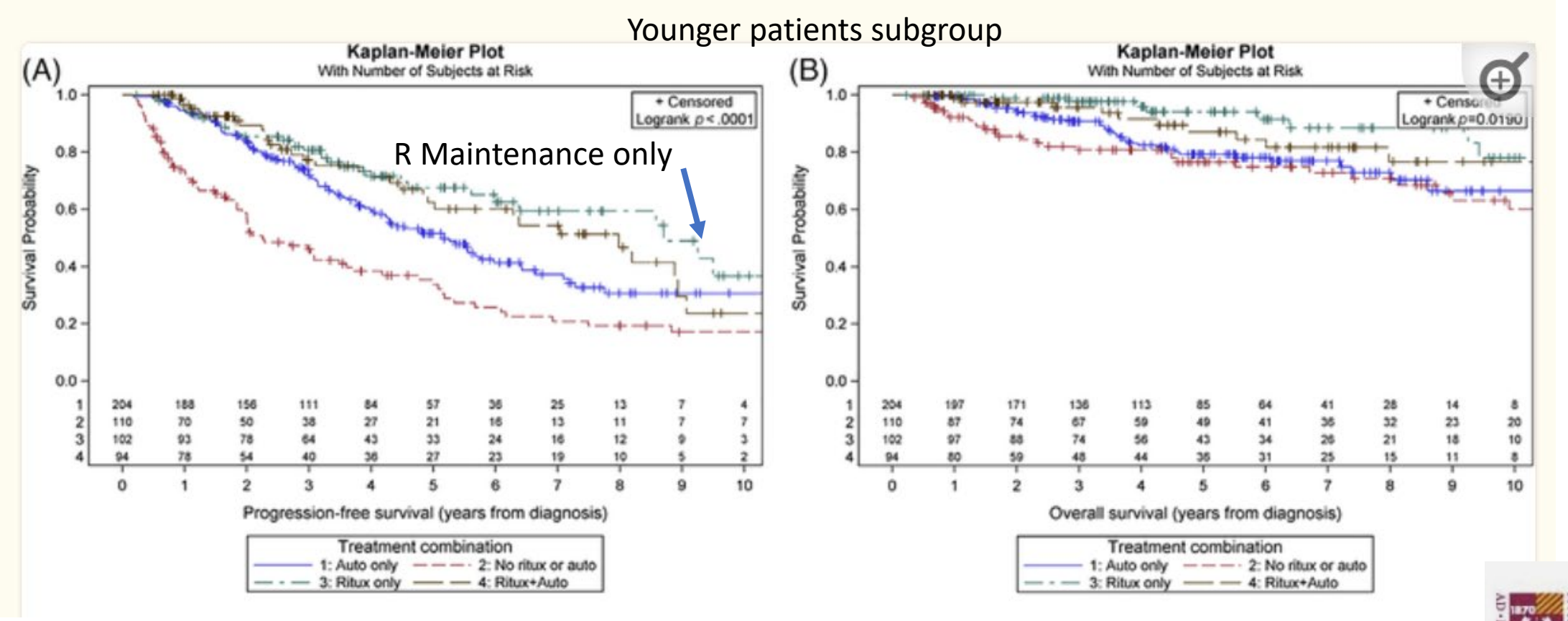
And not to bore you—here's another comparison published just in November 2021 showing in younger patients that actually maintenance rituximab without ASCT may be the best option for young patients

Multi-center analysis of practice patterns and outcomes of younger and older patients with mantle cell lymphoma in the rituximab era:

