22nd

INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 4 - 5, 2025

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22nd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

Role of transplant and cellular therapy in relapsed/ refractory mantle cell lymphoma

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Disclosures

In the past 24 months:

- I have served as a consultant for: AbbVie, Adaptive Biotechnologies, ADC Therapeutics, AstraZeneca, Beigene, Ipsen, Kite (Gilead), Lilly/Loxo and Ono Therapeutics

- I have served as a speaker for: AstraZeneca, Beigene, Kite (Gilead), SeaGen

- I may discuss:
  - on-label indications for the products brexucaptagene autoleucel (Kite/Gilead), acalabrutinib (AstraZeneca), zanubrutinib (Beigene) and pirtobrutinib (Lilly/Loxo),
  - an off-label use of the clonoSEQ assay (Adaptive Biotechnologies)

Outline

- Potential role for transplant and cellular therapy (auto-HCT, allo-HCT, CAR-T) in the management of R/R MCL
  - Auto-HCT
  - Allo-HCT
  - CAR-T
- Special focus on how pts with R/R are likely to be different than in prior years
  - and how this may affect selection of TCT options

Debates in Lymphoma: Autologous SCT *Should* Be a Treatment Option for Relapsed Mantle Cell Lymphoma

Too little too late?
Lesser of two evils?
Or a reasonable option in some cases?

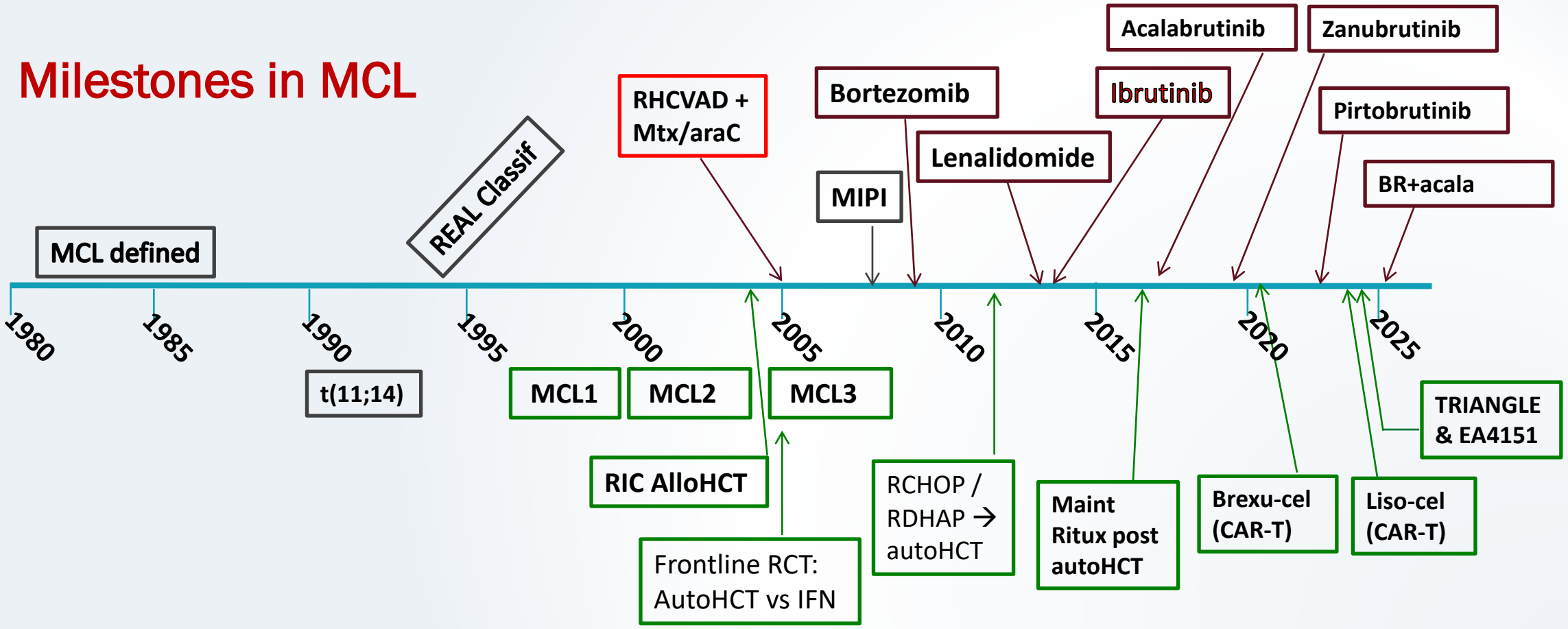
Timothy S. Fenske, MD

April 25, 2015

12TH INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM
APRIL 24 – 25, 2015 I CHICAGO, ILLINOIS
W CHICAGO CITY CENTER

So what has changed in recent years?

A LOT !! – many new options

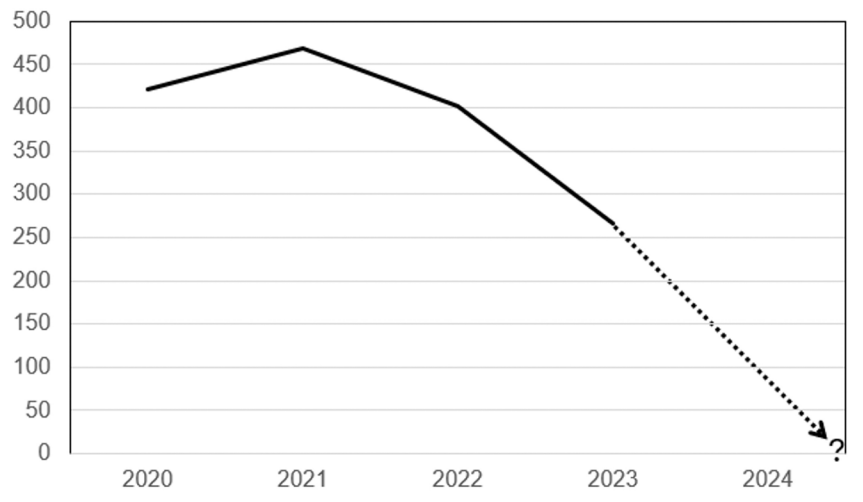


So what has changed in recent years?

More recently, fewer patients going to auto in first remission

Based on TRIANGLE, EA4151

Declining numbers of frontline autotransplants for MCL



Characteristic	2020	2021	2022	2023
Number of patients	421	469	402	266

Brian T. Hill, MD, PhD, "The End of Transplant for Mantle Cell Lymphoma, *The Hematologist*, Jan 2025

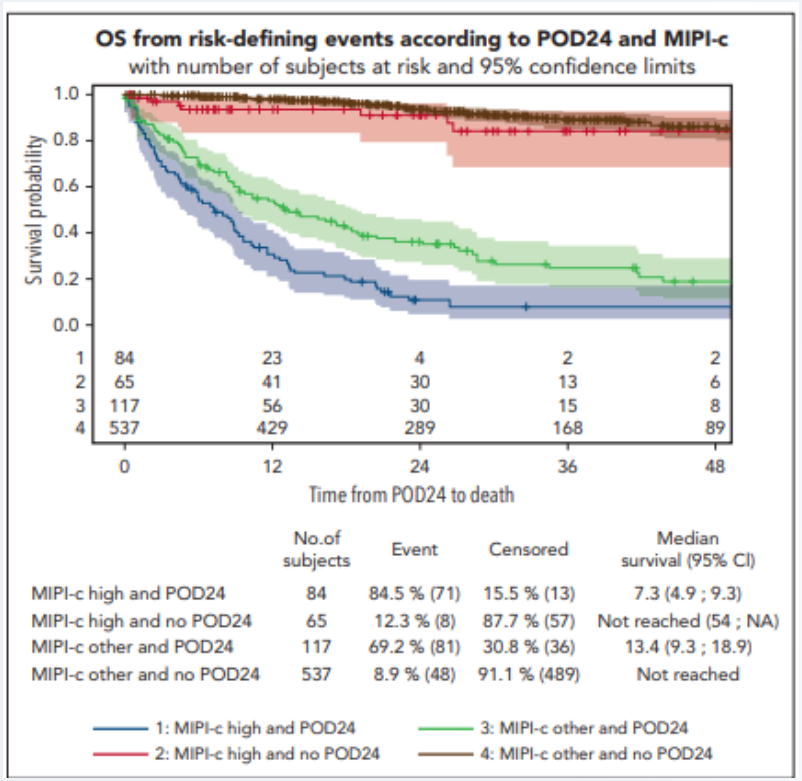
So… soon we will likely be seeing more R/R MCL pts who did not have an auto in first remission

We will have multiple cell therapy options: auto-HCT, allo-HCT, CAR-T

How will we choose?

Prognosis in R/R MCL

- POD24 pts do particularly poorly
  - European MCL Network study: median **OS 7.3 mo** (high MIPI-c) vs **13.4 mo** (other MIPI-c)
  - Nordic study: **5 yr OS** if POD24: **10%** (POD24 after BR); **25%** (POD24 after Nordic or RCHOP)



