Mantle cell lymphoma

Allo stem cell transplantation in relapsed and refractory patients

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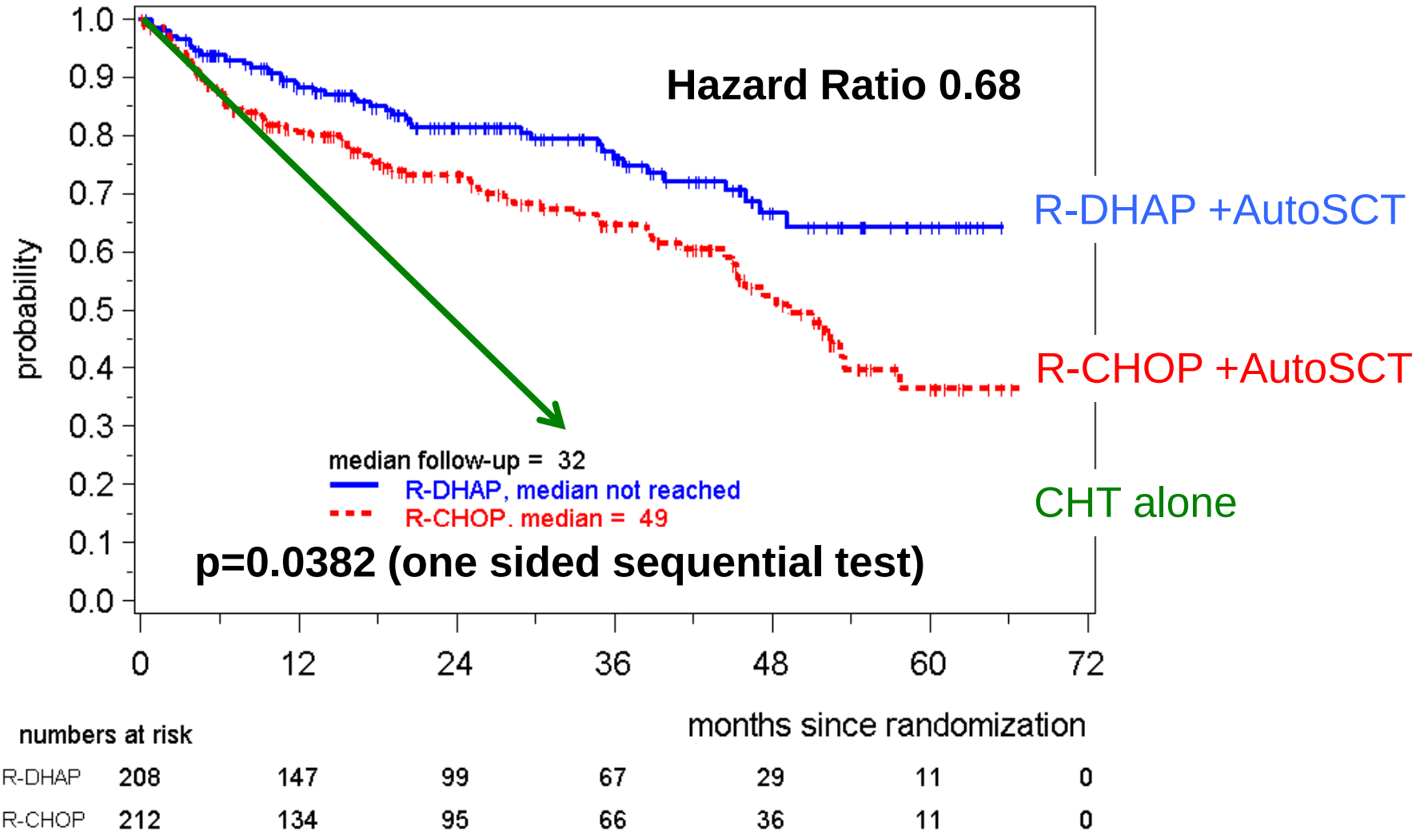
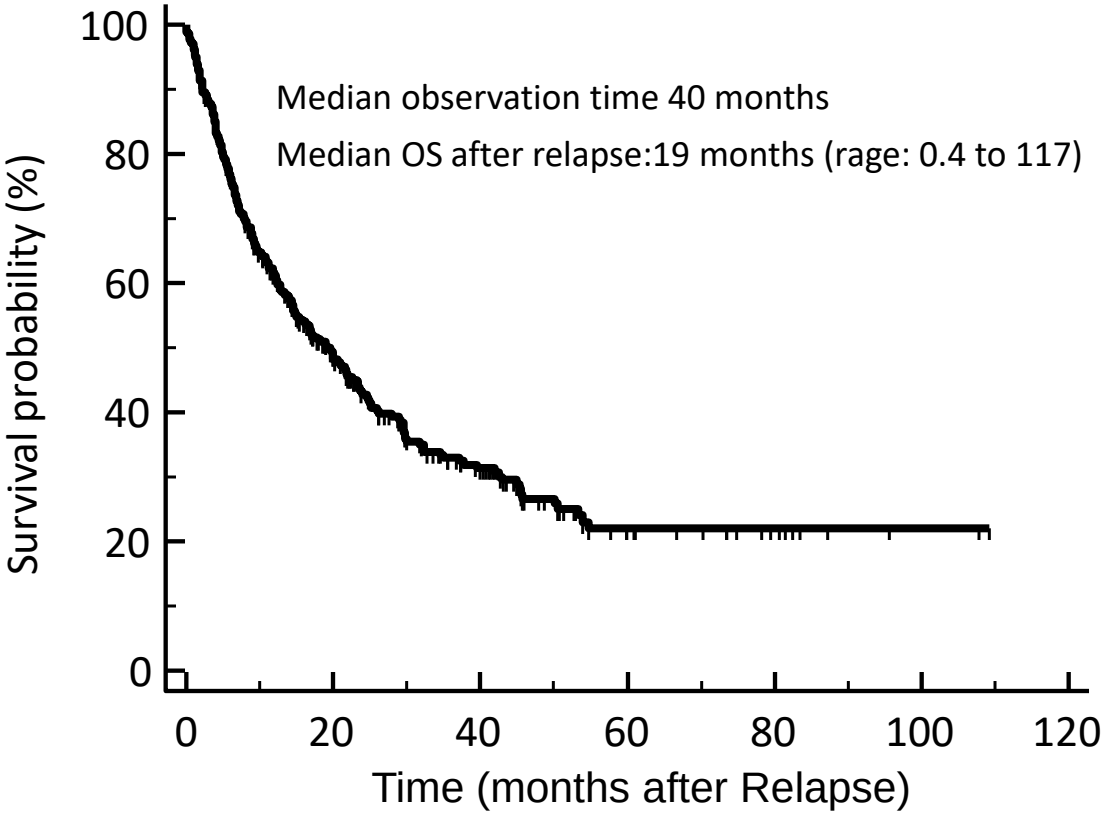
European MCL Network MCL Younger Trial



