

Tratamiento de primera linea para linfoma de células de manto en LATAM: es TRIANGLE el nuevo estándar? *Si*

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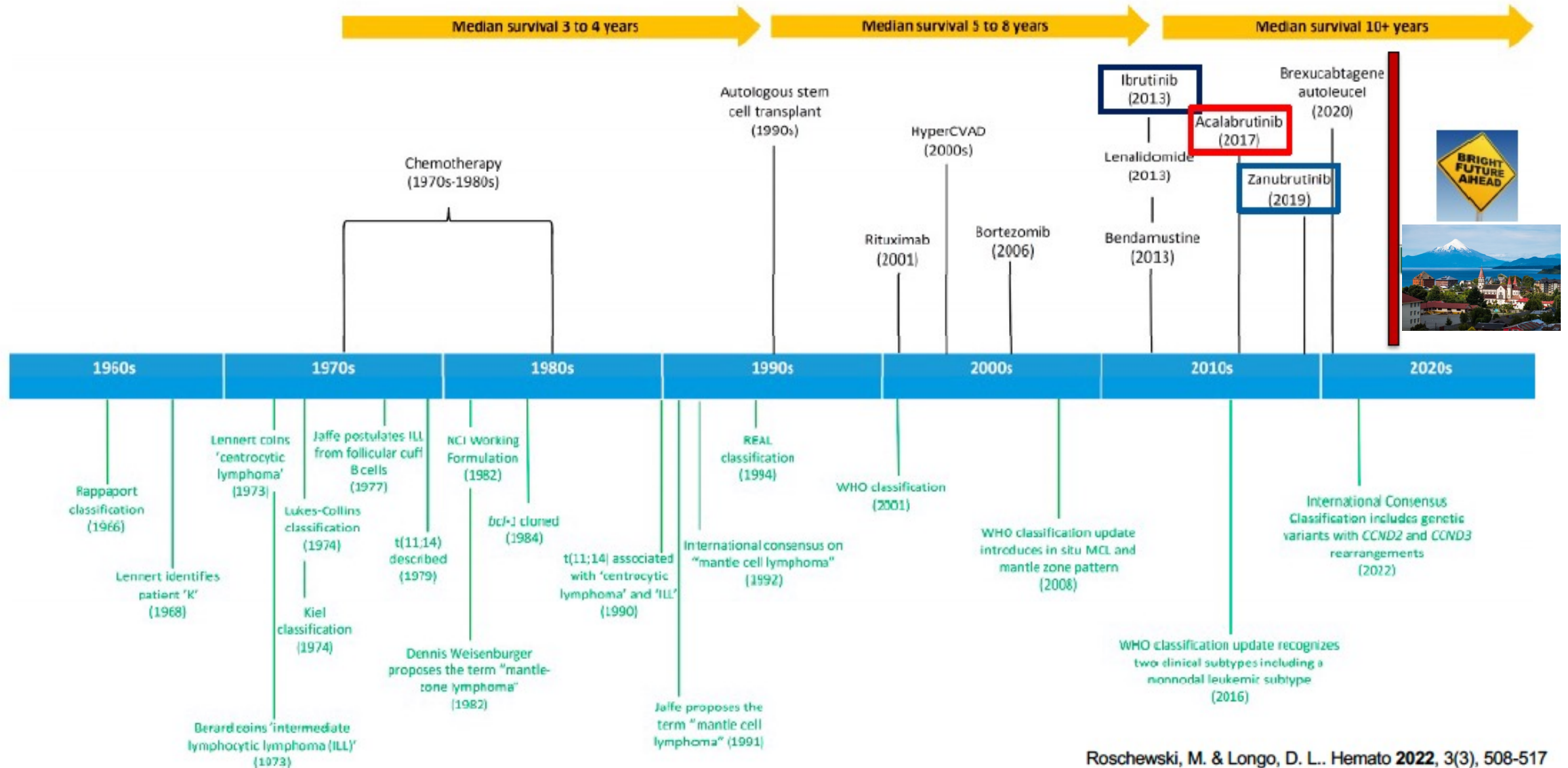
Conflicts of Interest

- **Speaker:** Pfizer
- **Advisory Board:** Janssen, MassiveBio, ADC therapeutics, Genmab, BeiGene, AbbVie, BMS, Genentech, Roche, Novartis, Acrotech.

Mantle cell lymphoma (MCL)

- Uncommon B-cell NHL (~6%) with a median age at diagnosis of 68 years and is most prevalent in men.
- Most cases have cyclin-D1 overexpression via t(11;14) but there are other important pathogenic mutations affecting cell cycle (CDKN2), epigenetic regulation (KMT2D), DNA damage repair (TP53 and ATM), etc.
- For the most part patients present with stage III-IV involving BM and GI tract.
- Special subtype: Leukemic non-nodal MCL
- **Currently not curable but very treatable (the “in between B cell NHL”)**
- **The goals should be:**
 - ✓ **Treat when appropriate.**
 - ✓ **Long lasting disease control with improvement of QoL and survival**

The diagnostic and therapeutic evolution of MCL



Examples of Triangles in Daily Life



Roof Trusses



Bridges



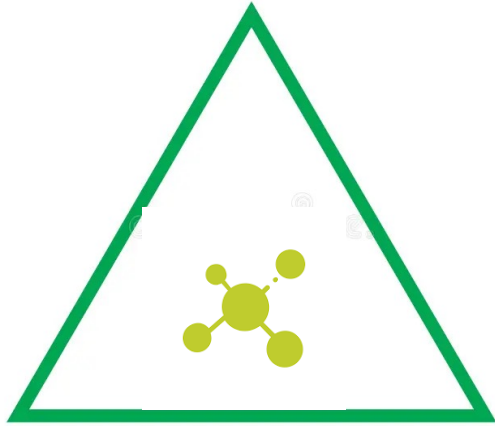
Traffic Signs



Bicycle Frames



Pyramids



EUROPEAN

mcl

NETWORK



Ibrutinib + CIT with or without AutoHCT vs CIT with AutoHCT in younger pts with previously untreated MCL:

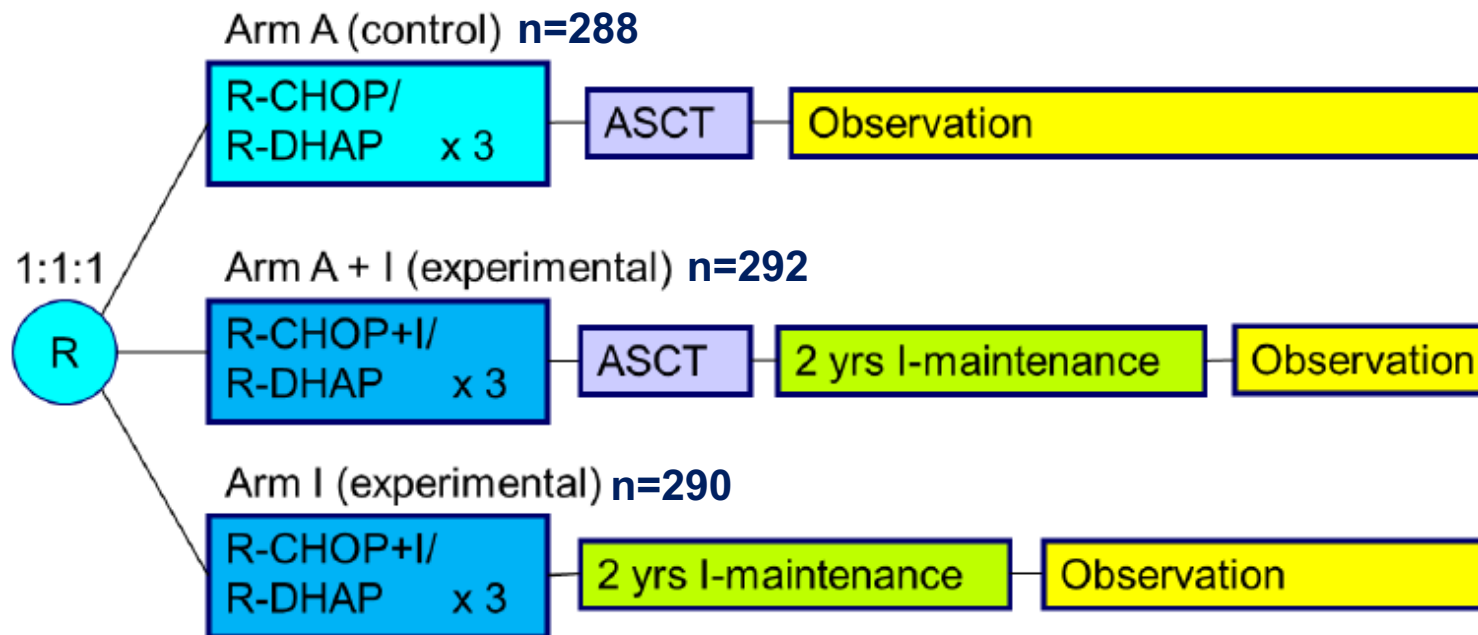
TRIANGLE TRIAL (Phase III RCT)

- Previously untreated AutoHCT eligible stage II-IV MCL pts (≤ 65 yo).

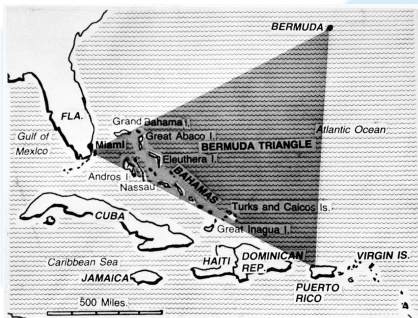
• **Primary Outcome:** FFS

• **Secondary outcome:**

- ✓ RR
- ✓ PFS
- ✓ OS
- ✓ Safety



- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 67% (N=155), 64% (N=151), 59% (N=159) of A/A+I/I randomized patients.