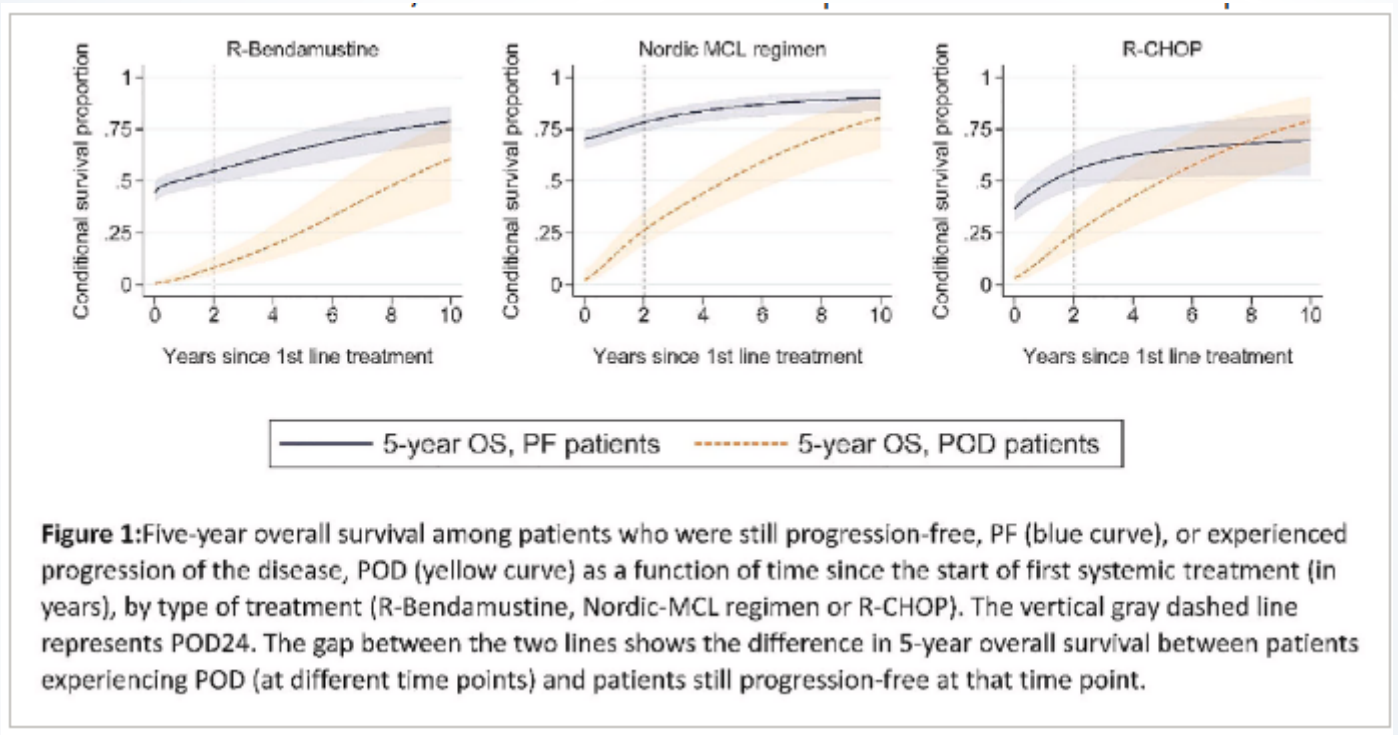
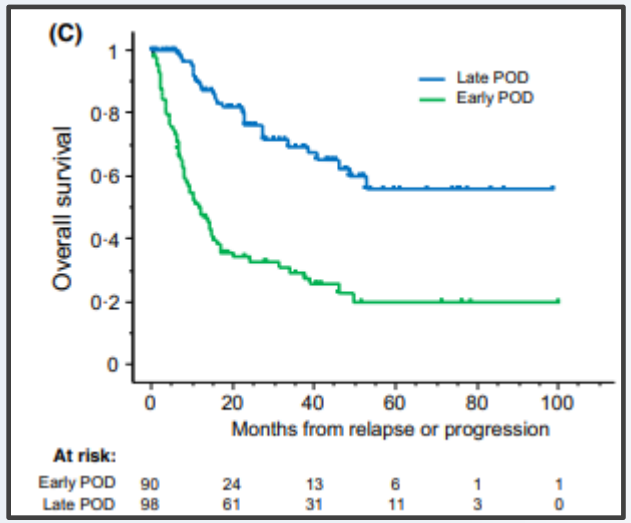


Figure 1: Five-year overall survival among patients who were still progression-free, PF (blue curve), or experienced progression of the disease, POD (yellow curve) as a function of time since the start of first systemic treatment (in years), by type of treatment (R-Bendamustine, Nordic-MCL regimen or R-CHOP). The vertical gray dashed line represents POD24. The gap between the two lines shows the difference in 5-year overall survival between patients experiencing POD (at different time points) and patients still progression-free at that time point.

Sarkozy et al, Blood 2023 (Suppl 1): 299;
Ekberg et al, Lugano 2023

Prognosis in R/R MCL

- POD 24 pts do particularly poorly
  - Italian studies:
    - focused on younger pts who relapsed after 1L HDAC regimens (about 75% with autoHCT)



POD24: median OS **12 mo**

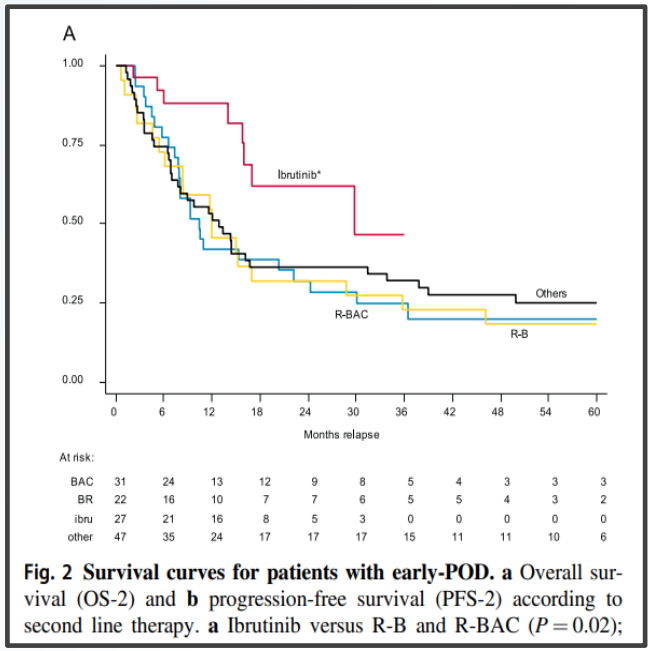


Fig. 2 Survival curves for patients with early-POD. a Overall survival (OS-2) and **b** progression-free survival (PFS-2) according to second line therapy. **a** Ibrutinib versus R-B and R-BAC ($P = 0.02$);

POD24: median OS about 1 yr except if BTKi given, then 2-3 yr

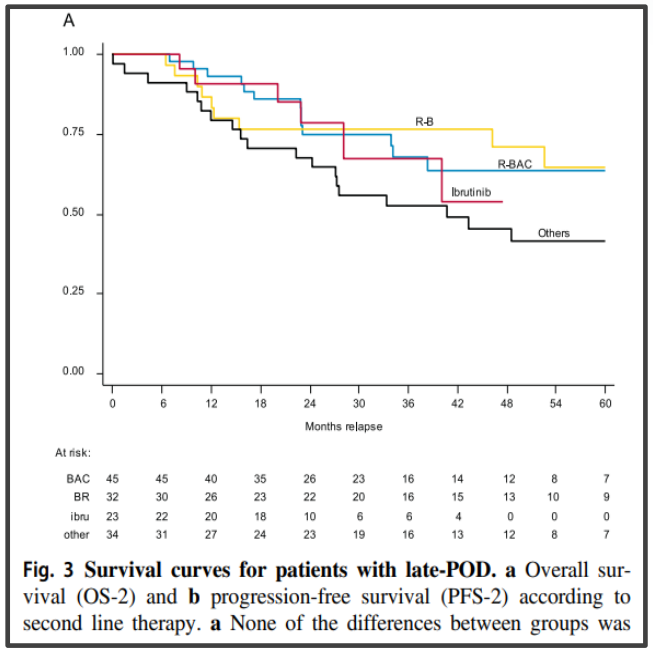


Fig. 3 Survival curves for patients with late-POD. a Overall survival (OS-2) and **b** progression-free survival (PFS-2) according to second line therapy. **a** None of the differences between groups was

Late POD: median OS 3+ yrs regardless if CIT vs BTK

Visco et al, Br J Haem, 2018

Visco et al, Leukemia, 2021

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Autologous HCT for R/R MCL

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Guideline

American Society of Transplantation and Cellular Therapy, Center of International Blood and Marrow Transplant Research, and European Society for Blood and Marrow Transplantation Clinical Practice Recommendations for Transplantation and Cellular Therapies in Mantle Cell Lymphoma

Pashna N. Munshi[1], Mehdi Hamadani[2,*,**], Ambuj Kumar[3], Peter Dreger[4], Jonathan W. Friedberg[5], Martin Dreyling[6], Brad Kahl[7], Mats Jerkeman[8], Mohamed A. Kharfan-Dabaja[9], Frederick L. Locke[10], Mazyar Shadman[11], Brian T. Hill[12], Sairah Ahmed[13], Alex F. Herrera[14], Craig S. Sauter[15], Veronika Bachanova[16], Nilanjan Ghosh[17], Matthew Lunning[18], Vaishalee P. Kenkre[19], Mahmoud Aljurf[20], Michael Wang[21], Kami J. Maddocks[22], John P. Leonard[23], Manali Kamdar[24], Tycel Phillips[25], Amanda F. Cashen[26], David J. Inwards[27], Anna Sureda[28], Jonathon B. Cohen[29], Sonali M. Smith[30], Carmello Carlo-Stella[31], Bipin Savani[32], Stephen P. Robinson[33], Timothy S. Fenske[34]

Table 4
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T Cell Treatments for R/R MCL

Consensus Statement	Grading of Recommendation*	Panelists in Agreement, %
1. If a TP53 mutation (or biallelic deletion) is present, the panel does not recommend autologous transplantation in relapsed MCL patients achieving a complete or partial remission after second or subsequent lines of therapy.	B	100
9. Among eligible MCL patients lacking a TP53 mutation (or biallelic deletion) not undergoing autologous transplant consolidation following first-line therapies, the panel recommends considering autologous transplantation consolidation therapy in patients who have achieved a complete remission after second-line chemoimmunotherapies.	B	97

* Agency of Healthcare Research and Quality grading of recommendations based on level of evidence [15]:
A: There is good research-based evidence to support the recommendation.
B: There is fair research-based evidence to support the recommendation.
C: The recommendation is based on expert opinion and panel consensus.
X: There is evidence of harm from this intervention.

"The Consensus Panel acknowledges that in the modern era of novel immunotherapies, auto-HCT likely will have a limited role in the management of R/R MCL, particularly in the presence of TP53 aberrations…
However, **among standard-risk MCL patients** (eg, those lacking a TP53 mutation or biallelic deletion) **not having undergone auto-HCT in first remission**, the panel felt that considering HDT consolidation therapy **in the subset of patients who have achieved complete remission after second-line chemoimmunotherapy, particularly after a long first remission, is reasonable** and supported by observations in more recent registry and other retrospective studies"