Outcome after autoSCT failure

360 patients with relapse after autoSCT

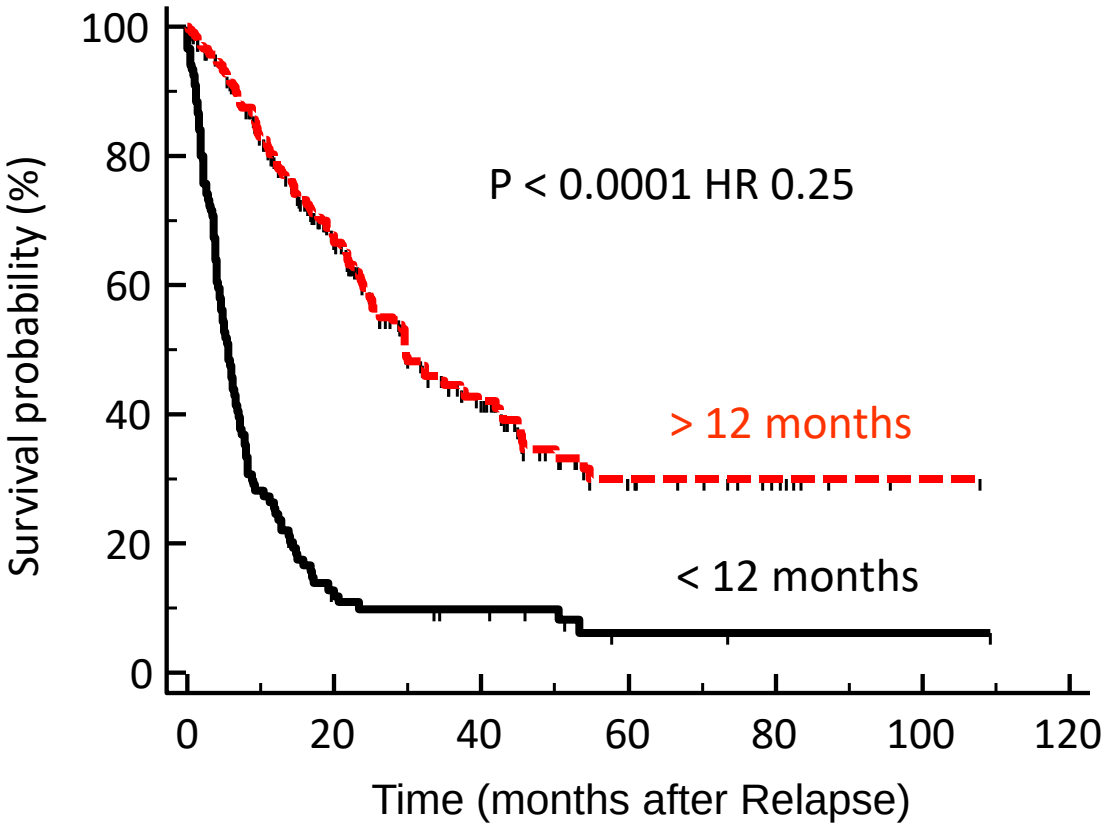


Prognostic factors after autoSCT failure

OS by remission duration after autoSCT

< 12 months 120 (33%)

> 12 months 240 (67%)



EBMT Registry Analysis, Ann. Onc. 2014, S. Dietrich

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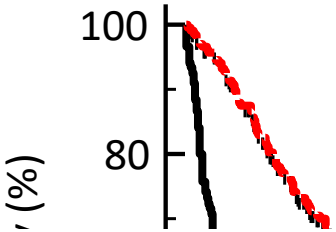
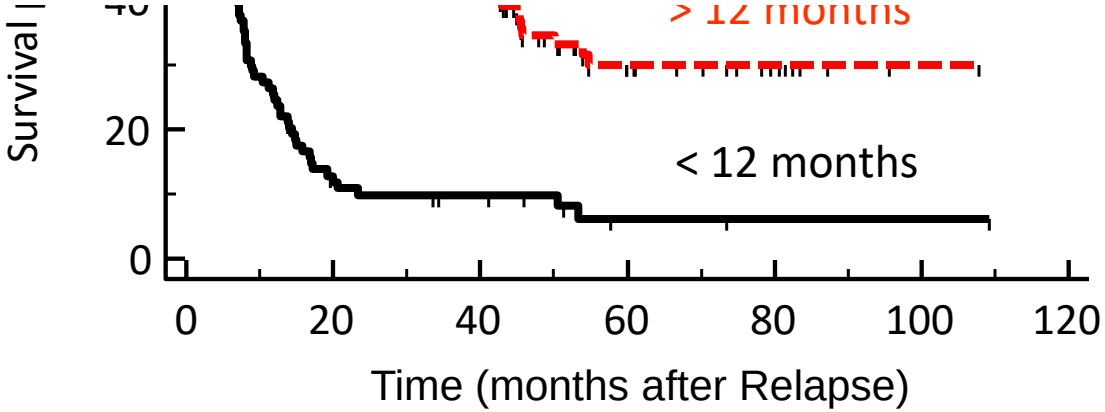