Younger patients subgroup



Karmali, et al Am J of Hematol; 2021

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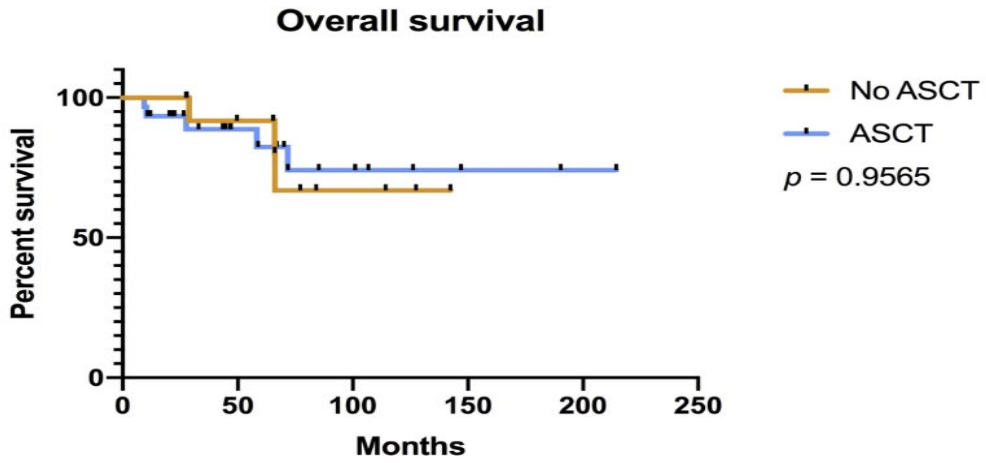
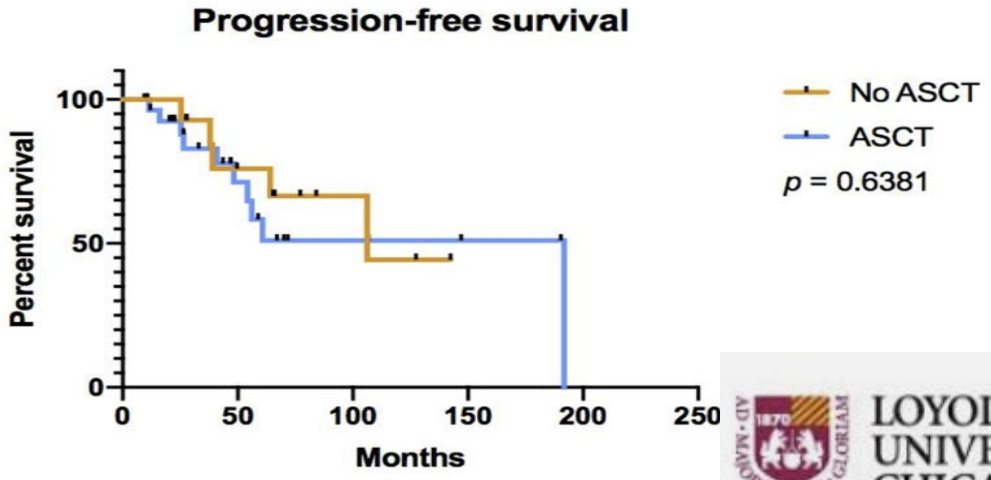
What About a Response Adapted Approach to ASCT in first Remission in Mantle Cell Lymphoma?

N = 44 patients: 30 transplant; 14 no transplant
Induction: R-HyperCVAD with MRD/PET/CT after cycles 1 B and 3 B
If negative, 2 years of maintenance rituximab and no transplant (not randomized though)
Transplant was with Bu/mel, BEAM or BCV in 30 pts
Median age = 59
Median f/u 65 months
2 patients post-ASCT died of sepsis

Tan et al, EHA 2020





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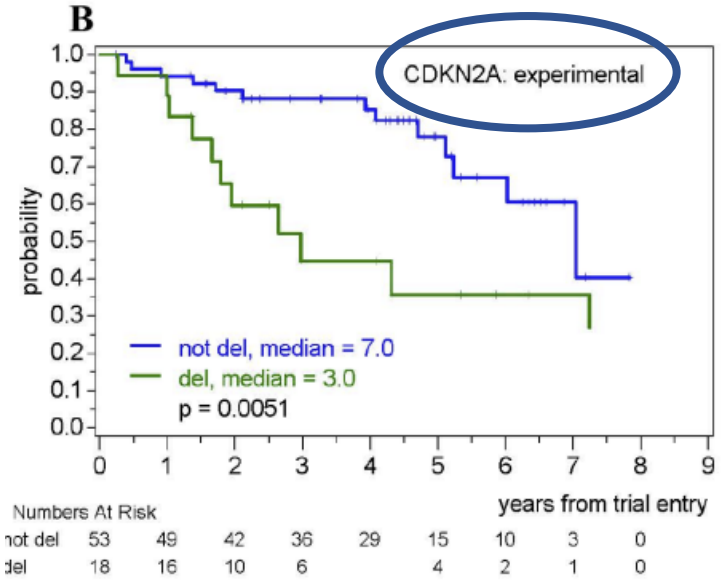
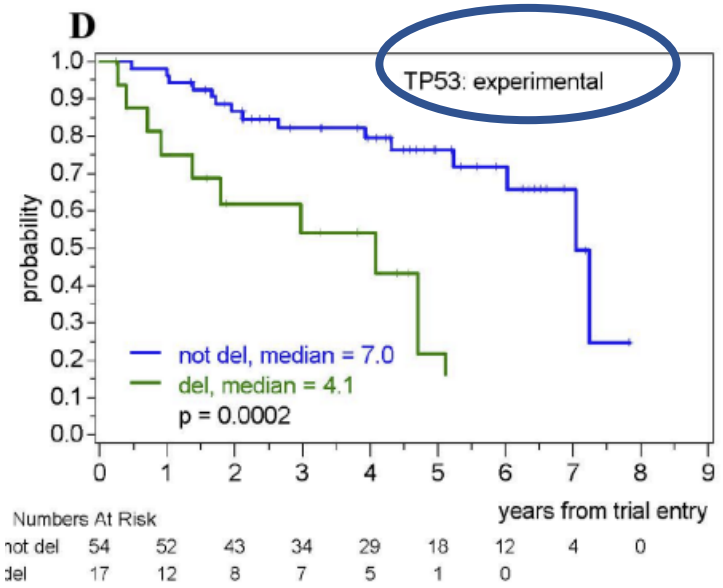
Even if You Think that Patients should get an 1st Remission ASCT, There are Some MCL Patients who Should Just Never Get a Standard ASCT in First Remission