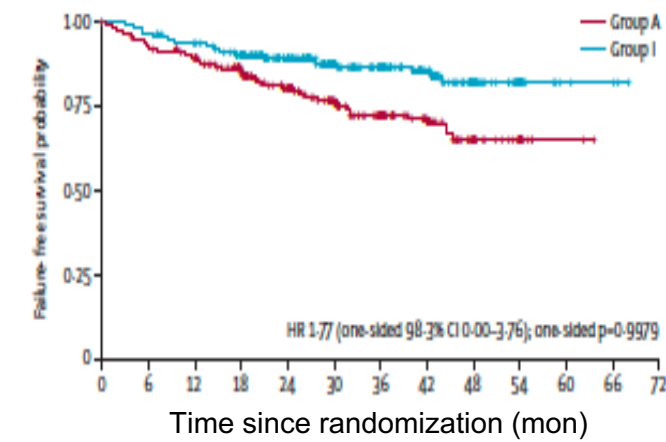
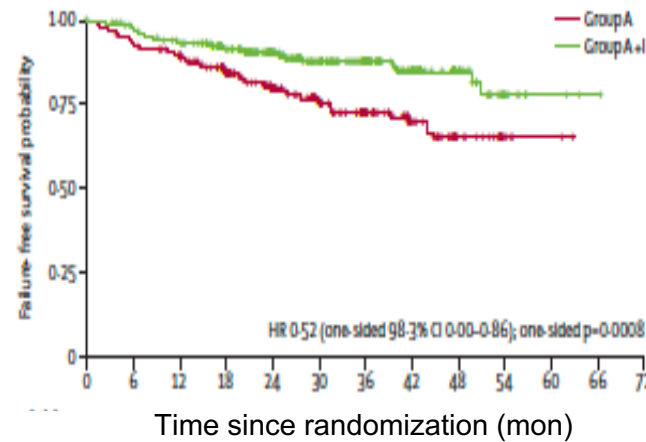


TRIANGLE TRIAL: Baseline characteristics

Characteristic	Group A (n = 288)	Group A+I (n = 292)	Group I (n = 290)
Median age, yr (range)	57 (52-61)	57 (52-61)	57 (52-61)
Stage III-IV	96%	96%	94%
MIPI score			
Low	58%	58%	58%
Intermediate	27%	27%	27%
High	14%	15%	16%
Ki67 index \geq 30%	33%	31%	32%
Blastoid	11%	13%	12%
P53 expression > 50%	11%	14%	16%

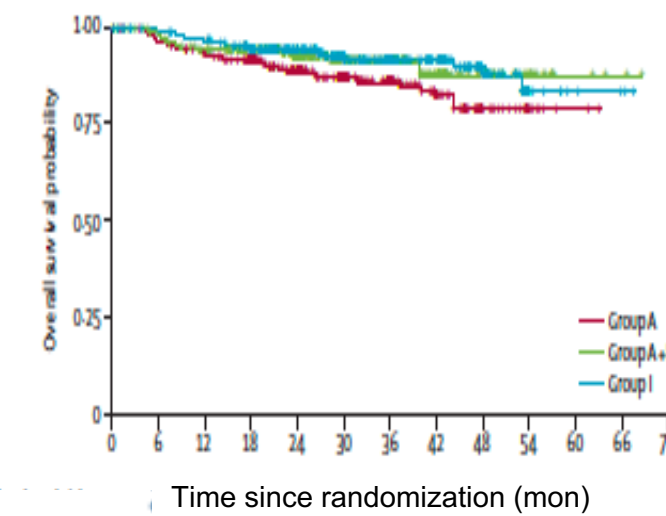
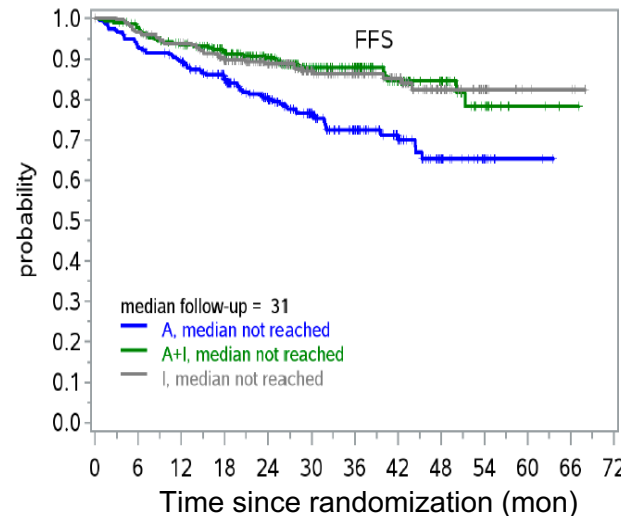
TRIANGLE TRIAL: Results (median f/up: 31 months)

	Ibrutinib +/- AutoHCT (n=559)	AutoHCT (n=272)	P-Value
ORR, %	98%	94%	0.0025
CR, %	45%	36%	0.0203



FFS and OS: Ibru + AutoHCT vs. AutoHCT

	Ibrutinib + AutoHCT (n=292)	AutoHCT (n=288)	P-Value
3-yo FFS, %	88%	72%	0.0008
3-yo OS, %	91%	86%	-

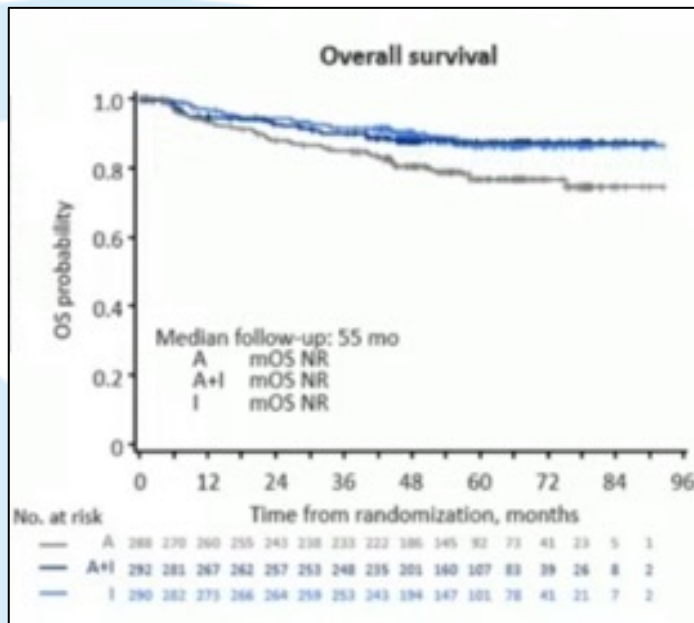


FFS and OS: AutoHCT vs. Ibru w/o AutoHCT

	AutoHCT (n=288)	Ibrutinib (n=290)	P-Value
3-yo FFS, %	72%	86%	0.9979
3-yo OS, %	86%	92%	-

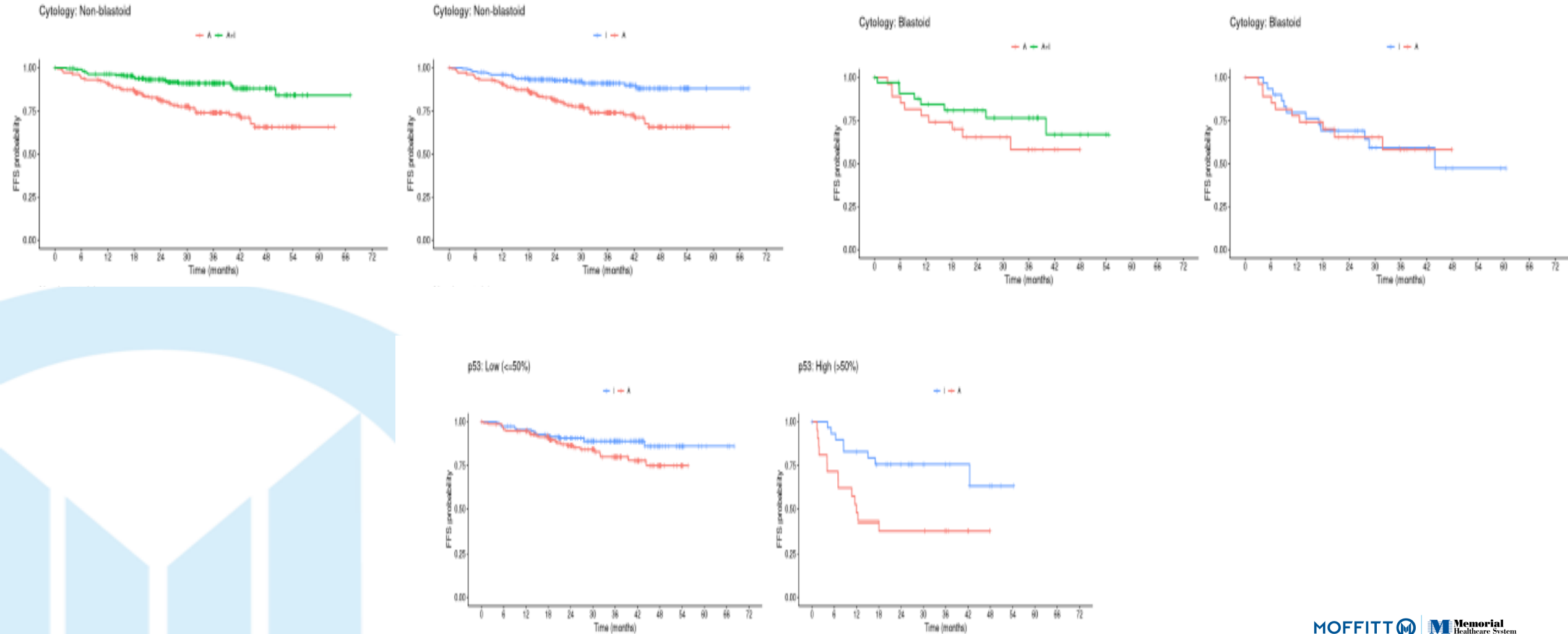
TRIANGLE TRIAL: Results (median f/up: 55 mon)

Regimens	4-Yr FFS, %	HR	P Value	Comparison
A + I vs A	82 vs 70	0.64	.0026	Superiority
A vs I	70 vs 81	1.29	.9890	Superiority rejected with A vs I Retrospective superiority with I vs A ($P = .0208$)
A + I vs I	82 vs 81	.83	.21	Superiority rejected