P < 0.0001 HR 0.25

* Low sMIPI >5y / in high sMIPI (>>1/2 cases) 0.9y



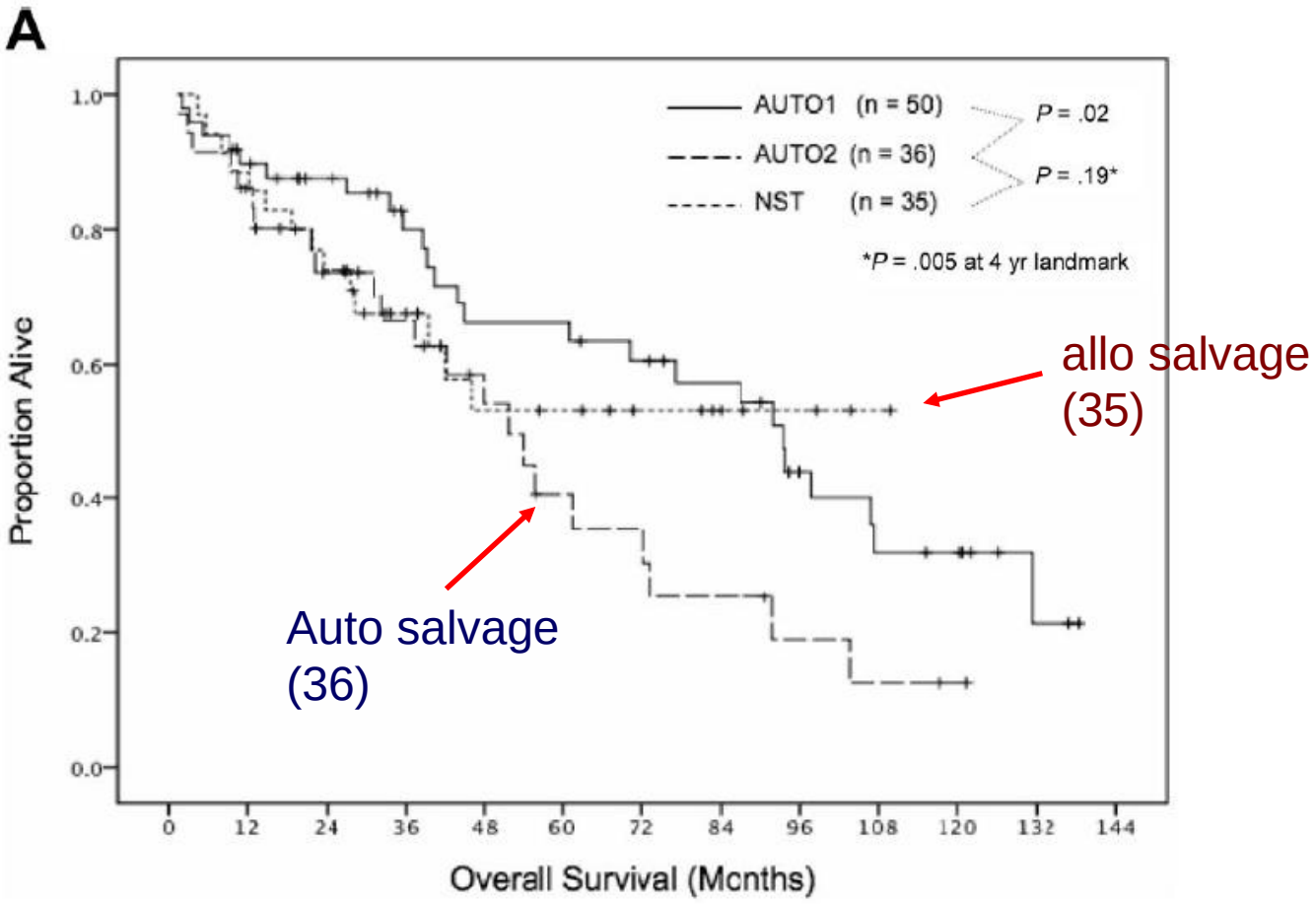
EBMT Registry Analysis, Ann. Onc. 2014, S. Dietrich