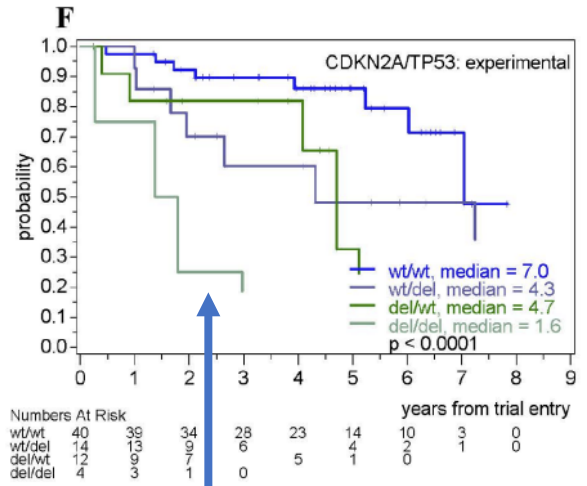
CDKN2A (22% of patients) AND TP53 DELETIONS (25% of patients) PREDICT ADVERSE OUTCOME IN YOUNGER MANTLE CELL LYMPHOMA PATIENTS, INDEPENDENT OF TREATMENT AND MIPI, a European MCL Network Study as Measured by Overall Survival

Delfau-Larue; Blood, 2015.

Also…Complex Karyotype patients







Both CDKN2A + TP53 (10%)

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Among Emerging Alternatives to ASCT: The Combination of Venetoclax, Lenalidomide, and Rituximab in Patients with Newly Diagnosed Mantle Cell Lymphoma Induces High Response Rates and MRD Undetectability

Phase I/II multicenter

Induction: 12 months

-V: MTD = 400 mg

-R: weekly x 4 then q 8 weeks

-L: 20 mg days 1-21 of 28-day cycle

Maintenance: 3 years

- R: every 8 weeks x 3 years

-L: 10 mg day 1-21 x 2 years

-V: 400 daily x 1 year

Transplant: none

MRD assessments: neg = ≤ 10^{-6}

Results

Age, years, median (IQR)	65 (57, 69)
Race, white, % (n)	100% (28)
Tx duration, d, median (IQR)	278 (170, 560)
Stage IV, % (n)	96% (27)
MIPI High, % (n)	64% (18)
Blast/Pleo, % (n)	21% (6)
Ki-67 ≥30%, % (n)	68% (19)
ORR	**96%**
CR/CRu	**89%**
MRD -	**71%**