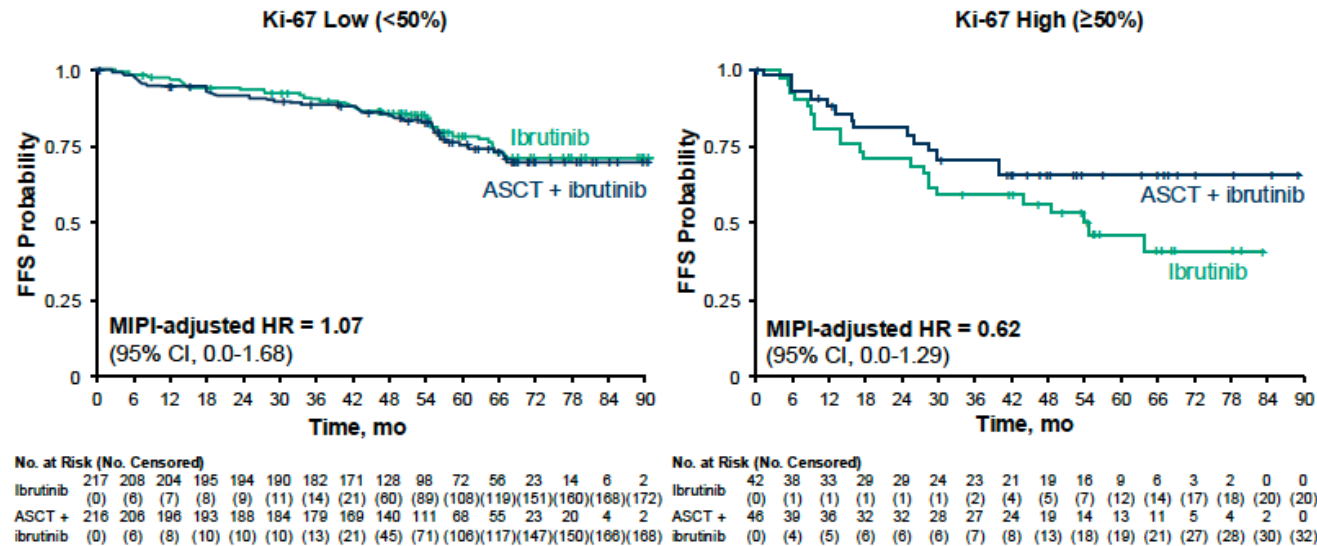
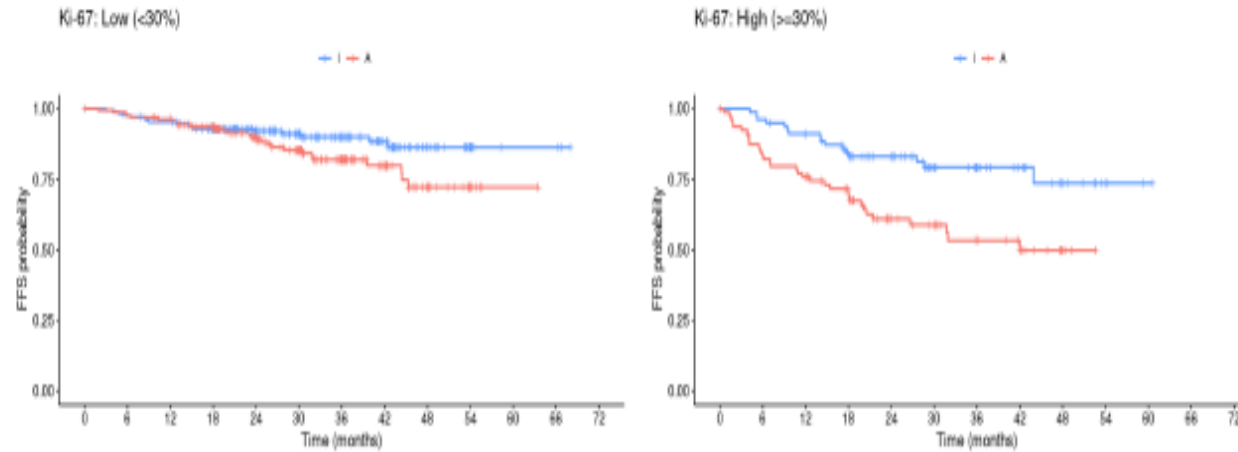


- 3-year OS 85% → Arm A
- 3-year OS of 90% → Arm A+I ($p=0.0069$, HR 0.61).
- 3-year OS of 91% in I ($p=0.0041$, HR 0.59).

TRIANGLE TRIAL: Results (median f/up: 53 mon)



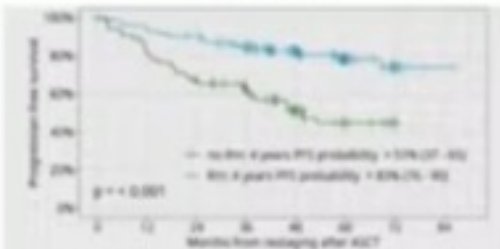
Could there be a role AutoHCT + BTKi in some patients with high risk MCL?



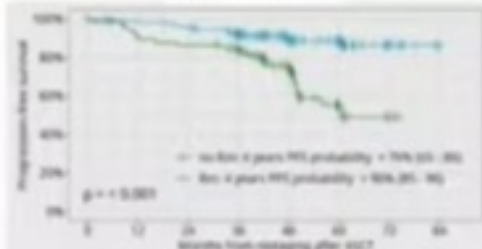
Impact of Rituximab Maintenance Added to Ibrutinib-Containing Regimens with and without ASCT in Younger, Previously Untreated MCL Patients: An Analysis of the Triangle Data Embedded in the Multiply Project

PFS according to Rm

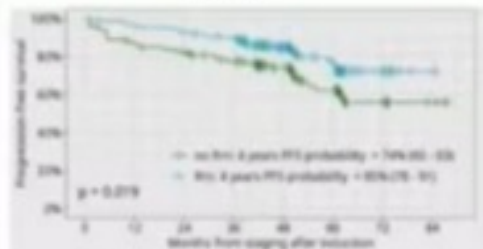
ARM A



ARM A + I



ARM I



Endpoint PFS from end of induction/ASCT

Variables

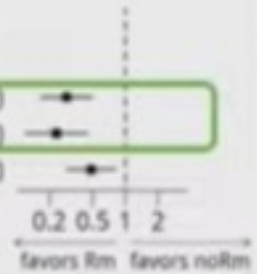
HR (95% CI)

Adjusted for MIPI, Ki67, cytology response after induction/ASCT

Rm vs. noRm in A 0.29 (0.17 - 0.49)

Rm vs. noRm in A+I 0.23 (0.12 - 0.44)

Rm vs. noRm in I 0.48 (0.29 - 0.81)



Benefit appears greater in A and A+I

4 year PFS (KM):

✓ Arm A

- 83% RM vs. 54% no RM (log-rank p <0.001)

✓ Arm A+I

- 89% RM vs. 75% no RM (log-rank p <0.001)

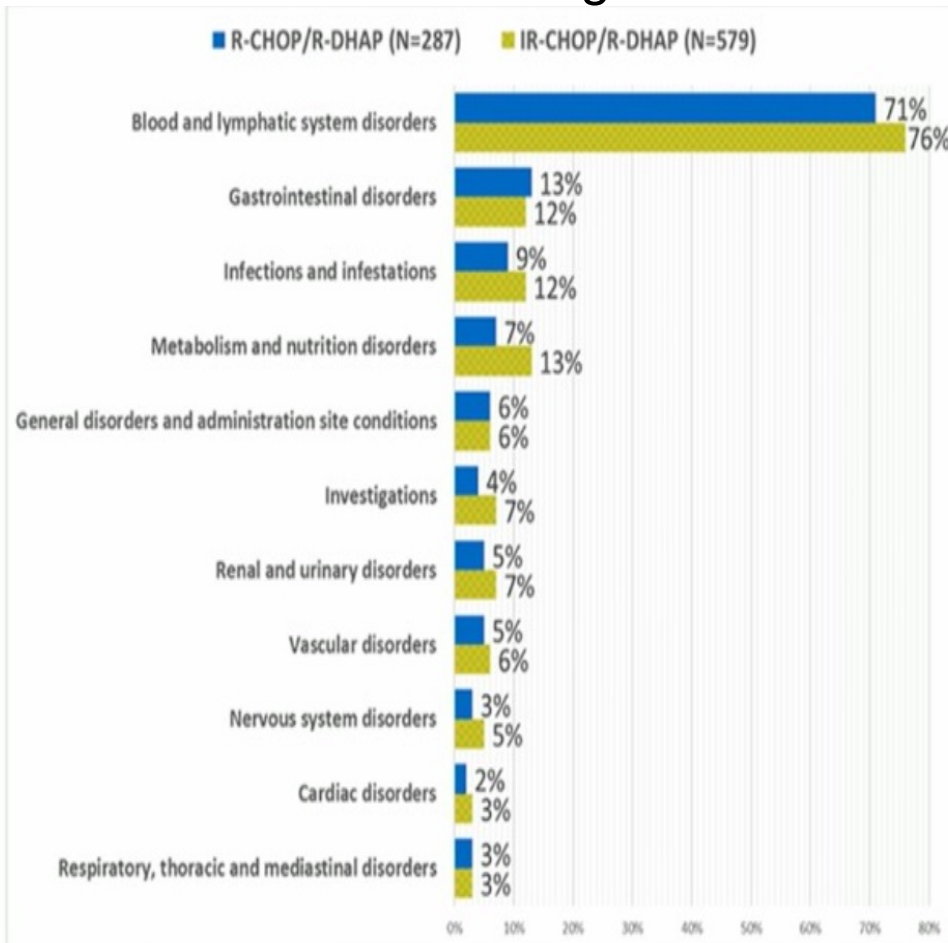
✓ Arm I

- 86% RM vs. 76% no RM (log-rank p <0.016)

- No differences in PFS according to histology or TP53 mut status
- No differences in OS

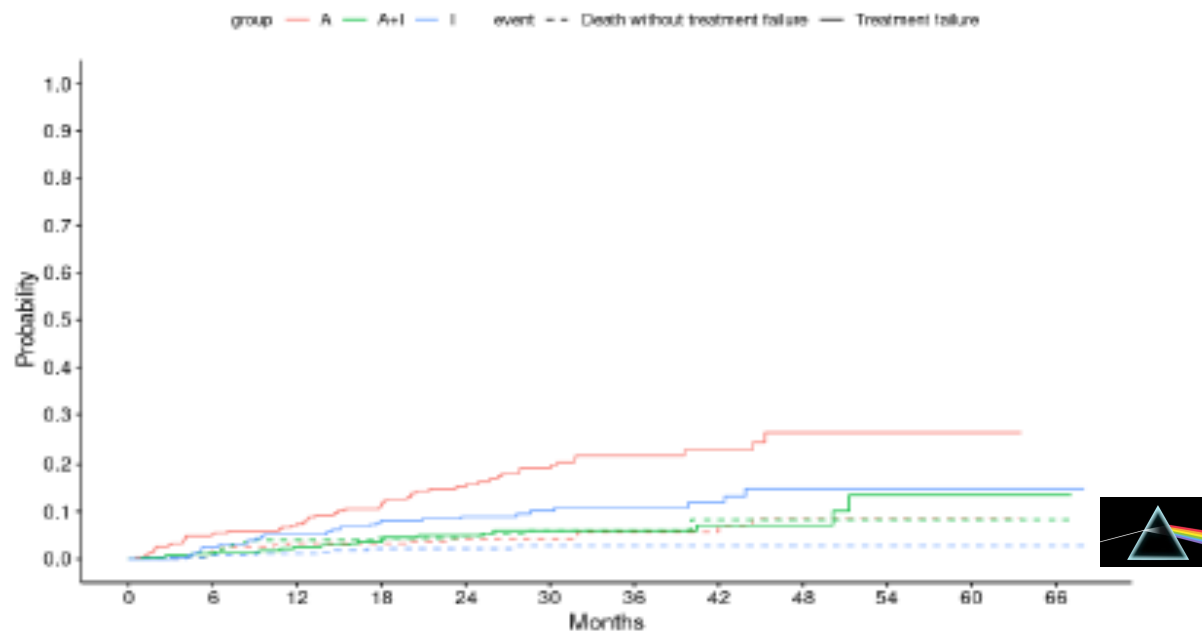
TRIANGLE TRIAL: AEs and causes of death

During induction tx, ibrutinib was associated with higher AEs.