Transplantation and Cellular Therapy

Transplantation and Cellular Therapy 27 (2021) 720–728

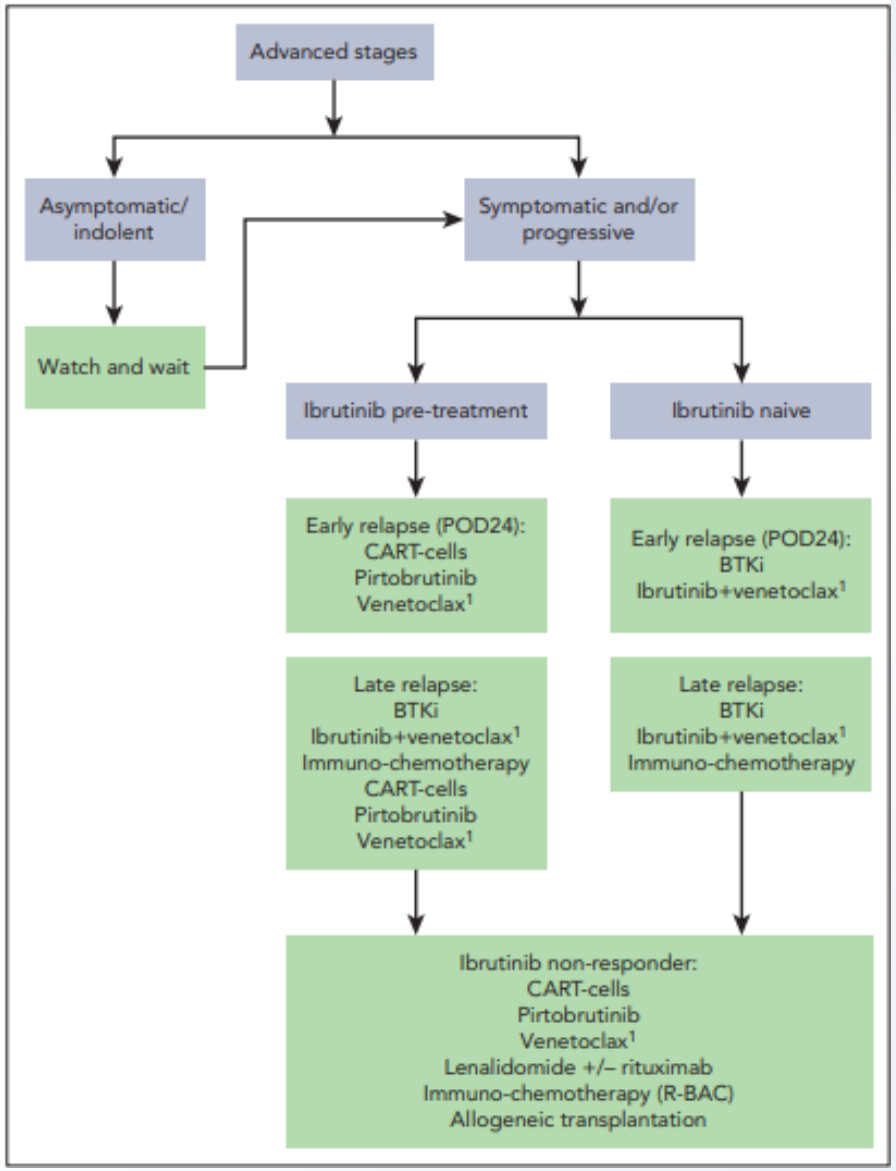
Although “reasonable”, rarely considered

MANTLE CELL LYMPHOMA

Treatment of relapsed/refractory MCL

Elisabeth Silkenstedt and Martin Dreyling

Department of Medicine III, Ludwig Maximilian University Hospital, Munich, Germany



Silkenstedt E and Dreyling M, Blood, 2025;

Outcome of autologous transplantation for mantle cell lymphoma: a study by the European Blood and Bone Marrow Transplant and Autologous Blood and Marrow Transplant Registries

Elisabeth Vandenberghe,[1] Carmen Ruiz de Elvira,[2] Fausto R. Loberiza,[3] E Conde,[4] A. López-Guillermo,[5] C. Gisselbrecht,[6] F. Guilhot,[7] Julie M. Vose,[8] Koen van Biesen,[9] J. Douglas Rizzo,[3] Dennis D. Weisenburger,[8] Peter Isaacson,[2] Mary M. Horowitz,[3] Anthony H. Goldstone,[2] Hillard M. Lazarus[10] and Norbert Schmitz[11] [1]*Department of Haematology, St*

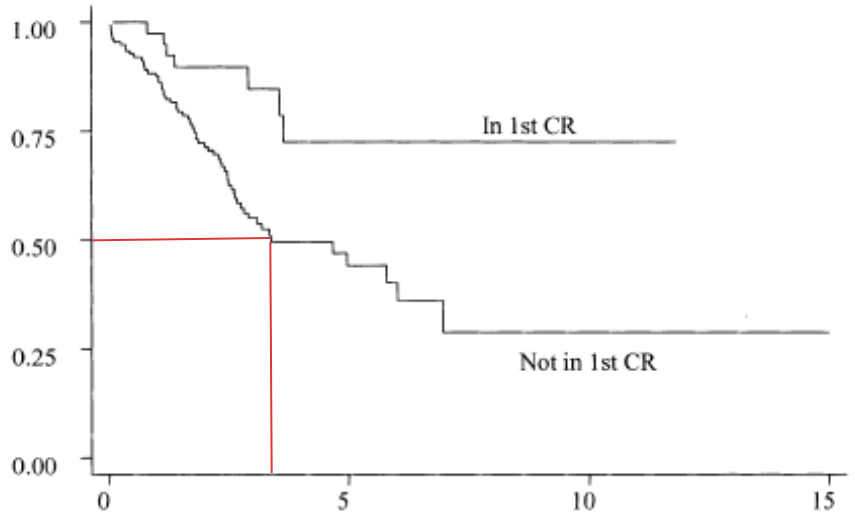


Fig 1. Overall survival from time of transplantation by disease status.

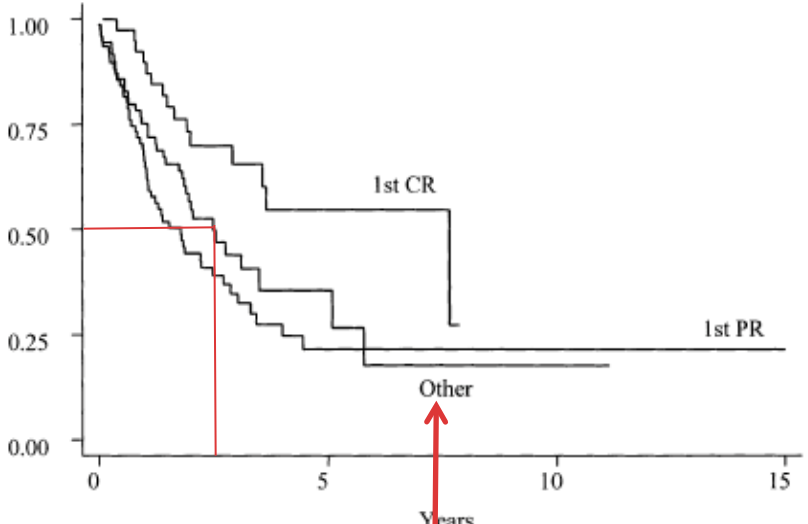


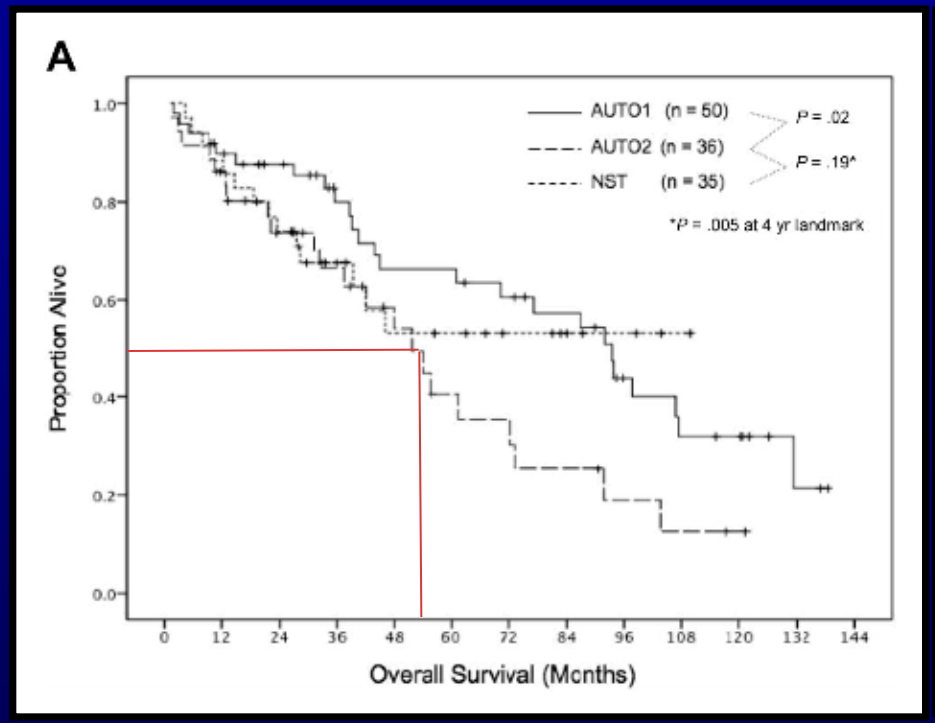
Fig 2. Progression-free survival from time of transplantation by disease status.

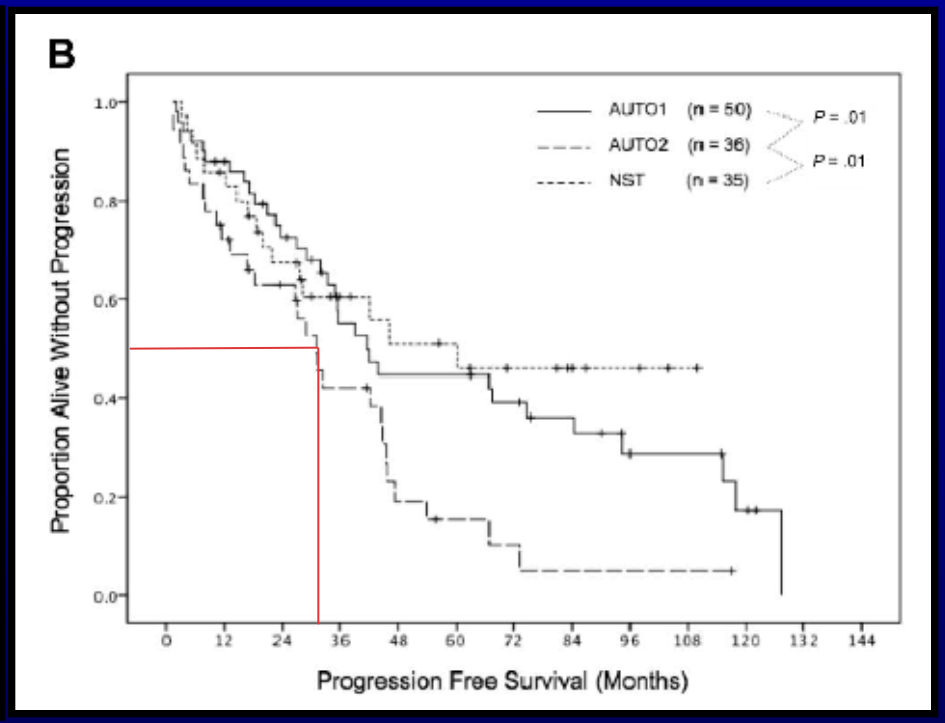
56/78 pts (72%) were relapsed pts

British Journal of Haematology, 2003, **120**, 793–800

Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma

Constantine S. Tam,[1,2] Roland Bassett,[3] Celina Ledesma,[2] Martin Korbling,[2] Amin Alousi,[2] Chitra Hosing,[2] Partow Kebraei,[2] Robyn Harrell,[3] Gabriela Rondon,[2] Sergio A. Giralt,[2] Paolo Anderlini,[2] Uday Popat,[2] Barbara Pro,[4] Barry Samuels,[5] Frederick Hagemeister,[4] L. Jeffrey Medeiros,[6] Richard E. Champlin,[2] and Issa F. Khouri[2]





"AUTO2" pts were relapsed or refractory

blood®

BLOOD, 30 APRIL 2009 • VOLUME 113, NUMBER 18

Autologous or Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation for Chemotherapy-Sensitive Mantle-Cell Lymphoma: Analysis of Transplantation Timing and Modality