Relapses and Allo SCT

- In relapse, allo SCT is the only curative procedure
- However, allo SCT is associated to a significant NRM and new targeted therapies may improve prognosis and may induce long term response/cure
- Allo SCT in relapse
  - Which patients ?
  - Which treatment to bridge to AlloSCT ?
  - Which conditionning regimen ?
  - Which type of graft ?
  - Which follow up ?

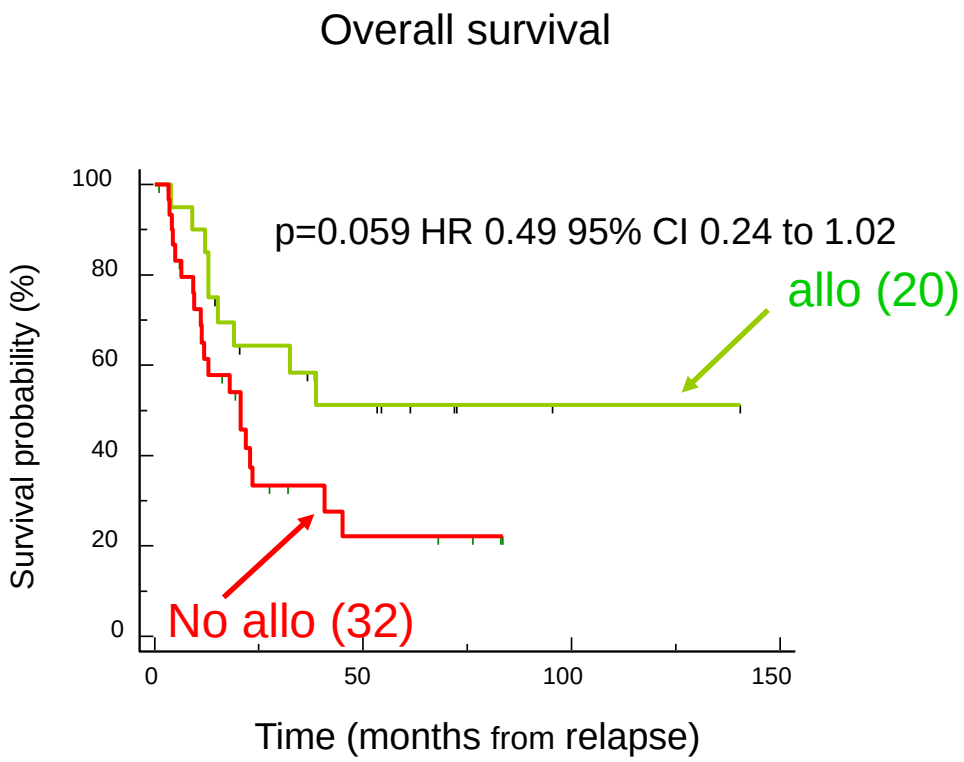
Allo vs Auto at relapse

Mature results of MDACC MCL transplants: OS



Tam et al. Blood 113:4144 (2009)