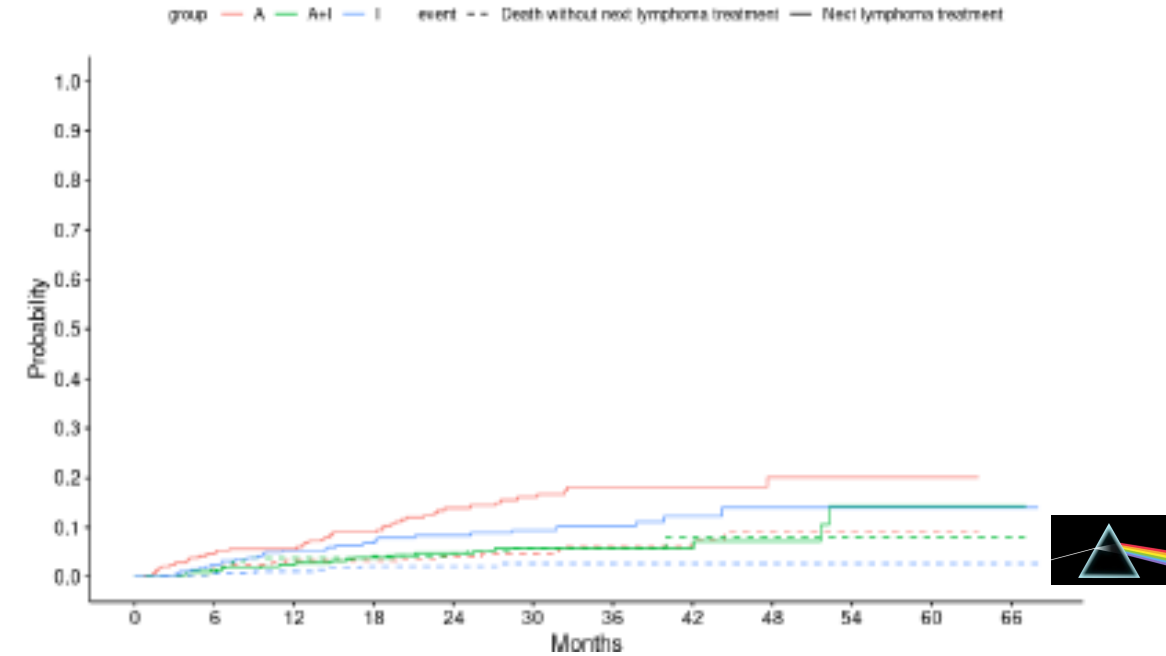


Cause of death	A n=39/288 (13,5%)		A+I n=25/292 (8,6%)		I n=23/290 (7,9%)	
Lymphoma	16	5,6%	4	1,4%	11	3,8%
Concomitant disease	11	3,8%	7	2,4%	5	1,7%
Lymphoma and concomitant disease	0	0%	1	0,3%	1	0,3%
Secondary malignancy	1	0,3%	2	0,7%	0	0%
Therapy	4	1,4%	3	1,0%	0	0%
Therapy and concomitant disease	1	0,3%	0	0%	0	0%
Unknown	6	2,1%	8	2,7%	6	2,1%

Cumulative incidence of **tx failure** and **death without tx failure** for three treatment groups



Cumulative incidence of **next lymphoma tx** and **death without next lymphoma tx** for three treatment groups



What is the current role of AutoHCT in MCL?

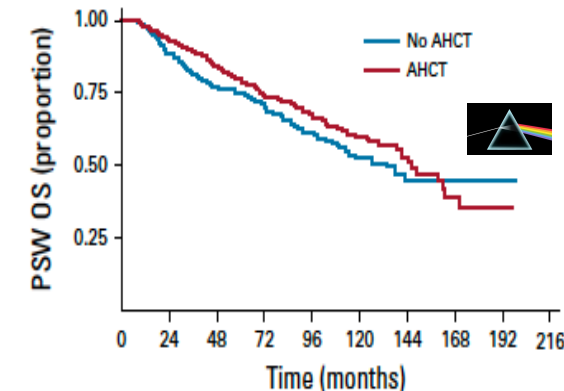
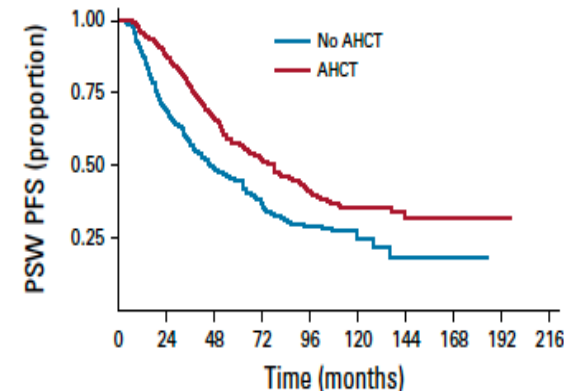
Selected Studies of Auto-HCT for MCL

Study, Year Published [Reference]	No. of Patients	Induction	High-Dose Therapy Regimen	Maintenance	NRM, %	Follow-up, mo	PFS	OS
Dreyling et al., 2005 [22]	122	CHOP-like	Cyclo/TBI	None	3.2	25	Auto-HCT 39 mo vs IFN 17 mo ($P = .01$)	Auto-HCT: 83% vs IFN: 77% ($P = .18$)
Delarue et al., 2013 [32]	60	RCHOP × 3 + RDHAP × 3	TAM6 BEAM HD-Cy	None	1.6	67	64% (5-year)	75% (5-year)
Geisler et al., 2008 [30]	160	Maxi-CHOP × 3 + HD-Cy × 2	BEAM BEAC	None	NA	47	73% (4-year)	81% (4-year)
Hermine et al., 2016 [33]	497	RCHOP × 6 vs RCHOP/RDHAP × 6	Cyclo/TBI or AraC Mel/TBI	None	3.4	73.2	45% (CHOP) 73% (DHAP) (5-year)	69% (CHOP) 76% (DHAP) (5-year)
Le Gouill et al., 2017 [14]	299	4 × RDHAP	R-BEAM	Rituximab vs none	NA	54.4	67.8% (4-year)	78% (4-year)
Le Gouill et al., 2020 [66]	86	O-DHAP	O-BEAM	Obinutuzumab	NA	14.6	94% (1-year)	96% (1-year)

Year	Trial	Relevant design	Age, y	Outcome
2005	European MCL Network ^{4,17}	(R)-CHOP → ASCT vs (R)-CHOP → interferon- α	≤65	Median PFS: 3.3 y vs 1.5 y favoring ASCT Median OS: 7.5 y vs 4.8 y in all patients regardless of receiving R
2022*	TRIANGLE ⁴⁵	Ibrutinib + R-CHOP/R-DHAP → maintenance Ibrutinib + R vs R-CHOP/R-DHAP → ASCT → maintenance R	≤65	3-y FFS: 86% vs 72% favoring omission of ASCT when ibrutinib included in induction and maintenance

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

Variable	All Patients	No AHCT	AHCT	P
Patients	1,029 (100)	372 (36)	657 (64)	
Reason for no transplantation	NA		NA	NA
Clinician choice		249 (67)		
Patient preference		66 (18)		
Other		12 (3)		
Missing		45 (12)		
Sex				.62
Female	240 (23)	90 (24)	150 (23)	
Male	789 (77)	282 (76)	507 (77)	
Age, years				< .01
Median	57	58	56	
Range	22-65			
Cytogenetics				.05
Normal	674 (65)	231 (60)	443 (68)	
p53	28 (3)	11 (3)	17 (3)	
Complex	87 (8)	26 (7)	61 (9)	
Missing	240 (24)	104 (31)	136 (20)	
Cyclin D1				.73
Positive	915 (89)	327 (89)	588 (90)	
Negative	40 (4)	16 (4)	24 (3)	
Missing	74 (7)	29 (7)	45 (6)	
Induction				< .01
CHOP-like	443 (43)	158 (44)	285 (43)	
Intensive*	454 (44)	147 (39)	307 (47)	
Bendamustine based	119 (11)	56 (15)	63 (10)	
Other	13 (1)	11 (2)	2 (1)	
Anti-CD20 with induction				< .01
Yes	973 (95)	342 (92)	631 (96)	
No	56 (5)	30 (8)	26 (4)	
Cytarabine with induction				< .01
No	556 (54)	229 (61)	327 (50)	
Yes	473 (46)	143 (38)	330 (50)	
Novel agent with induction				< .01
No	1,003 (97)	353 (95)	650 (99)	
Yes	26 (3)	19 (5)	7 (1)	
Response to induction				.54
CR	783 (76)	279 (75)	504 (77)	
PR	246 (24)	93 (25)	153 (23)	
Maintenance				< .01
No	644 (62)	216 (57)	428 (65)	
Rituximab	306 (30)	107 (30)	199 (30)	



	Weighted No. at risk:									
AHCT	370	236	140	76	36	14	7	3	0	0
No AHCT	636	484	290	165	79	33	14	4	1	0

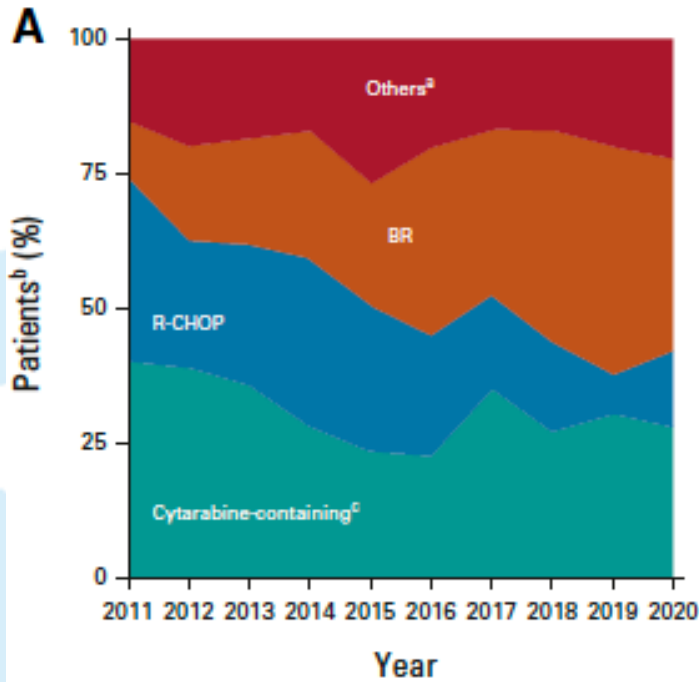
Survival	HR	95% CI	P
PFS (n = 1,003)	0.70	0.59 to 0.84	< .01
OS (n = 1,003)	0.87	0.69 to 1.10	.24

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PSW, propensity score weighted.