Timothy S. Fenske, Mei-Jie Zhang, Jeanette Carreras, Ernesto Ayala, Linda J. Burns, Amanda Cashen, Luciano J. Costa, César O. Freytes, Robert P. Gale, Mehdi Hamadani, Leona A. Holmberg, David J. Inwards, Hillard M. Lazarus, Richard T. Maziarz, Reinhold Munker, Miguel-Angel Perales, David A. Rizzieri, Harry C. Schouten, Sonali M. Smith, Edmund K. Waller, Baldeep M. Wirk, Ginna G. Laport, David G. Maloney, Silvia Montoto, and Parameswaran N. Hari

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JOURNAL OF CLINICAL ONCOLOGY

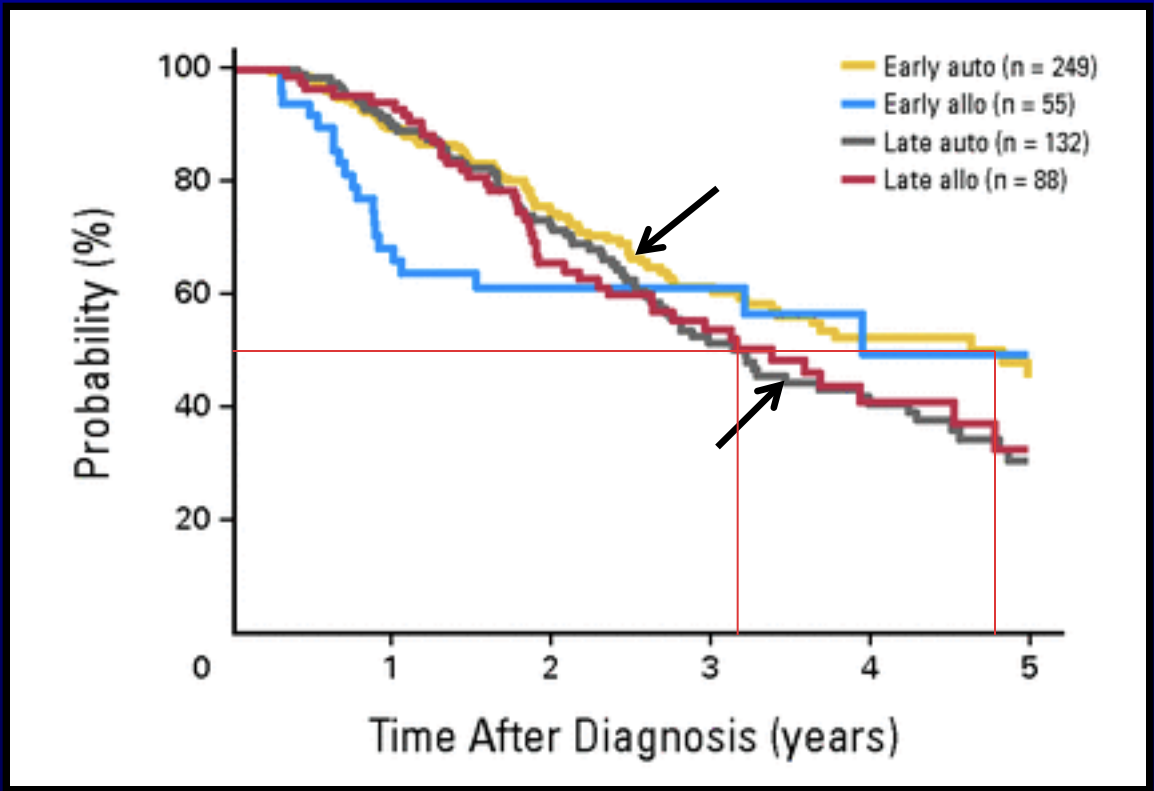


Fig A1.

Overall survival from time of diagnosis. Allo, allogeneic hematopoietic cell transplantation; auto, autologous hematopoietic cell transplantation.

"Late" = relapsed, or >2 lines of therapy prior to transplant

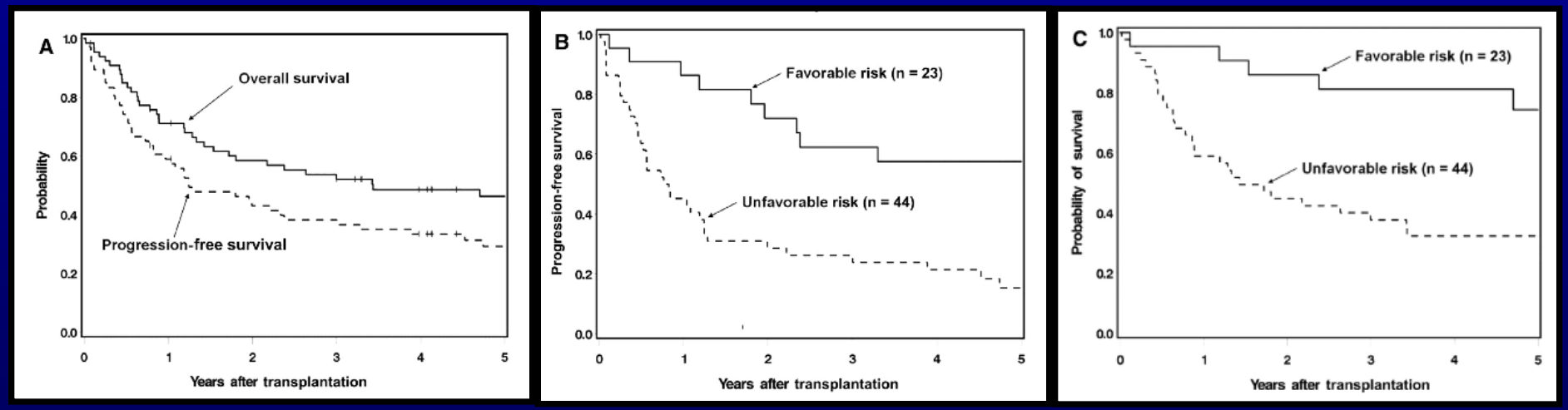
Left-truncated analysis looking at survival from time of diagnosis. Shows benefit of early auto (versus late auto), among those who survive 2 yrs post diagnosis.

Specific Features Identify Patients with Relapsed or Refractory Mantle Cell Lymphoma Benefitting from Autologous Hematopoietic Cell Transplantation

Ryan D. Cassaday [1,2], Katherine A. Guthrie [1], Elizabeth L. Budde [1,2], Leslie Thompson [1,2], Brian G. Till [1,2], Oliver W. Press [1,2], Thomas R. Chauncey [1,2,3], John M. Pagel [1,2], Stephen H. Petersdorf [1,2], Maria Corinna Palanca-Wessels [1,4], Mary Philip [1,4], William I. Bensinger [1,2], Leona A. Holmberg [1,2], Andrei Shustov [1,4], Damian J. Green [1,2], Edward N. Libby [1,2], David G. Maloney [1,2], Ajay K. Gopal [1,2,*]

Biology of Blood and Marrow Transplantation
The Official Journal of the American Society for Blood and Marrow Transplantation

Biol Blood Marrow Transplant 19 (2013) 1393–1411



- "Favorable" defined using a combination of sMIPI score (at autoHCT); B symptoms at diagnosis; and "Remission Quotient" (RQ)
- RQ = Time from Dx to AutoHCT (in months) / number of prior treatments
- sMIPI >3 or RQ <6: poor outcome

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Allogeneic HCT for R/R MCL

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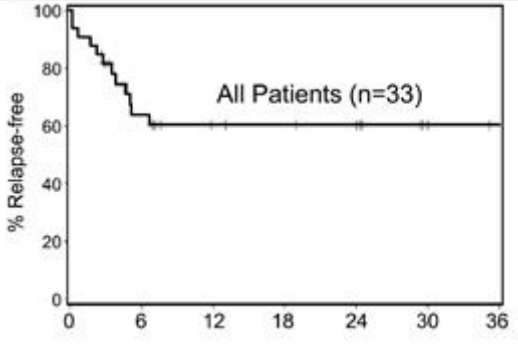
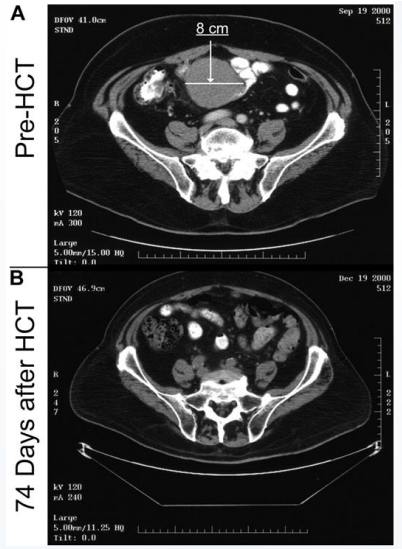
Studies of alloHCT for rel-refr MCL

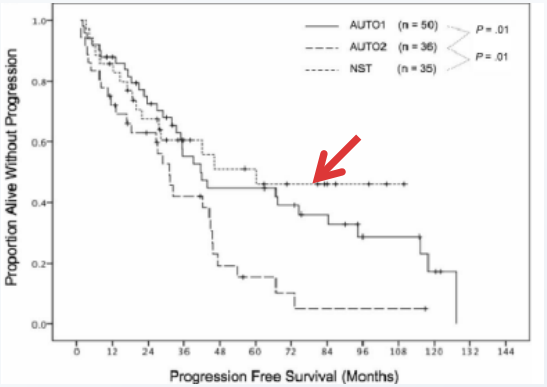
RIC conditioning, at least 2 yr f/u

Study	Regimen	TRM	Relapse	PFS	OS	Follow up
Seattle[1] (n=33)	Flu/TBI 42% w/ prior auto	24% 1-2yr	9%	60%	65%	2 yrs
MDACC[2] (n=35)	FCR	9% 1yr	NR	46%	53%	6 yrs
Britain[3] (n=70)	FluMel or Flu/Bu +/- Alem	18% 1yr 21% 3 yr	65%	14%	37%	5 yrs
France[4] (n=70)	RIC 67% w/ prior auto	32%**	NR	50% 60% sens	53% 60% sens	2 yrs
CIBMTR[5] (n=138)	RIC (early) RIC (late) None w/ prior auto	25% 1yr 17% 1yr ≈30% 3yr	15% 38%	55% 24%	62% 31%	5 yrs 5 yrs
France[6] (n=106)	RIC All w/ prior auto	28% 1 yr 32% 3 yr	≈20%	≈35%	≈55%	4 yrs
MSKCC[7] (n=42)	RIC 64% w/ prior auto	20% 2yr	19%	61% 2y	78% 2y	2 y
Italy[8] (n=55)	80% RIC 78% w/ prior auto	7% 1yr 23% 3 y	26%	45% 5y	50% 5y	3.5 y