Phillips, et al ASCO, 2021

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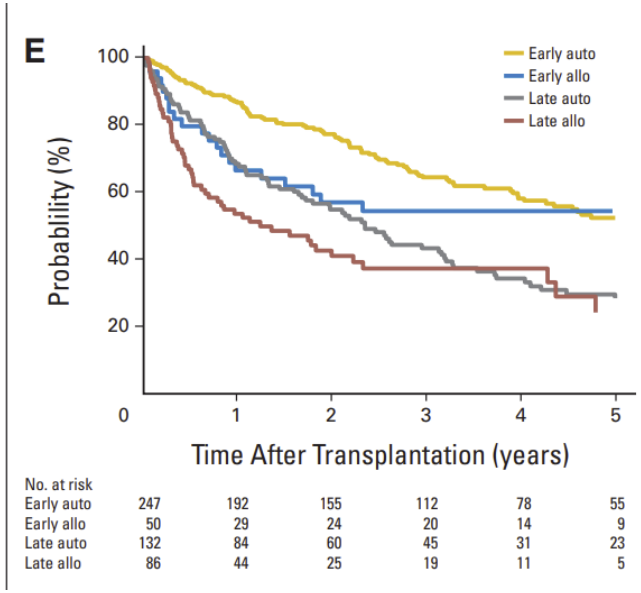
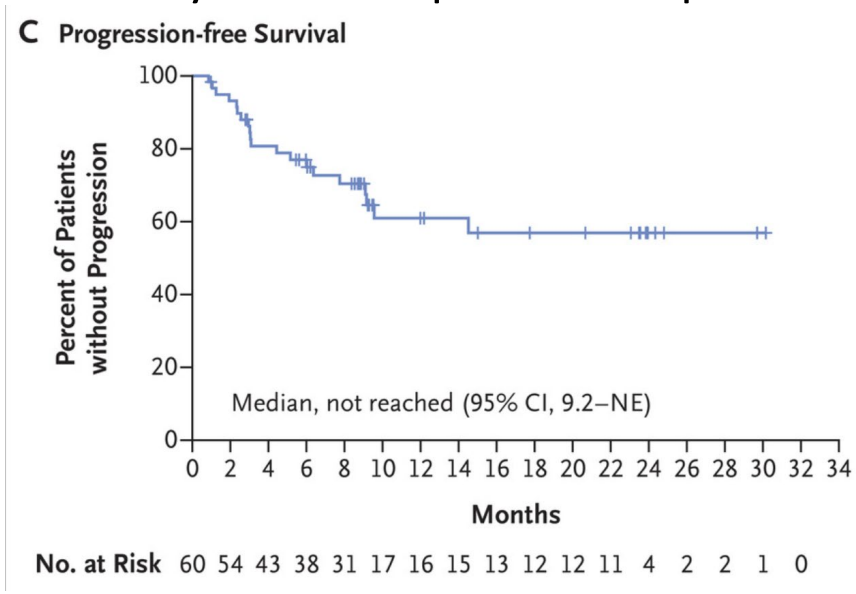
To date all *TP*53+ did not achieve MRD- at the end of therapy and only these have progressed

So If The Goal for the Treatment of MCL is Long Term DFS—Early ASCT doesn't do it, but…

- What do we know that could actually lead to cures?:
  - Several options move the PFS needle a bit (Cytarabine-containing regimens, Hyper-CVAD, and BTK containing up front studies (Phase 3 SHINE study)-so start with these….
  - And then and only then hen you need them add:
    - There is a Graft vs Lymphoma Effect for patients undergoing allografts that equates with cure
    - The early data of CAR-T therapy for double refractory MCL is impressive—?potential cures like DLBCL



All recipients of an auto-HCT or RIC allo-HCT between 1996 and 2007 as a first HCTforMCL reported to the CIBMTR were included; Fenske; JCO, 2014



ZUMA-2: disease that had relapsed or was refractory after the receipt of up to five previous therapies; all patients had to have received BTK inhibitor therapy previously. Wang; NEJM 2020