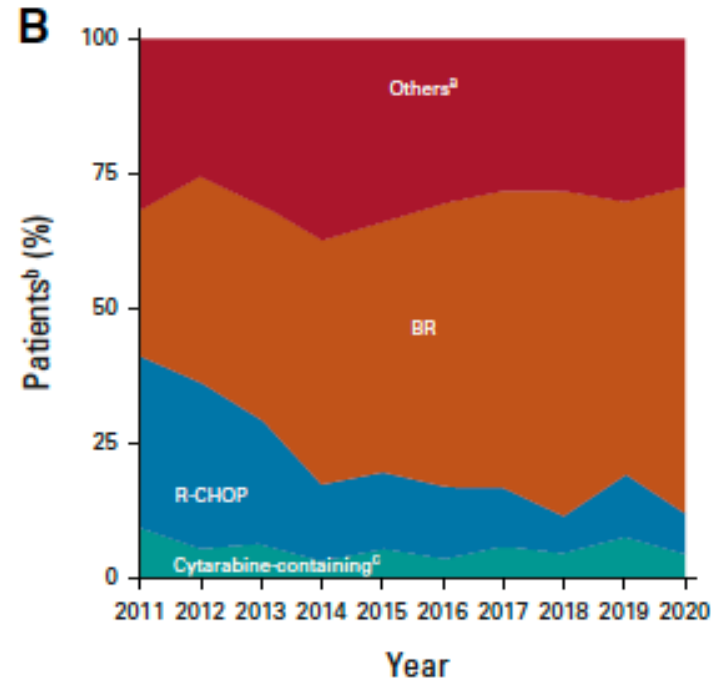
Treatment Outcomes and Roles of Transplantation and Maintenance Rituximab in Patients With Previously Untreated Mantle Cell Lymphoma: Results From Large Real-World Cohorts

First line Tx in MCL by age and year

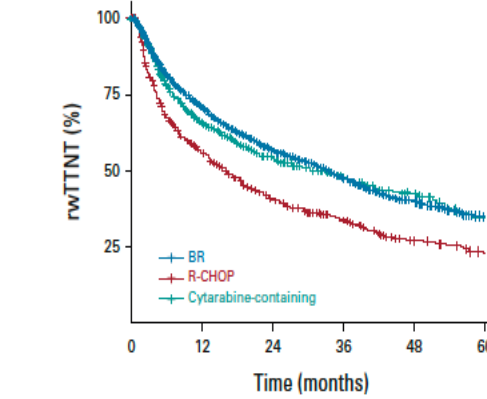
Pts < 65 years (N=1,265)



Pts ≥ 65 years (N= 2,329)



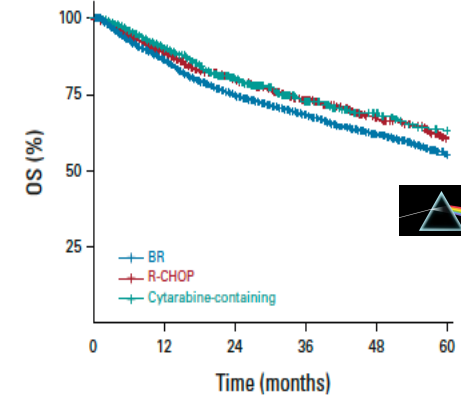
B



Patients at risk:

	BR	R-CHOP	Cytarabine-containing
BR	1,501	898	612
R-CHOP	636	326	217
Cytarabine-containing	514	283	196

	BR n = 1,501	R-CHOP n = 636	Cytarabine-containing n = 514
Median rwTTNT (95% CI), months	34.4 (31.1 to 37.9)	16.0 (13.2 to 19.0)	31.0 (24.2 to 41.7)
rwTTNT rate at 3 years, % (95% CI)	48 (45 to 51)	34 (30 to 38)	48 (43 to 53)

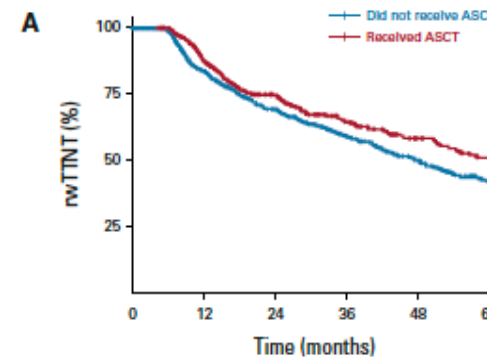


Patients at risk:

	BR	R-CHOP	Cytarabine-containing
BR	1,501	1,079	778
R-CHOP	636	497	408
Cytarabine-containing	514	382	286

	BR n = 1,501	R-CHOP n = 636	Cytarabine-containing n = 514
Median OS (95% CI), months	68.2 (63.8 to 80.9)	79.2 (70.0 to 90.3)	93.4 (80.7 to NE)
OS rate at 3 years, % (95% CI)	68 (66 to 71)	74 (70 to 77)	73 (68 to 77)

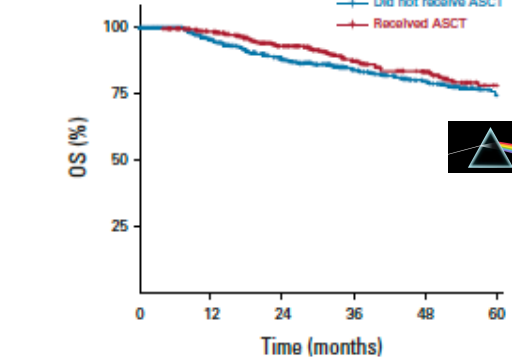
A



No. at risk:

	Did not receive ASCT	Received ASCT
Did not receive ASCT	680	451
Received ASCT	282	222

	Age < 65 Years and ASCT-Eligible n = 962	
	Received ASCT n = 282	Did Not Receive ASCT n = 680
Median rwTTNT (95% CI), months	53.9 (51.3 to 75.6)	48.3 (41.9 to 53.6)
rwTTNT rate at 3 years, % (95% CI)	65 (59 to 71)	59 (55 to 64)
HR (95% CI)	0.84 (0.68 to 1.03)	
Log-rank test P	.10	

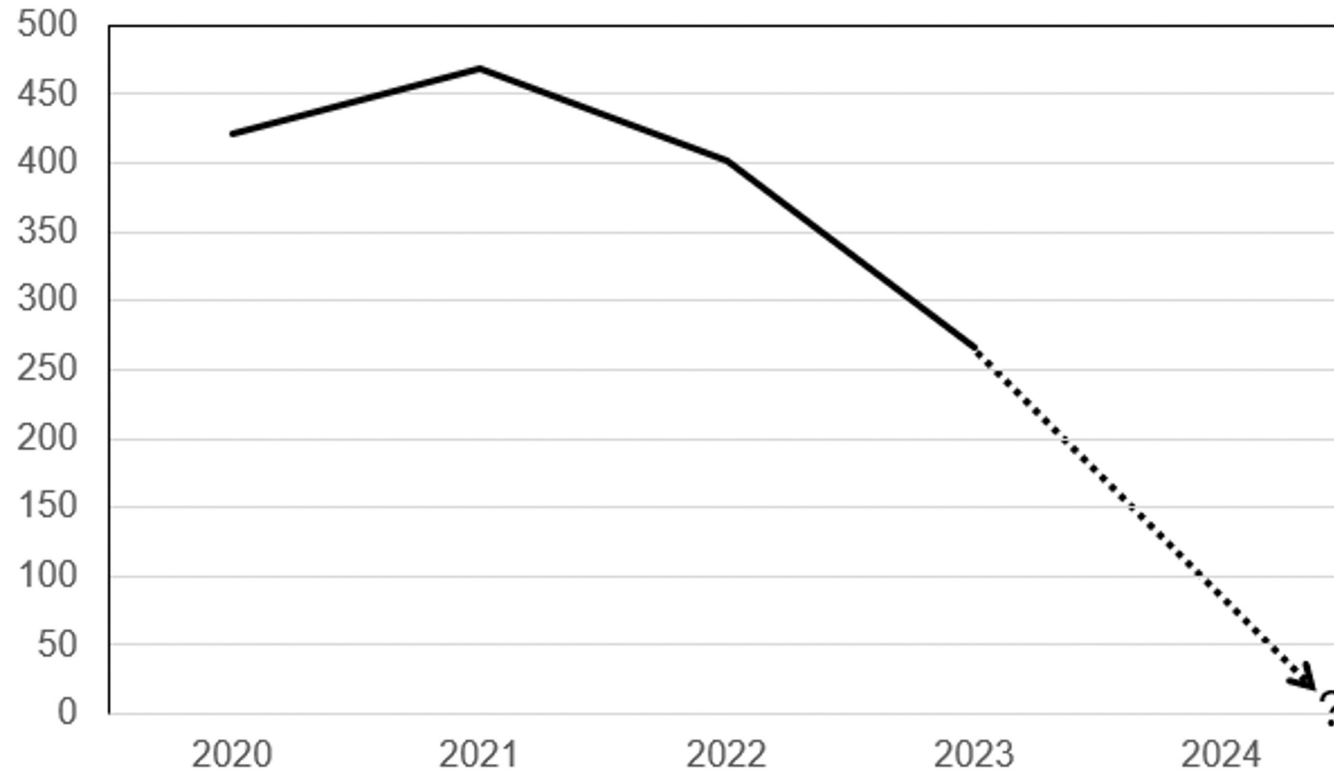


No. at risk:

	Did not receive ASCT	Received ASCT
Did not receive ASCT	680	616
Received ASCT	282	251

	Age < 65 Years and ASCT-Eligible n = 962	
	Received ASCT n = 282	Did Not Receive ASCT n = 680
Median OS (95% CI), months	109 (96.1 to NE)	113 (102.9 to NE)
OS rate at 3 years, % (95% CI)	88 (83 to 92)	84 (81 to 88)
HR (95% CI)	0.86 (0.63 to 1.18)	
Log-rank test P	.4	