[1]Maris, Blood (2004); [2]Tam, Blood (2009); [3]Cook, BBMT (2010); [4]LeGouill, Ann Onc (2012);
[5]Fenske, J Clin Onc (2014); [6]Tessoulin, BMT (2016); [7]Lin, BJHaem (2018); [8]Arcari, Leuk&Lym (2021)







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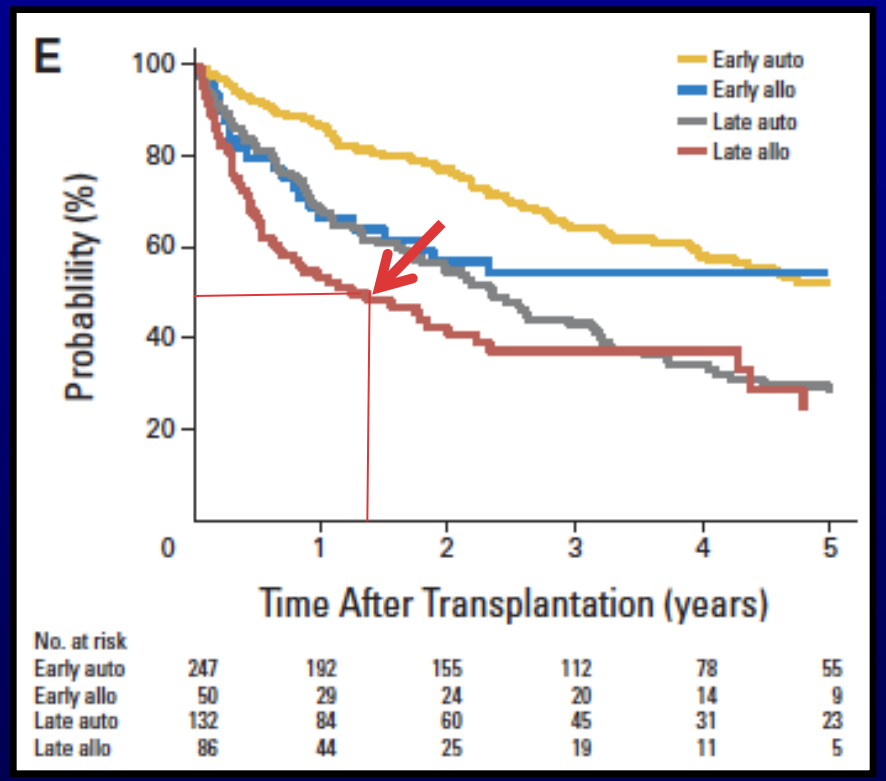

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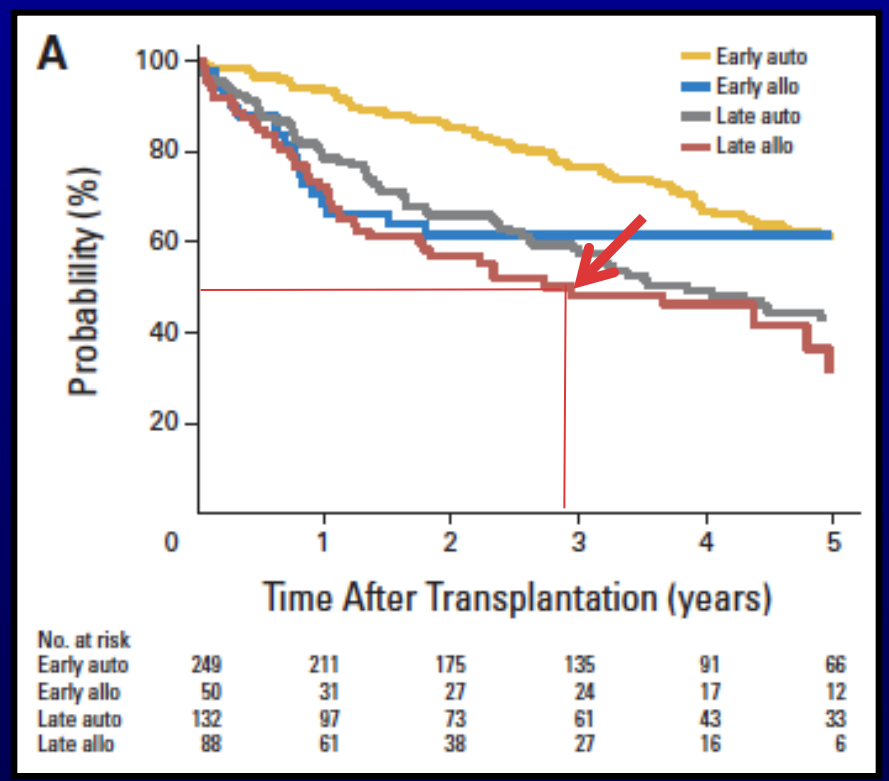
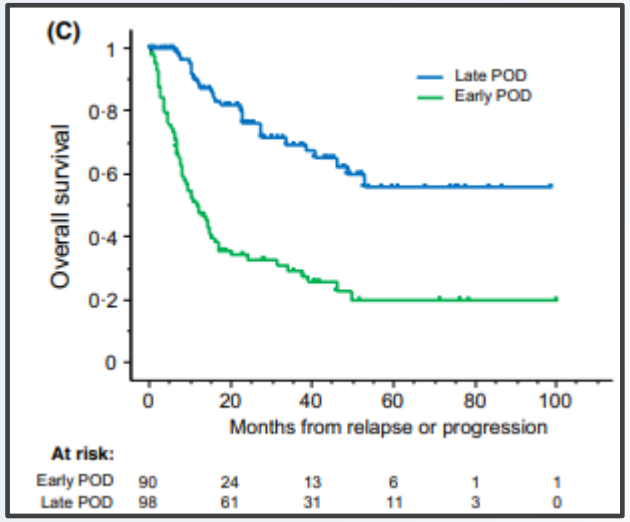
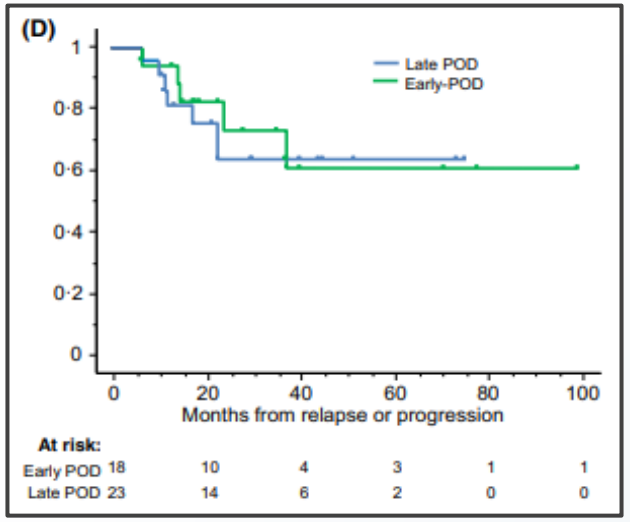


"Late" = relapsed, or >2 lines of therapy prior to transplant

What about allo-HCT in POD24 MCL?

- Allo-HCT appears to overcome the adverse prognosis assoc with POD24
  - POD24 pts who underwent allo-HCT had similar outcome to late POD pts undergoing allo
  - Both groups appear to have plateau of OS curves

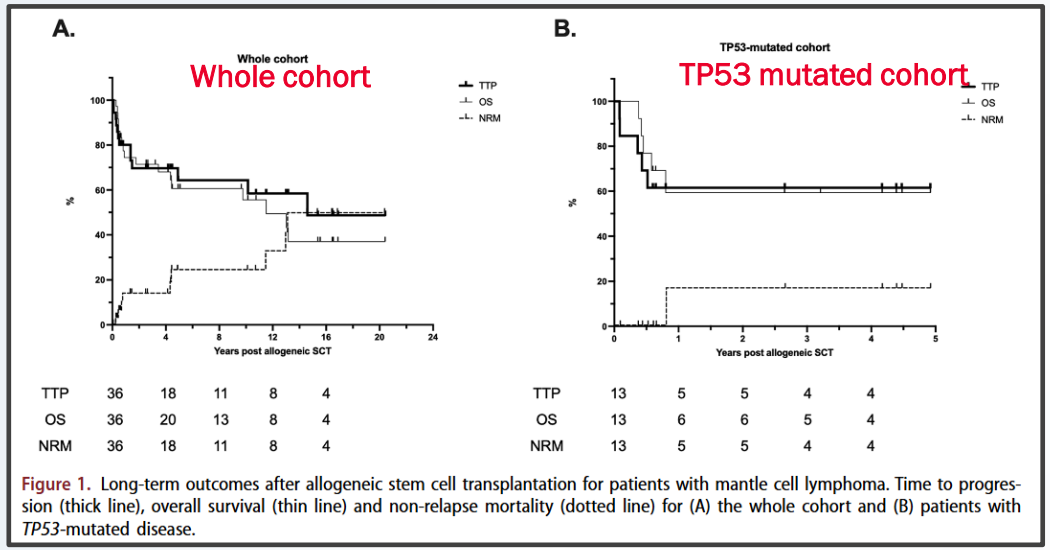




Visco et al, Br J Haem, 2018

What about allo for TP53-mutated MCL?

- 2 studies
- Allo appears to largely overcome the adverse prognosis associated with TP53 mutations



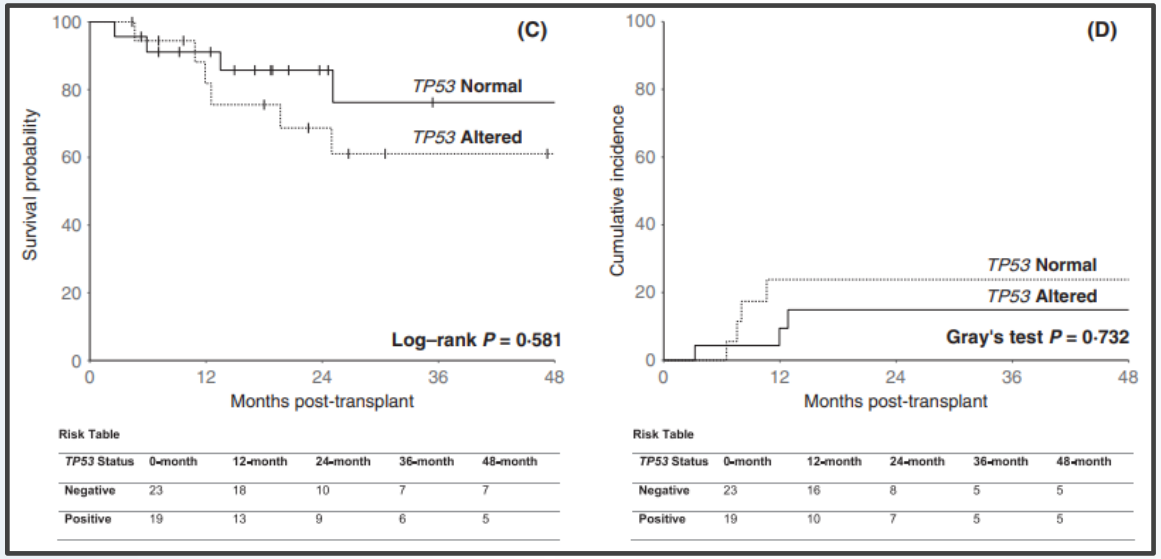
TTP	36	18	11	8	4
OS	36	20	13	8	4
NRM	36	18	11	8	4

TTP	13	5	5	4	4
OS	13	6	6	5	4
NRM	13	5	5	4	4

Figure 1. Long-term outcomes after allogeneic stem cell transplantation for patients with mantle cell lymphoma. Time to progression (thick line), overall survival (thin line) and non-relapse mortality (dotted line) for (A) the whole cohort and (B) patients with *TP53*-mutated disease.