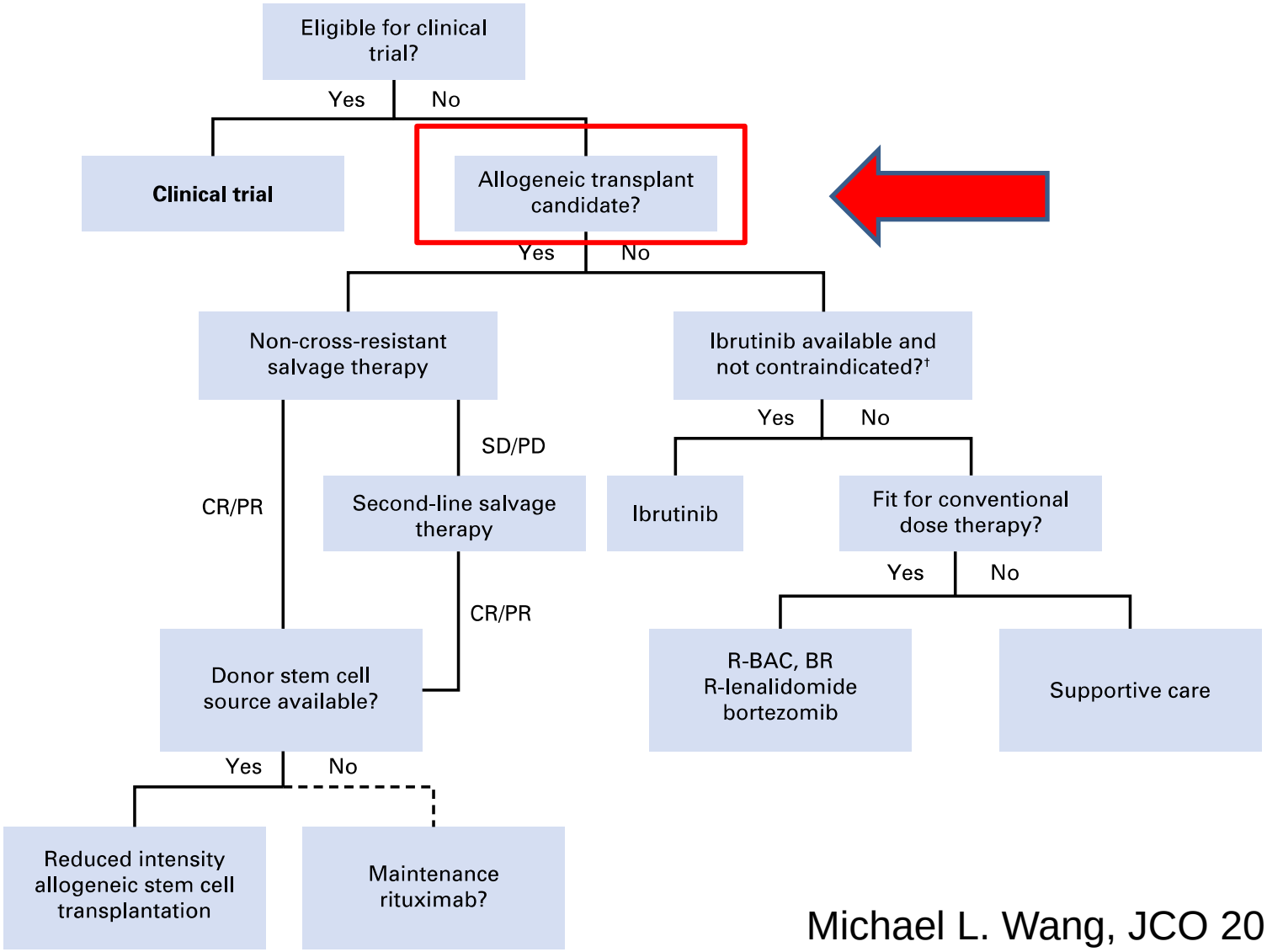
MCL: AlloSCT for autoSCT failure HD/KI/HH 1994-2008 (52 REL after 119 autotransplants)