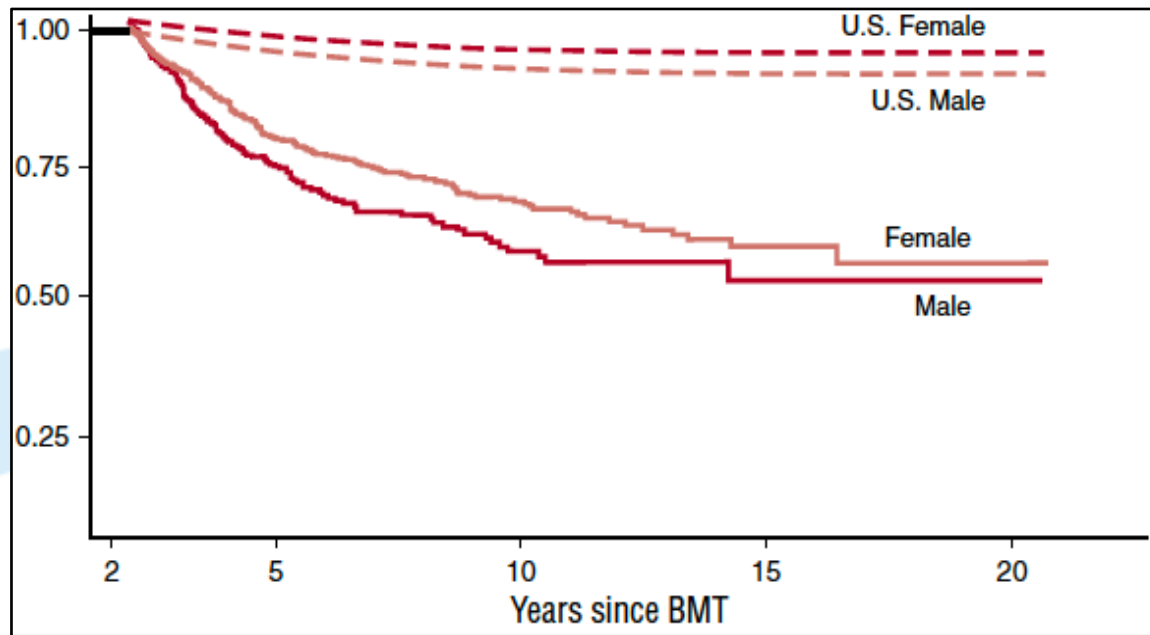
Number of AutoHCT for mantle cell lymphoma (preliminary data from CIBMTR)



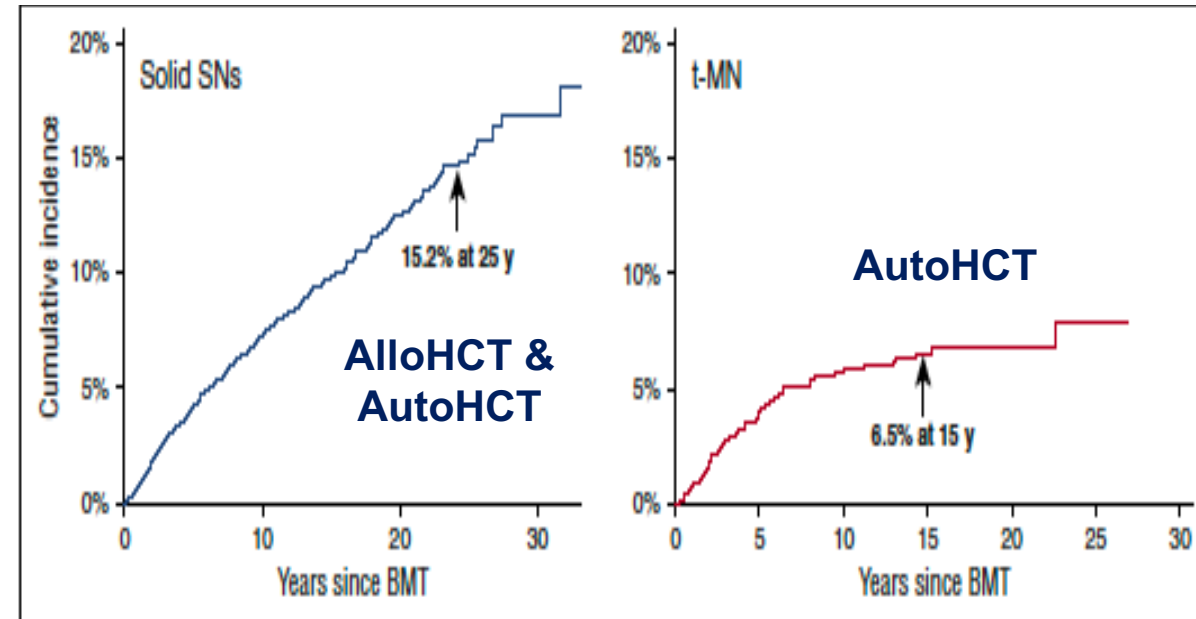
The analysis has not been reviewed or approved by the Advisory Scientific Committees of the CIBMTR.

AutoHCT is NOT a “benign” procedure

Late mortality after BMT (median f/up= 7.6 years)



Subsequent neoplasms after HCT from a single transplant center.



- 854 pts who had survived ≥ 2 years s/p AutoHCT.
- Median age= 36.5 years
- 10 year OS: 68.8%

1. Bhatia S et al. Blood. 2005;105(11):4215-4222.
2. Bhatia S, Bhatia R. Thomas' Hematopoietic Cell Transplantation. 5th ed. New York, NY: John Wiley & Sons, Ltd.; 2016:1275-1289.
3. Bathia S et al. Blood. 2017;130(11):1302-1314

Total late effect burden in long-term lymphoma survivors after high-dose therapy with autologous stem-cell transplant and its effect on health-related quality of life

	Total (N=271)	Low-medium burden (N=142)	High burden (N=129)	P
Sociodemographics				
Age at diagnosis in years, median (range)	42 (10-65)	40 (13-65)	45 (10-64)	0.04
Age at HDT-ASCT in years, median (range)	46 (19-67)	43 (19-66)	48 (19-67)	0.02
Age at survey in years, median (range)	56 (24-77)	53 (24-73)	59 (24-77)	0.001
Time diagnosis to survey in years, median (range)	12 (3-34)	11 (3-31)	13 (4-34)	0.03
Time HDT-ASCT - survey in years, median (range)	8.5 (3-25)	8 (3-25)	9.5 (3-25)	0.04
Female sex, N (%)	104 (38)	46 (32)	58 (45)	0.03
In a relationship ^a , N (%)	199 (74)	104 (74)	95 (74)	0.98
Education <13 years, N (%)	140 (52)	75 (53)	65 (51)	0.69
Unemployed, N (%)	68 (25)	23 (16)	45 (35)	<0.001
Household income low ^b , N (%)	145 (54)	66 (47)	79 (62)	0.01
Lymphoma and treatment				
Lymphoma type				0.32
Hodgkin lymphoma, N (%)	61 (23)	29 (20)	32 (25)	
Aggressive non-Hodgkin lymphoma ^c , N (%)	182 (67)	101 (71)	81 (63)	
Indolent non-Hodgkin lymphoma ^d , N (%)	28 (10)	12 (9)	16 (12)	
Stage III-IV at diagnosis, N (%)	186 (69)	96 (68)	90 (70)	0.77
B-symptoms at diagnosis, N (%)	95 (36)	38 (27)	57 (45)	<0.01
High-dose regime				0.04
Total body irradiation, N (%)	38 (14)	14 (10)	24 (19)	
BEAM, N (%)	233 (86)	128 (90)	105 (81)	

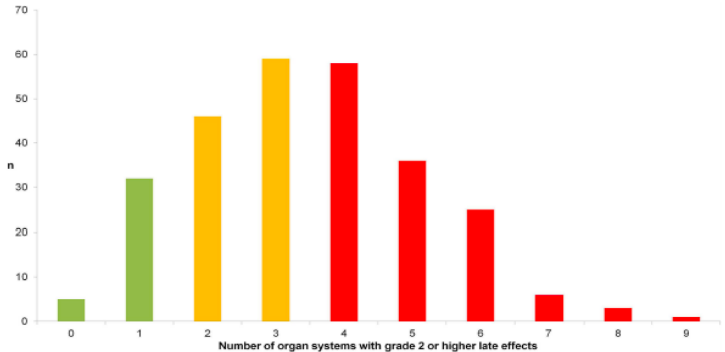
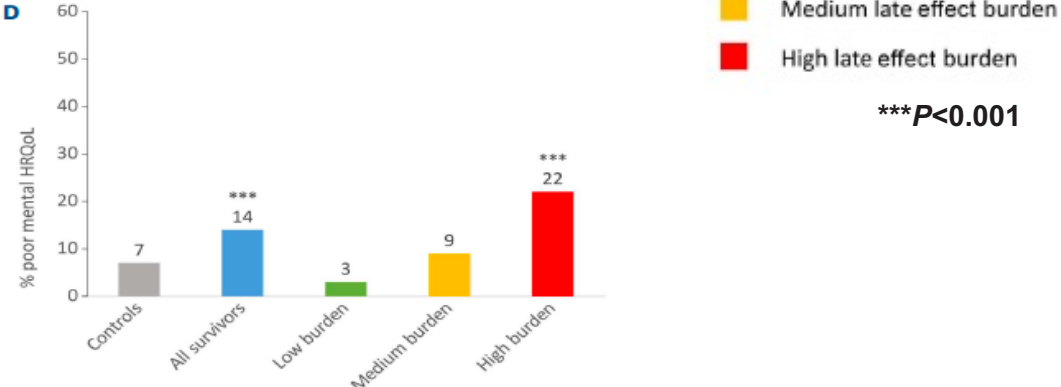
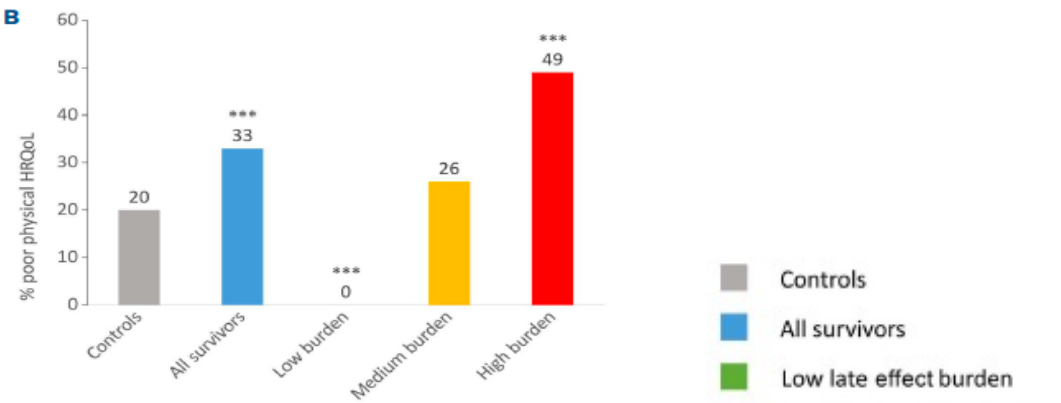
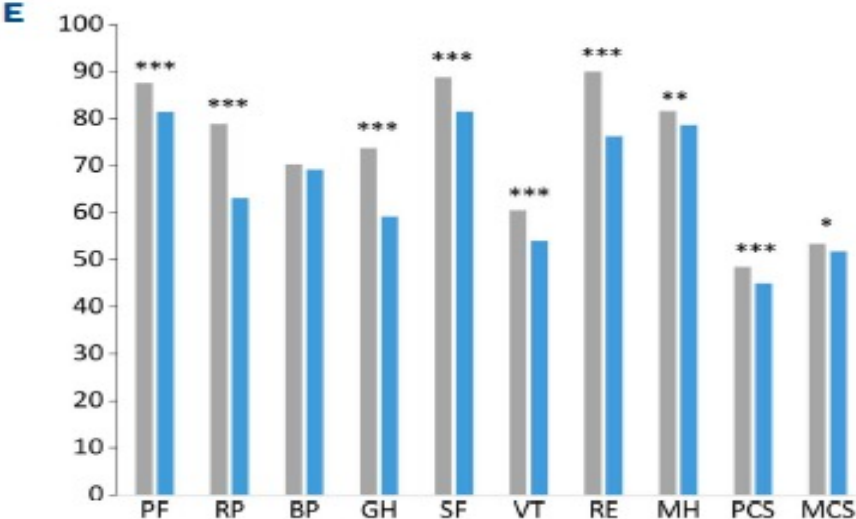


Figure 2. Number of organ-system categories with grade 2 or higher late effects per survivor. Green (0-1 organ system): low late effect burden (n=37); orange (2-3 organ systems): medium late effect burden (n=105); red (>3 organ systems): high late effect burden (n=129).