Melbourne, Australia group

Lew et al, Leuk & Lymhoma, 2023



Risk Table

TP53 Status	0-month	12-month	24-month	36-month	48-month
Negative	23	18	10	7	7
Positive	19	13	9	6	5

Risk Table

TP53 Status	0-month	12-month	24-month	36-month	48-month
Negative	23	16	8	5	5
Positive	19	10	7	5	5

MSKCC group

Lin et al, BJHaem,2018

So… fair to say that RIC allo-HCT is a potentially curative therapy for R/R MCL, and can overcome adverse prognosis associated with TP53mut and POD24

However TRM still 10-20% in first year, and 20-30% by 3 yrs

Can we do better with CAR-T?

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CAR-T for R/R MCL

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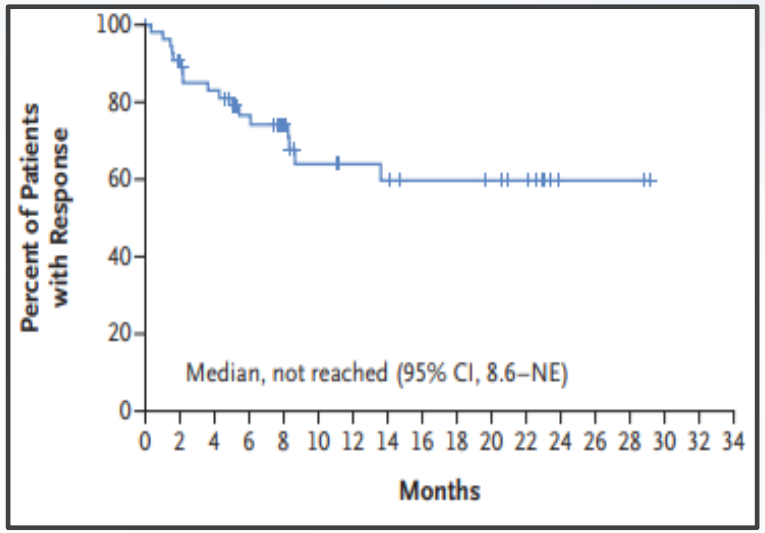
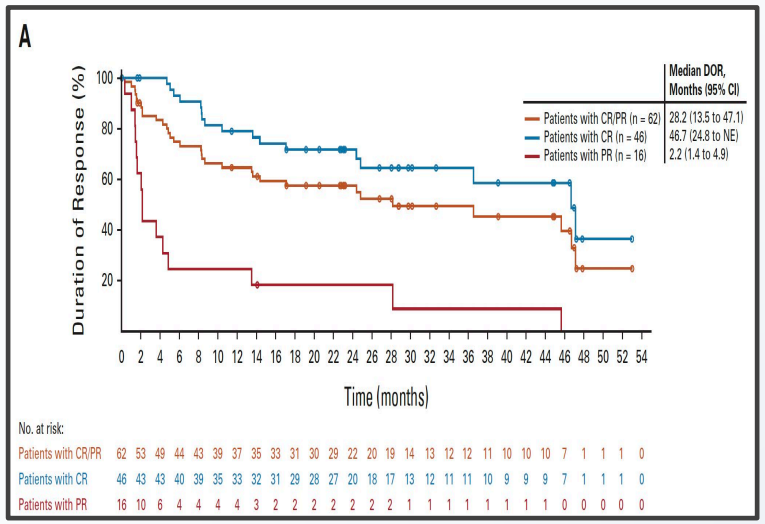
Commercial CAR-T for R/R MCL: Brexu-cel ZUMA-2 trial

- Brexu-cel, updated data from ZUMA-2
- N=68 pts
- Prior BTKi in 100% (88% BTK rel/refr)

- N=68 pts; median follow up now 35.6 month
- For all treated pts, ORR 91%; CR rate 68%
- ORR and peak CAR-T levels lower if benda <12mo
- Prior autoHCT: 43%
- TP53 mutations: 6/36 mutated. 32 unknown
- POD24: 33/68 (48%)
- NRM: (5/68) 7.3% by 37 mo
- mDOR 28 mo; 47 mo for patients achieving CR
  - Of note: of the 20 in CR at 2 yrs, 6 relapses between 2-4 yrs . **Is this curative?**



Wang et al, NEJM (2020)

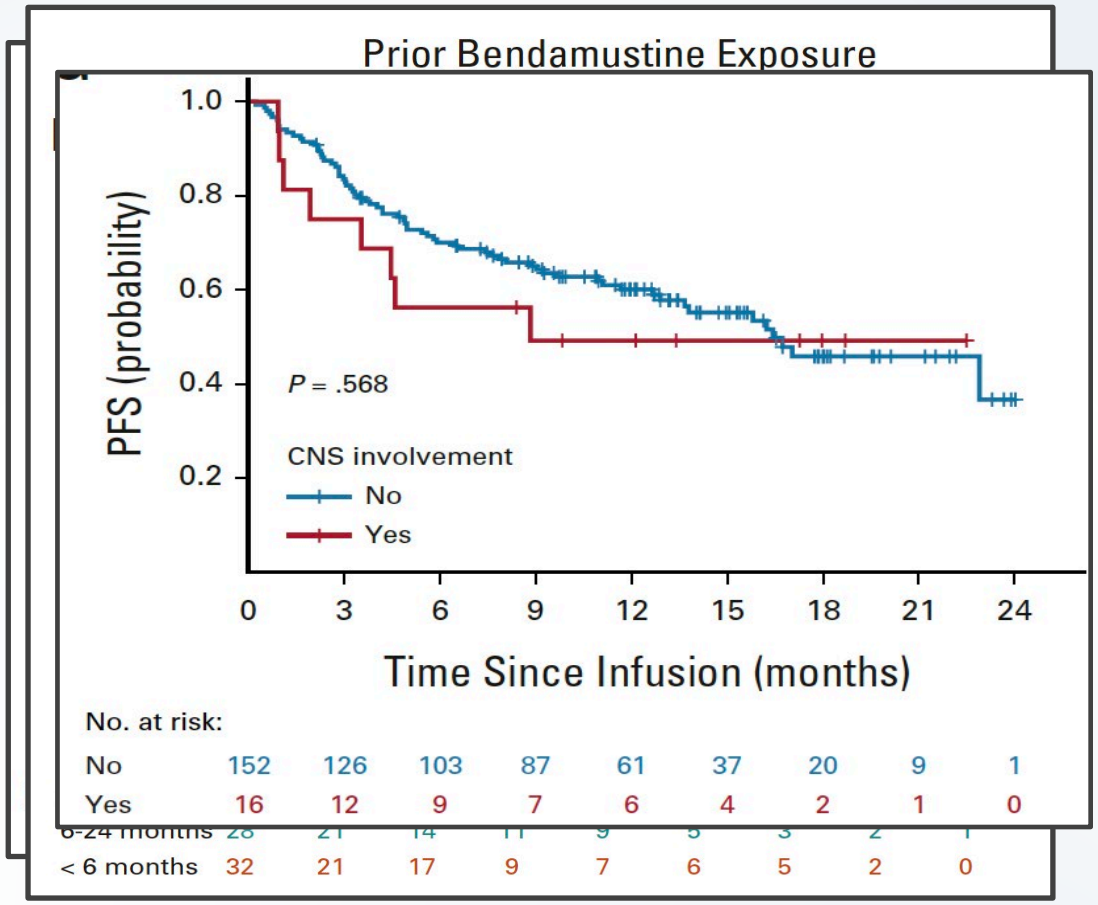


Wang et al, J Clin Onc (2023)

Commercial CAR-T for R/R MCL: Brexu-cel “real world” data

- Aug 2020 – Dec 2021 at 16 centers
- N=189 pheresed, 168 infused
- TP53 mutated: 53/110 (48%)
- POD24: 51%
- CNS involvement: 20
- Prior autoHCT: 28%
- BTKi refractory: 77%

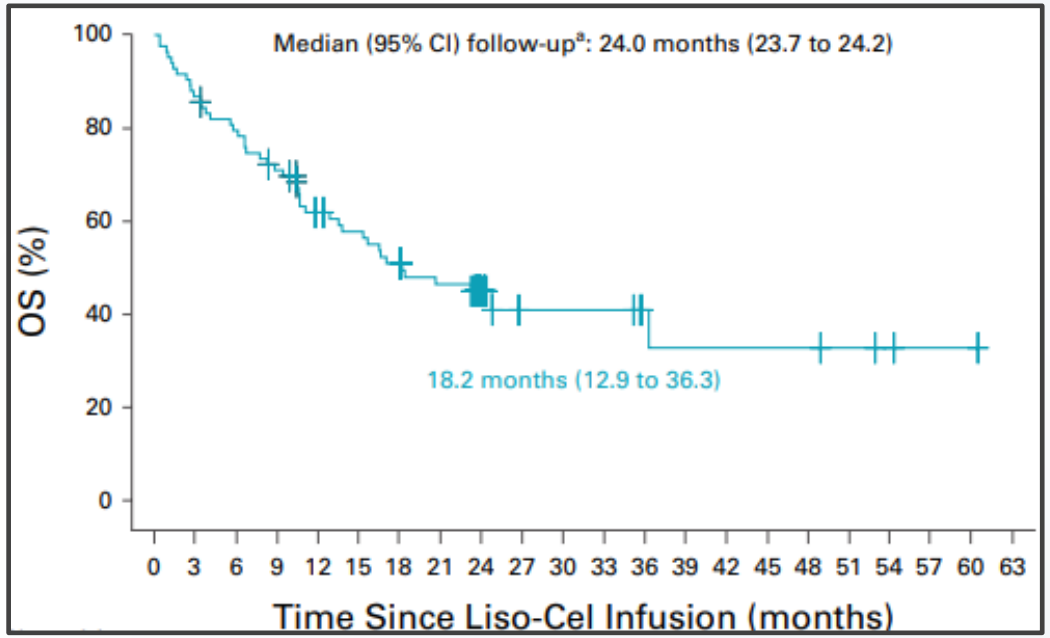
- ORR 90%; CR rate 82%
- DOR 65% at 1 year; med DOR 17 mo
- **1 year NRM 9.1%**
- Gr 3-4 CRS 8%; Gr 3-4 ICANS 32%
- Patients with recent bendamustine exposure (within 2 yrs of leukapheresis) had shorter PFS and OS