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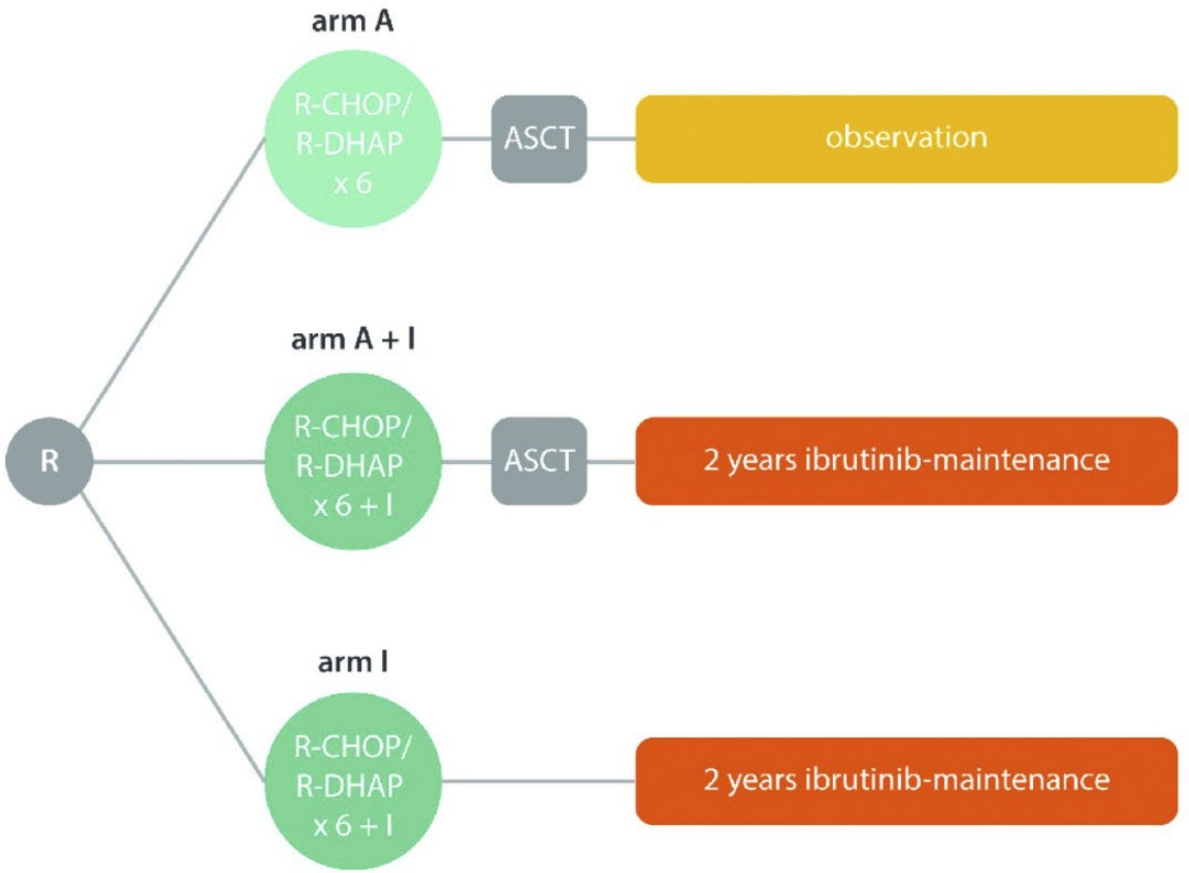
Summary of Early ASCT for Mantle Cell NHL: 2022

- Transplants for NHL should be done to improve survival. First Remission ASCT in MCL does not
- Young fit MCL patients currently routinely undergo transplants without defining Phase III data to indicate efficacy in the 'modern' induction treatment era (post-rituximab and Ara-C regimens), i.e. no data exist to suggest we are curing more with transplant—so these expensive, toxic procedures should be stopped
- Patients with MCL in first remission should go on the ECOG-led intergroup trial or receive maintenance rituximab or based on at least 1 study rituximab combined with lenalidomide (improved PFS)
- Are there subgroups that should get a first remission ASCT? No
  - Patients with MCL not in a first remission or with TP53, complex karyotype or CDKN2A have a dismal prognosis with or without an ASCT—in general this should never be offered in lieu of an allograft or down the line CAR-T therapy (needs to be proven)
  - If a clinical CR patient has detectable disease after induction therapy, I.e. are MRD positive, they really are not in a CR. There is data from a single well controlled study that ASCT after 'modern' induction does little to improve their outcome—10% increase in MRD negativity (European MCL Network "Younger" trial)
  - Data also exists that even a patient in a MRD negative CR1 does not have an improved survival after an ASCT as compared to maintenance rituximab, followed by as needed, effective salvage from therapies such as CAR-T cell therapy

ASCT for Mantle Cell NHL: 2022

- There is hope however for improving OS in the future:
  - Enhanced induction and maintenance with effective novel targeted therapies (Triangle Study)
  - Novel immune therapies: CAR-T, BiTes
  - Re-consideration of this NHL as a chronic NHL, like follicular NHL, with the the focus on minimally toxic yet effective initial therapy which can lead to years of healthy life, with curative therapies like allografts and ? CAR-T therapies utilized for late stage disease



European Triangle Study: results in 2026

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ARS Question

Given the toxicities both long and short term for ablative autotransplants for lymphoma the primary goal of a transplant should be to:

1. Increase remission duration
2. Increase disease-free survival
3. Increase time to next therapy
4. Increase overall survival