***P<0.001



*P<0.05, **P<0.01 and ***P<0.001.

What is the reality of our MCL patients in some (all?) LMIC?

Comparative Analysis of Novel Versus Standard High-Cost Therapies: The Role of Autologous Stem Cell

Transplantation for Mantle Cell Lymphoma in LMICs

Cristobal Augusto Frutos Ortiz, MD¹, Maria Elvira Enciso Arrua, MD², Aline Nicole Paats, MD², Lidiane Katherine Andino Neves, MD³, Victor Ladislao Salinas, MD^{2,4}, Dra. Milva Ibarrola, MD⁵, Luis Enrique Malpica Castillo, MD⁶, Bryan Valcarcel⁷

Blood 144 (2024) 7723–7724



Results

In the 5-years of the study period, a total of 42 patients with either Hodgkin (n=24) or non-Hodgkin lymphoma (n=18, 1 case with advanced NK T cell lymphoma) received auto-SCT as either consolidation (n=5) or upon relapse (n=37). The cost of auto-SCT in all these patients was determined to be \$26,000 USD (range: \$18,000 - \$43,000 USD), noting that no transplanted patient required an ICU admission and that all patients received BEAM (with or without rituximab) as conditioning regimen. Of these patients, 7 had MCL and received auto-SCT as either consolidation at first remission (n=3) or upon relapse (n=4). With a median follow up of 24.3 months, the median OS and PFS of the 7 MCL patients were 29.1 months and 28.7 months with a 2-year PFS and OS of 83%, respectively; 2 patients with refractory disease that received auto-SCT after 2nd and 3rd line of therapy died after 30 months and 3 months of being disease free post SCT, respectively.

During the study period, the cost of ibrutinib was obtained from publicly available online data on hospital purchases. IPS purchased ibrutinib at \$70 USD per capsule. Given current recommendations of during of therapy with ibrutinib of at least 2 years, the regimen of four capsules per day for 2 years (730 days) resulted in a total cost of \$204,400 USD. The use of generic ibrutinib did not significantly reduce this cost, offering less than a 1% difference per capsule compared to the brand name.

Discussion

The high cost of novel therapeutics, such as ibrutinib, poses significant challenges in LMICs, which already face difficulties with traditional high-cost treatments. While ibrutinib therapy is less toxic than auto-SCT, its cost limits accessibility. Despite the small sample size, the outcomes observed in MCL patients treated at our institution suggest that salvage SCT remains a viable and valuable rescue therapy for patients in LMICs. At a public health system level, the cost of treating one patient with ibrutinib could cover the cost of auto-SCT for approximately seven patients. This cost analysis highlights the need for cost-effective treatment strategies like auto-SCT in LMICs to maximize patient access to effective therapies.

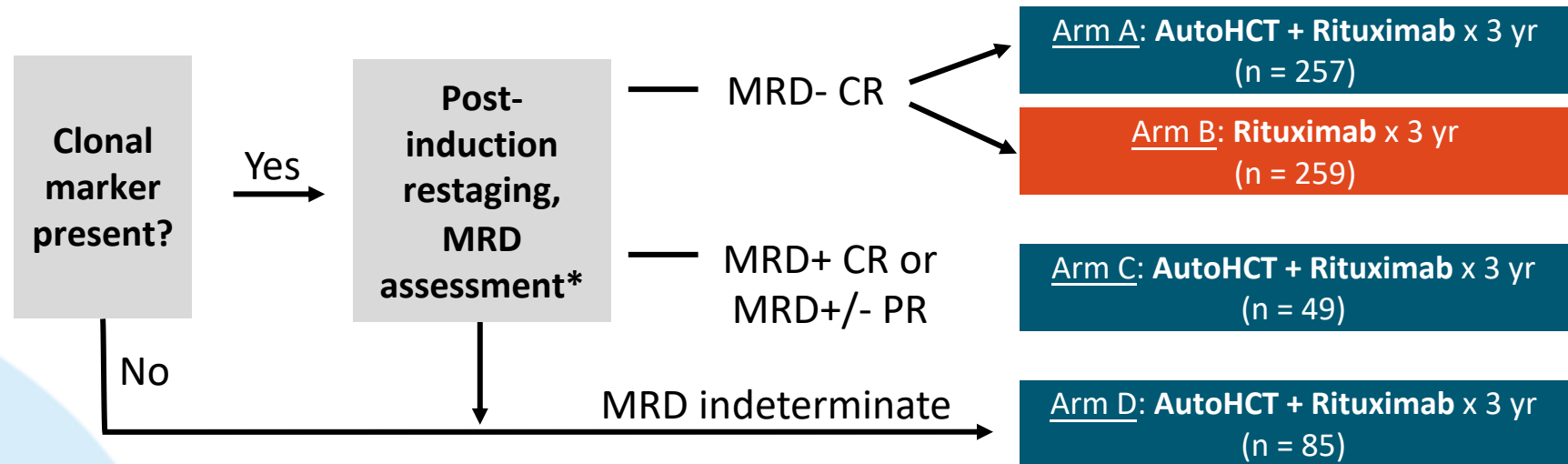
7 pts with MCL underwent AutoHCT

- ✓ 3 for 1st line consolidation
- ✓ 4 at relapse
- ✓ mPFS 28.1 mo
- ✓ mOs: 29 mo
- ✓ 2 y PFS and OS: 83%

ECOG-ACRIN EA4151: Autologous HCT in MRD-Negative Patients With MCL in First Complete Remission

- International, open-label, randomized phase III trial

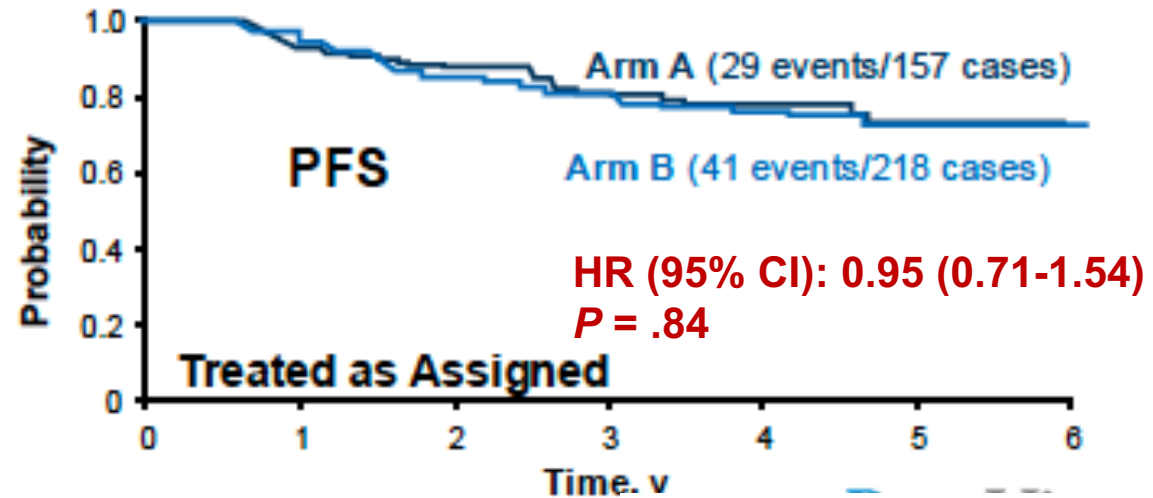
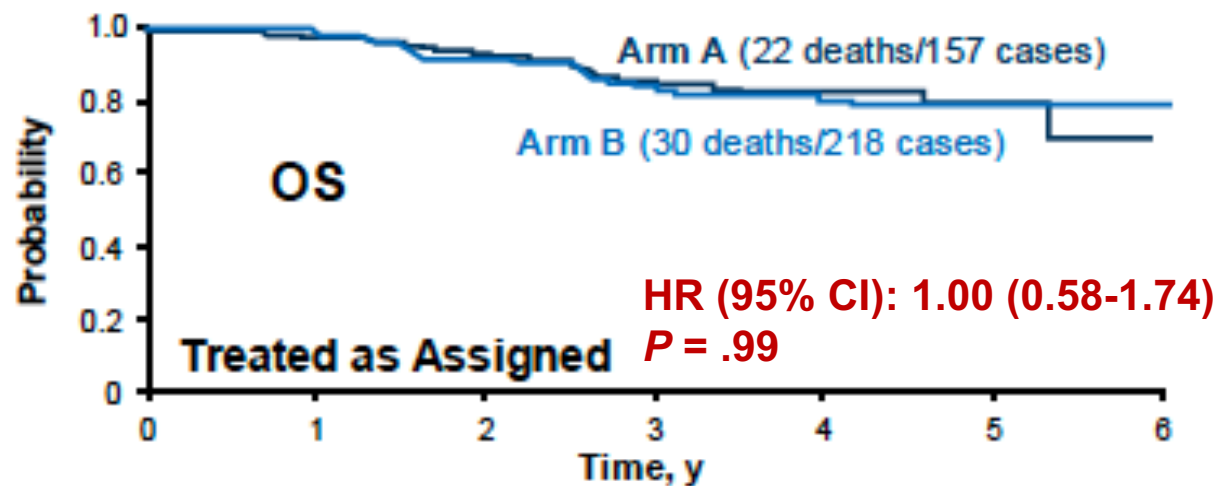
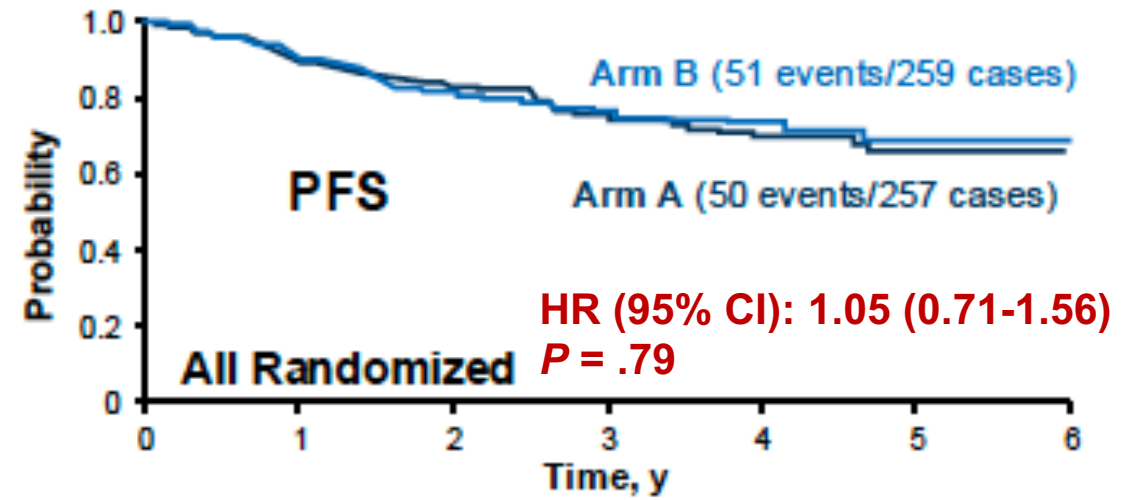
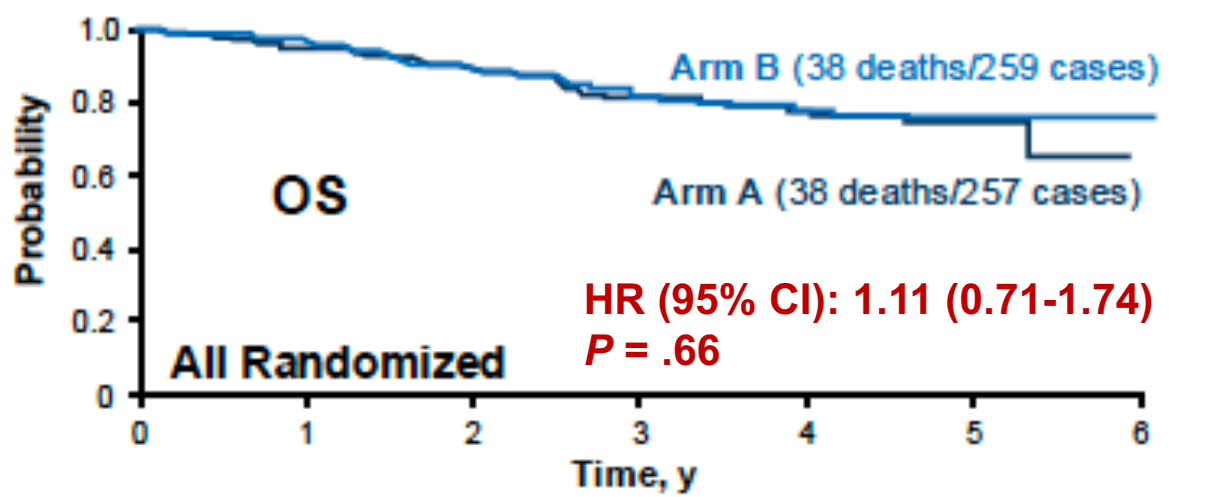
Patients aged ≥ 18 and ≤ 70 yr with MCL in first remission; considered candidates for autoHCT per treating physician; any rituximab-containing induction regimen allowed (including BTKi); if completed induction therapy, must be within 120 days prior to preregistration and < 300 days between first day of therapy and preregistration (N = 650)