Wang Y J Clin Onc (2023)

Commercial CAR-T for R/R MCL: Liso-cel

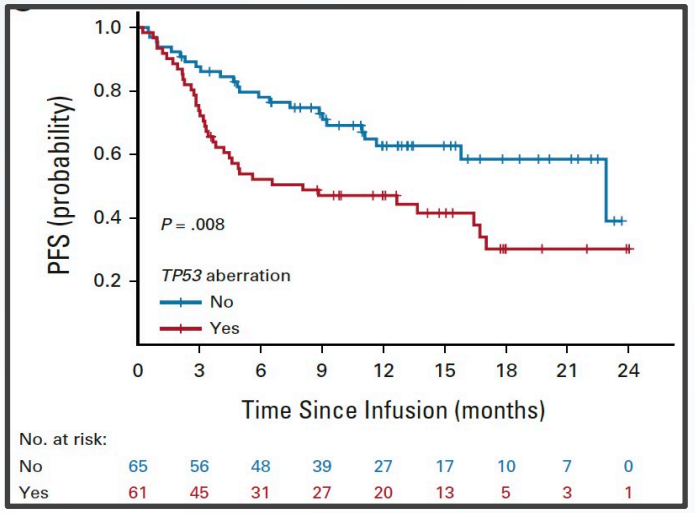
- Liso-cel, MCL cohort of TRANSCEND NHL
- N=104 pheresed, with 88 infused
- Median prior LOT = 3 (range 1-11)
- 53% BTKi refractory; 33% prior autoHCT
- 23% with TP53 mutations; %POD24 - NR
- 8% secondary CNS disease
- ORR 83% / CR 72%
- Median PFS 15.7 mo
- CRS in 61% (only 1% Gr3-4); NEs in 31% (9% Gr3-4)
- Prolonged cytopenias in 40%
- NRM: 12/88 infused = 13.6% (>50% were covid related)



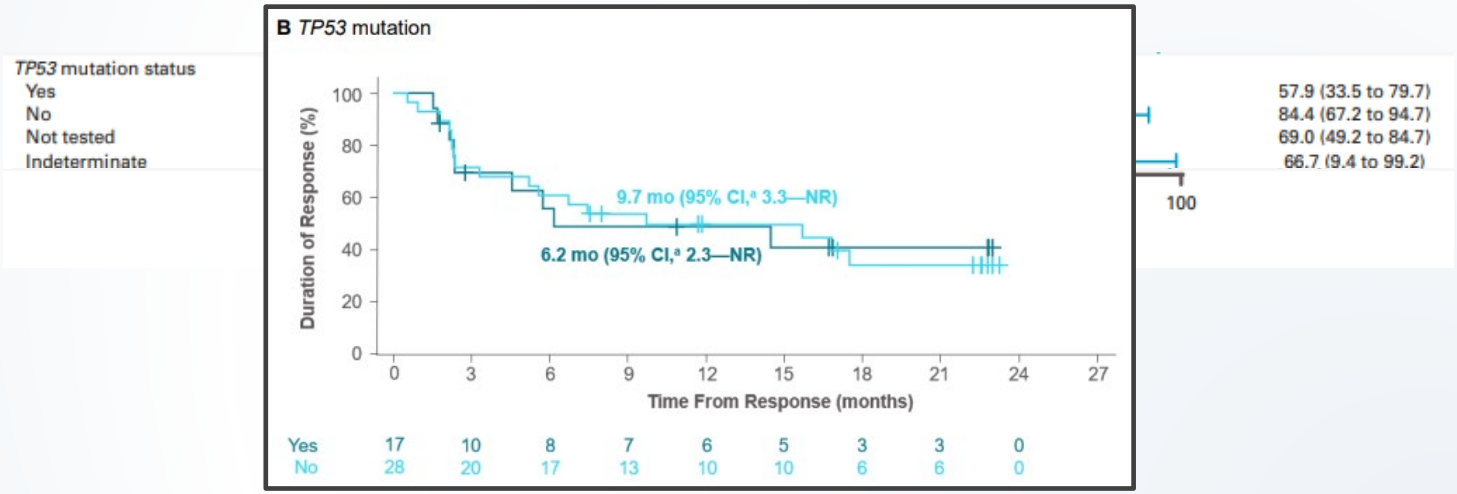
Wang M, J Clin Onc (2023)

How does CAR-T perform in TP53 mut pts?

- ZUMA-2 only had 6 TP53mut pts. All responded but 4 relapsed eventually
- In the Brexu-cel "real world" analysis TP53 mut pts had inferior PFS
- In the Liso-cel TRANSFORM MCL cohort, 19 pts had TP53mut. 17 responded but only 11 CR. DOR not diff than unmutated



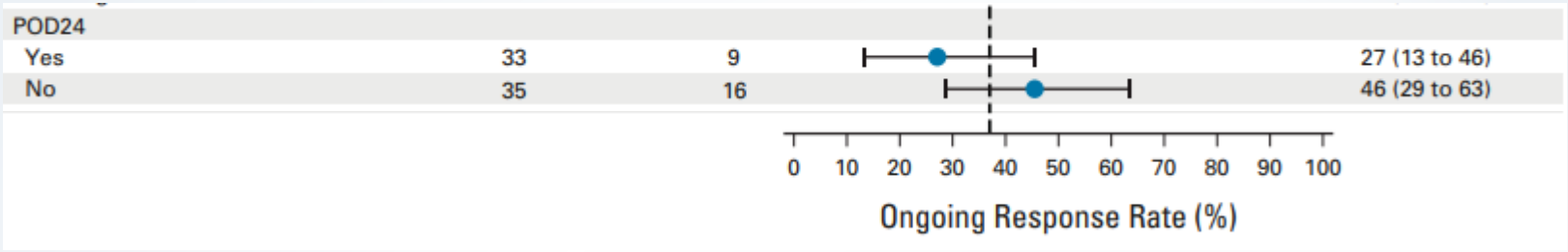
Wang Y J Clin Onc (2023)



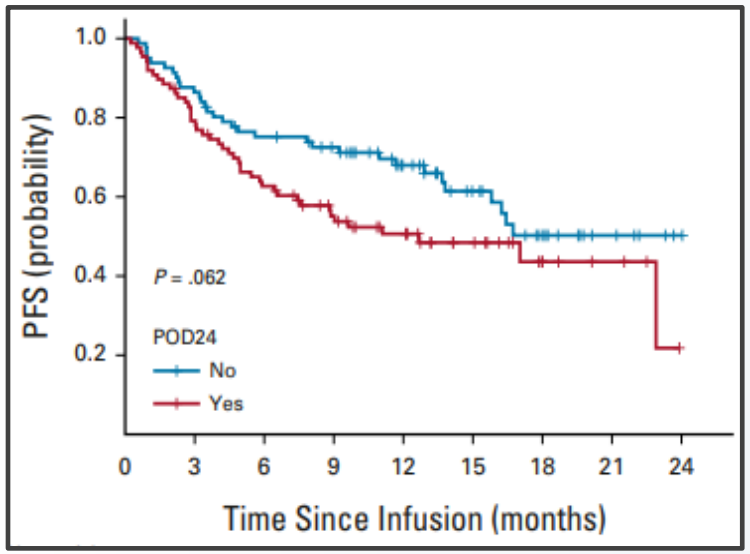
Wang M, J Clin Onc (2023)

How does CAR-T perform in POD24 pts?

- ZUMA-2
- Brexu-cel RWA
- Liso-cel: POD24 not capture/ reported on



Wang Y J Clin Onc (2023)



Wang Y J Clin Onc (2023)

How does CAR-T perform overall in R/R MCL patients?

- About 60-80% achieve CR
- However 60-70% relapse within 2-4 years. Curve doesn't appear to flatten out, more continuous pattern of relapse
- Doesn't appear curative
- Performs worse in POD24 and TP53 mutated patients
- NRM is probably at least 10% at 1-2 years, accounting for early toxicities and secondary malignancies
  - NRM still lower than allo-HCT
- Doing CAR-T does not preclude allo-HCT later
  - Higher NRM, but potentially curative
  - If patient can get 1-2 years post allo-HCT without relapse and without severe GVHD, lymphoma is likely cured

Phase I/II Study of Adaptive Manufactured LV20.19 CAR T Cells for Relapsed, Refractory Mantle Cell Lymphoma

Journal of Clinical Oncology®

Nirav N. Shah, MD, MS[1]; Alfredo S. Colina, BA[2]; Bryon D. Johnson, PhD[1]; Aniko Szabo, PhD[3]; Fateeha Furqan, MD[1]; Tyce Kearl, MD, PhD[1]; Dina Schneider, PhD[4]; Marlenny Vargas-Cortes, BS[5]; Jessica L. Schmeling, BS[5]; Michael B. Dwinell, PhD[2]; Katie Palen, BS[1]; Walter Longo, MD[1]; Peiman Hematti, MD[1]; Anthony E. Zamora, PhD[2]; Parameswaran Hari, MD, MS[1]; Daniel Bucklan, MD[6]; Ashley Cunningham, MD[7]; Mehdi Hamadani, MD[1]; and Timothy S. Fenske, MD[1]

- CD19/20 dual targeting using a tandem bispecific vector construct
- 2.5 million CAR T-cells / kg
- 8 to 12 day “adaptive” point of care production schema + modification of cytokines for expansion from IL-2 → IL-7+ IL-15
- Point of care production that meets GMP requirements (without a GMP facility), using Miltenyi CliniMACS Prodigy system

- Shah N et al, *J Clin Oncol* (Online Adv Pub 31 March 2025)

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Journal of Clinical Oncology®

- 17 patients with R/R MCL (3 phase 1, 14 phase 2)
- 94% BTKi exposed, 76% BTKi progressed
- 47% prior autoHCT; 12% prior alloHCT
- 4 median prior lines of therapy
- 76% prior bendamustine
- 35% with TP53 mutations
- All 17 pts reached target cell dose of 2.5 million CART/ kg
  - 13 pts in 8 days and 4 pts in 12 days

TABLE 1.