- Primary endpoint:** OS (Arm A vs Arm B)
- Key secondary endpoints:** PFS (Arm A vs Arm B), PFS (Arms C and D), MRD conversion rate post autoHCT, safety

*Included PET/CT, bone marrow biopsy, and MRD from peripheral blood measured using clonoSEQ, with a sensitivity of 1×10^{-6} .

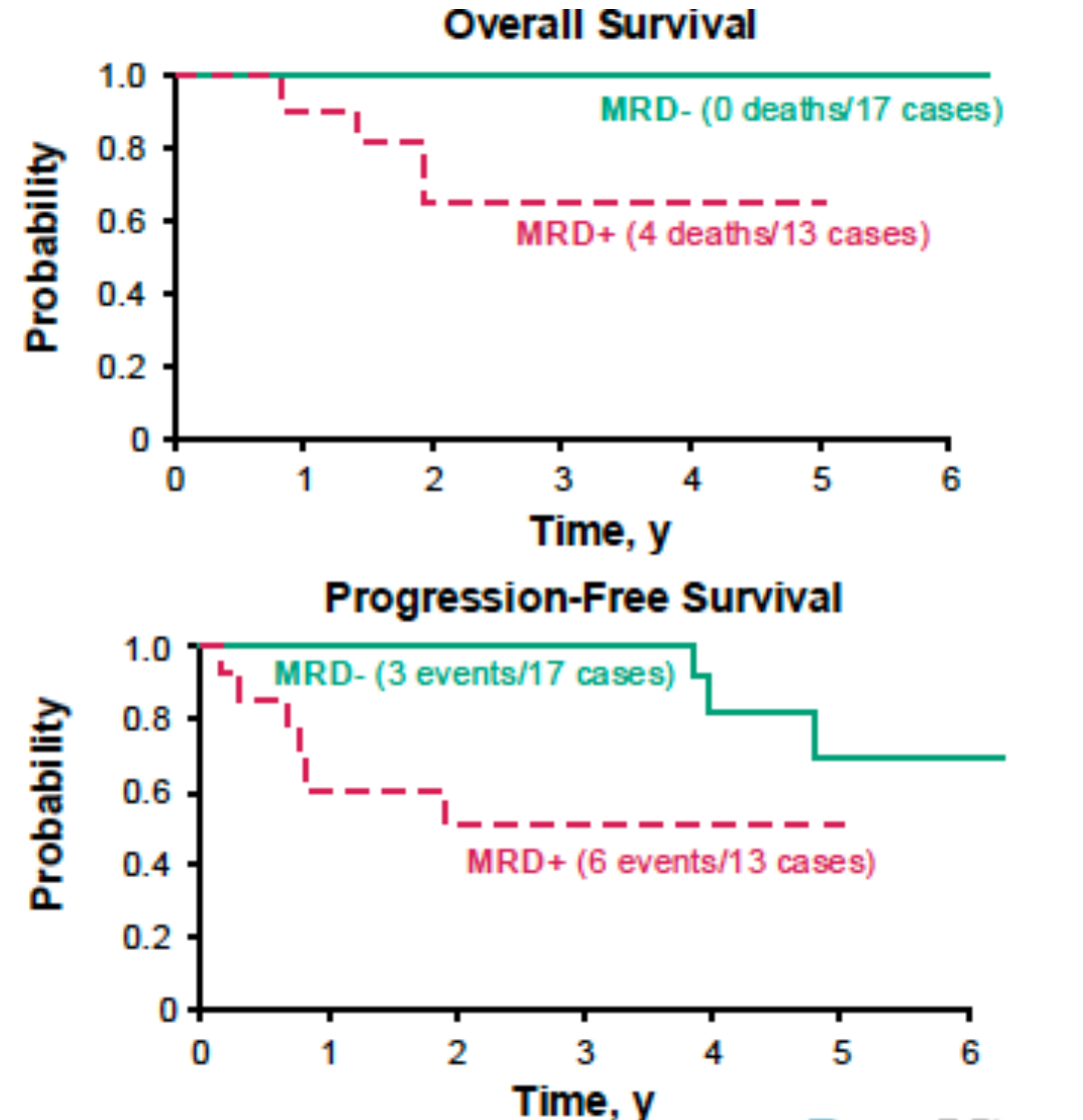
ECOG-ACRIN EA4151: Autologous HCT in MRD-Negative Patients With MCL in First Complete Remission



ECOG-ACRIN EA4151: Could there still be a role for AutoHCT in pts with MRD + (NGS) who are in 1st remission>

Arm C (MRD+ patients) by post-transplant MRD status

- Exploratory analysis of MRD+ patients (arm C) showed that 3-year OS in patients who converted to uMRD6 post auto-HCT (n = 17) was 100% versus 63.6% in those who remained MRD+
- Similarly, 3-year PFS in patients who converted to uMRD6 post auto-HCT was 100% versus 48.8% in those who remained MRD+



Discussing pharmaco-economics of TRIANGLE in the US:

(Parental advisory!: *the speaker doesn't know ANYTHING about this topic!*)

- Ibrutinib in the US: ~\$160,000 per year (~ \$320,000 for 2 years of maintenance).
- Cost of AutoHCT in US: ~\$140,792 (mean hospital stay of 21.8 days).
- Estimated the cost of rituximab maintenance therapy at around ~ \$54,588 for a 12 dose PRIMA regimen (3 years = ~ \$81,882).
- The CLFS rate for clonoSEQ[®] (PLA 0364U) was set at \$2,007 (x 1 test).

1. Patel KK et al. Blood. 2020;136(17):1946-1955
2. <https://www.medicare.gov/find-a-plan/questions/home.aspx>. Accessed 1 November 2019.
3. Chen Q et al. J Clin Oncol, 35 (2) (2017), pp. 166-174.
4. Brother MS et al. Am Health Drug Benefits 2017 Oct;10(7):366–374.
5. Chen Q et al. Value Health. 2015 Mar;18(2):189–197.

Conclusions (Vote SI! for TRIANGLE..sometimes)



- First line treatment of MCL is actively changing and AutoHCT consolidation will disappear (*vanished to the dark side of the moon....*). **Have we ever proven that AutoHCT is useful with non-RCHOP induction regimens + rituximab maintenance?**
- BTKi “augmented” cytarabine-based CIT induction followed by BTKi AND rituximab maintenance (**TRIANGLE approach**) is the SoC for ≤ 65 pts in places where this strategy is feasible.
Would this eliminate the utility of MRD as a predictive marker? How about a sequential approach?
- MRD adapted AutoHCT consolidation with RM after CIT (**EA4151 approach**) could be an alternative if it is cost-effective and reproducible with global external validity.
Would the MRD adapted 1L tx eliminate the benefit of frontline BTKi and save it for later?
- Personalized cancer treatment not only considers the biology of the disease, but multiple other aspects of the patient as a unique individual. Frontline therapy in fit/young MCL patients is not the exception!

Gracias por su atención.



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