Patients With MCL (n = 17)	Phase I = 3, Phase II = 14
Age, years, median (range)	63 (50-74)
Male sex, No. (%)	15 (88)
Previous auto-HCT, No. (%)	8 (47)
Previous allo-HCT, No. (%)	2 (12)
LDH >normal on day 0, No. (%)	6 (35)
Marrow involvement before CAR infusion, No. (%)	14 (82)
BTKi exposed, No. (%)	16 (94)
BTKi progressed, No. (%)	13 (76)
Noncovalent (pirtobrutinib) BTKi progressed, No. (%)	6 (35)
Previous lines (including transplant), median (range)	4 (2-8)
Previous bendamustine, No. (%)	13 (76)
Previous bendamustine <1 year, No. (%)	2 (12)
MIPI at diagnosis (n = 14), No. (%)	
Low	6 (35)
Intermediate	4 (31)
High	4 (31)
Missing	3 (18)
Complex cytogenetics, No. (%)	3 (18)
p53 aberrations, No. (%)	8 (47)
p53 mutation	6 (35)
17p deletion by FISH or cytogenetics	3 (18)

Shah N et al, *J Clin Oncol* (Online Adv Pub 31 March 2025)

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- 100% ORR; 88% CR
- Med PFS and OS – NR at median f/u of 15.8 months
- 94% CRS, all Gr1-2; 18% ICANS, 12% Gr3; 12% IEC-HS, all reversible
- 2 late ICANS (d+41 and d+58), both with very high CSF WBC (1005 and 386) with signif % CAR-T cells. Both resolved ICANS with one dose of IT hydrocort
- 3 NRM events: 1 each covid, GNR sepsis, meningoenceph – all in context of ongoing B-cell aplasia
- 2 pts died from relapsed MCL
- Day 90 clonoSEQ predictive of relapse
- Able to rapidly get pts to CAR (start LD 4 days after pheresis), much faster than commercial CARs, with less ICANS than Brexu-cel? (need larger numbers)

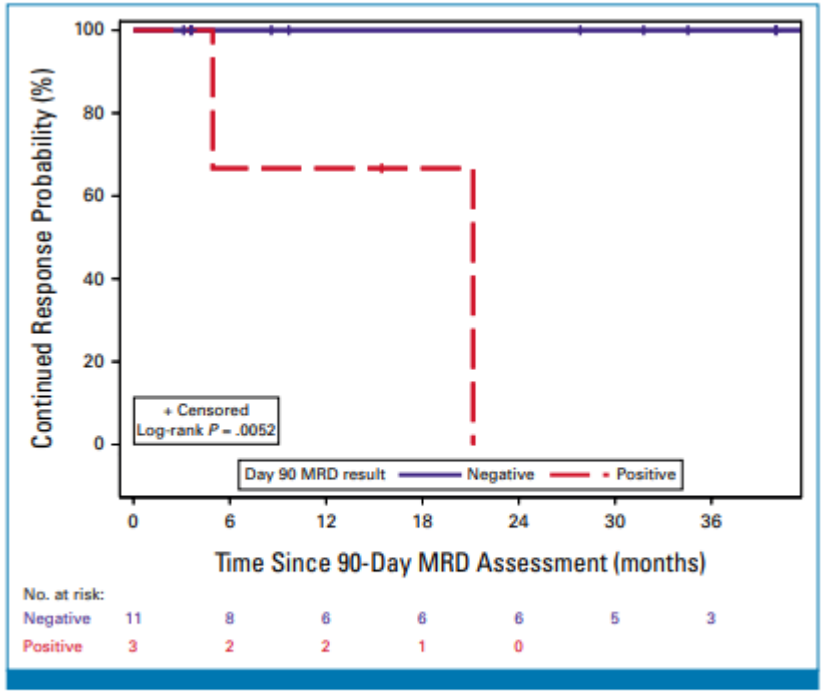
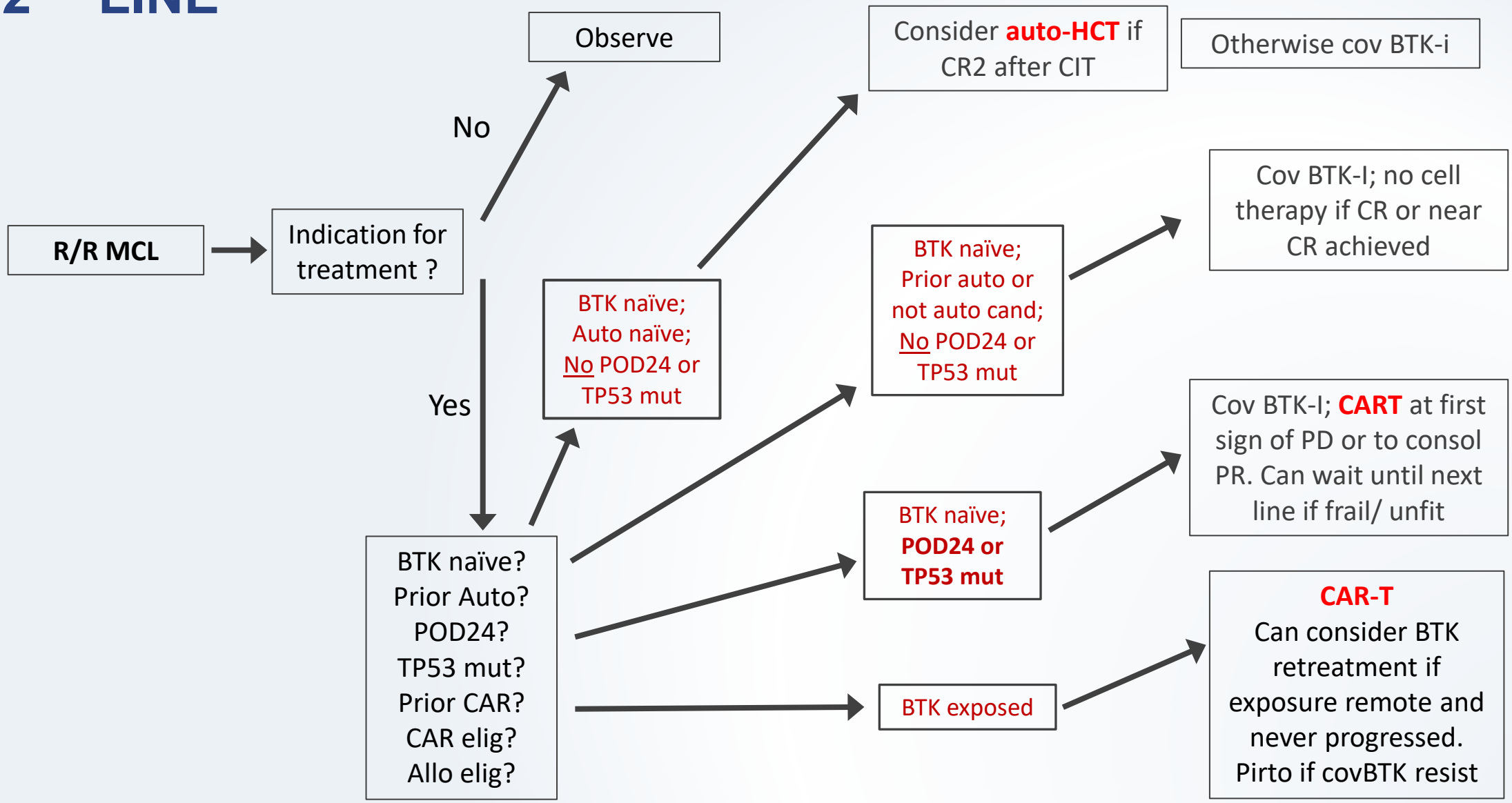


FIG 3. Day-90 clinical response and correlation of MRD to duration of response. Duration of response on the basis of MRD status at day 90 after treatment with LV20.19 CAR T cells ($P = .0052$). MRD, minimal residual disease.

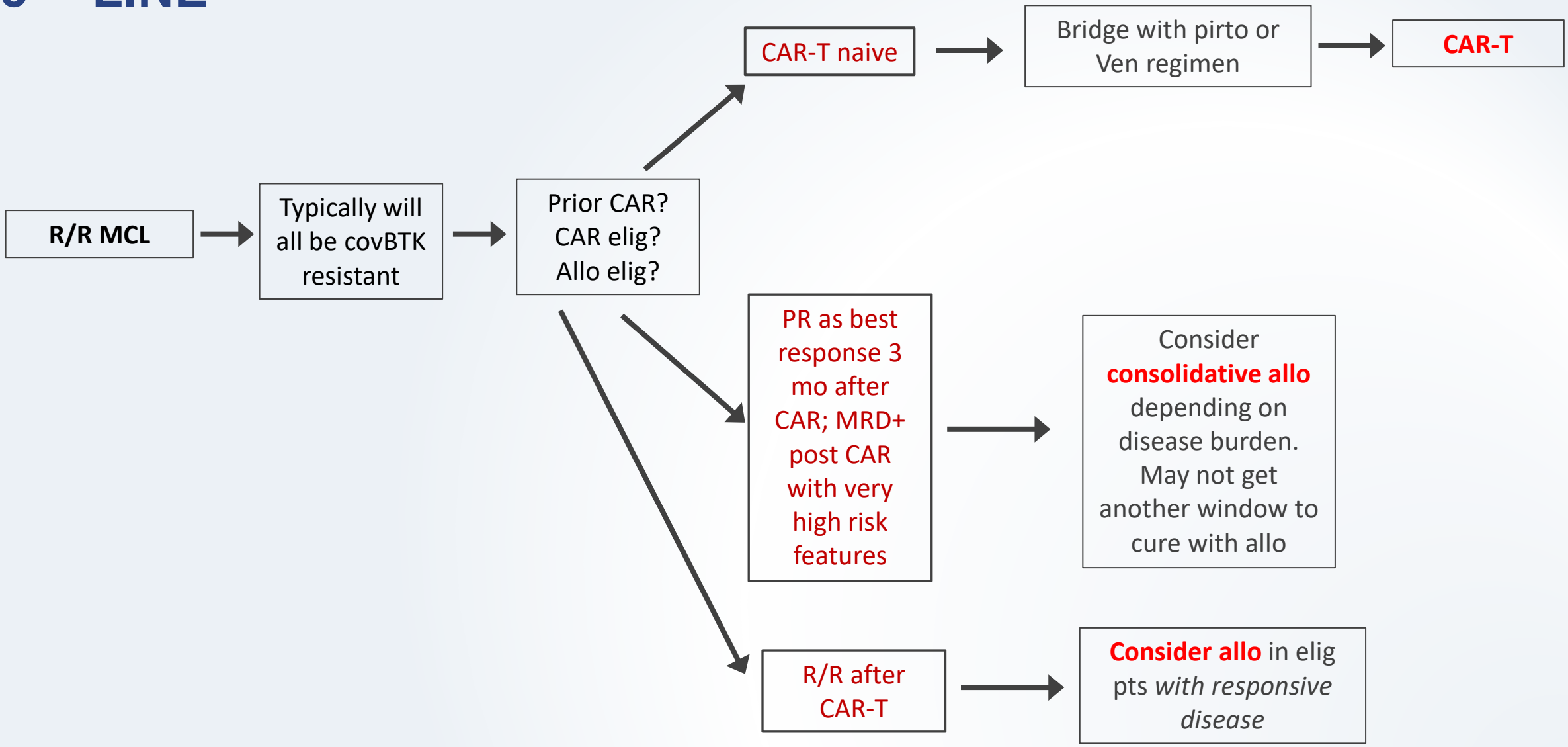
Shah N et al, *J Clin Oncol* (Online Adv Pub 31 March 2025)

So where do we stand now in 2025?
2ND LINE



Modified from: Dreger et al, How we treat mantle cell lymphoma with cellular therapy in 2025: the European and American perspectives, in preparation

So where do we stand now in 2025?
3RD LINE



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