Cancer

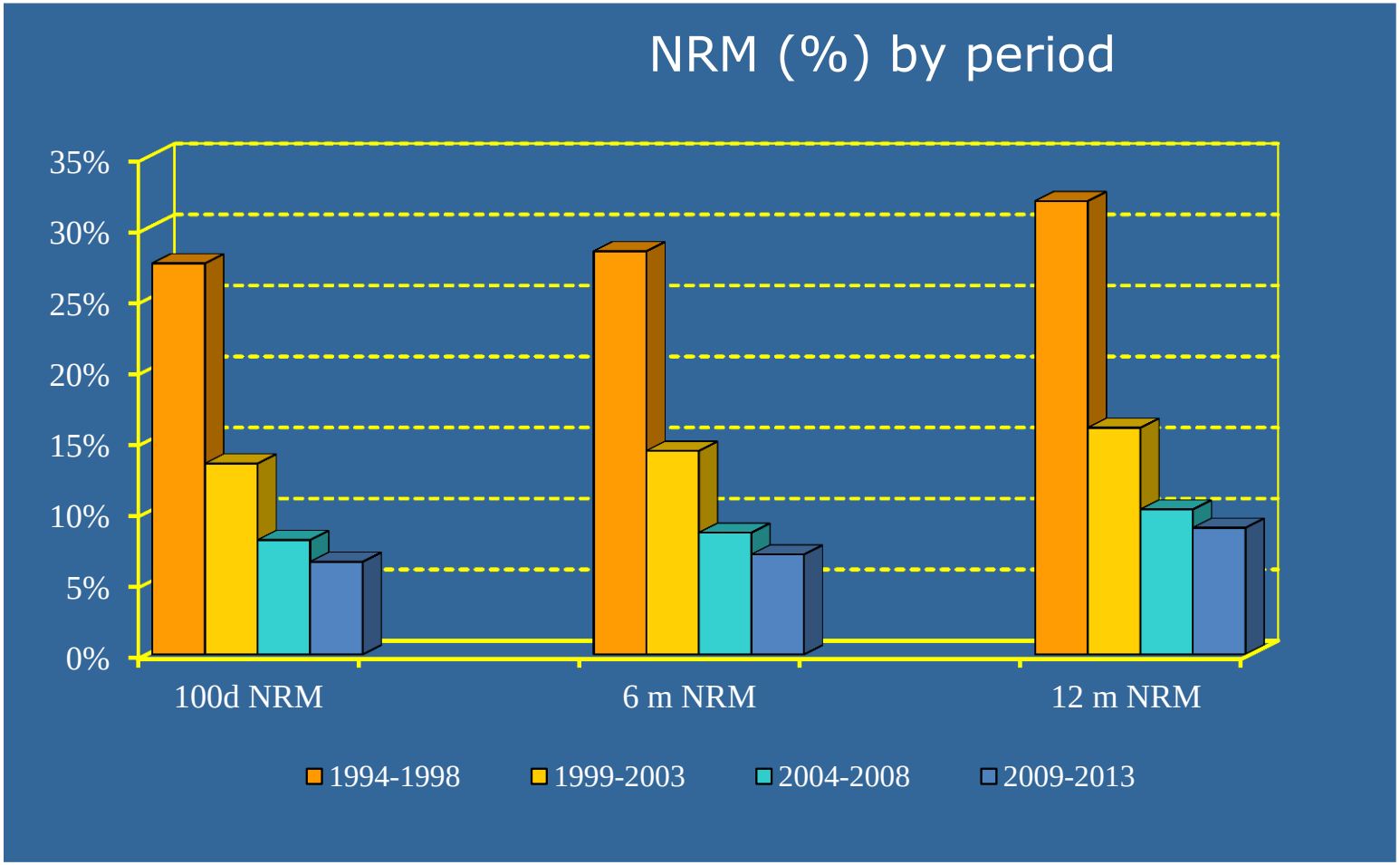
Dietrich et al, Cancer May 1, 2011

Mantle Cell Lymphoma
Relapse

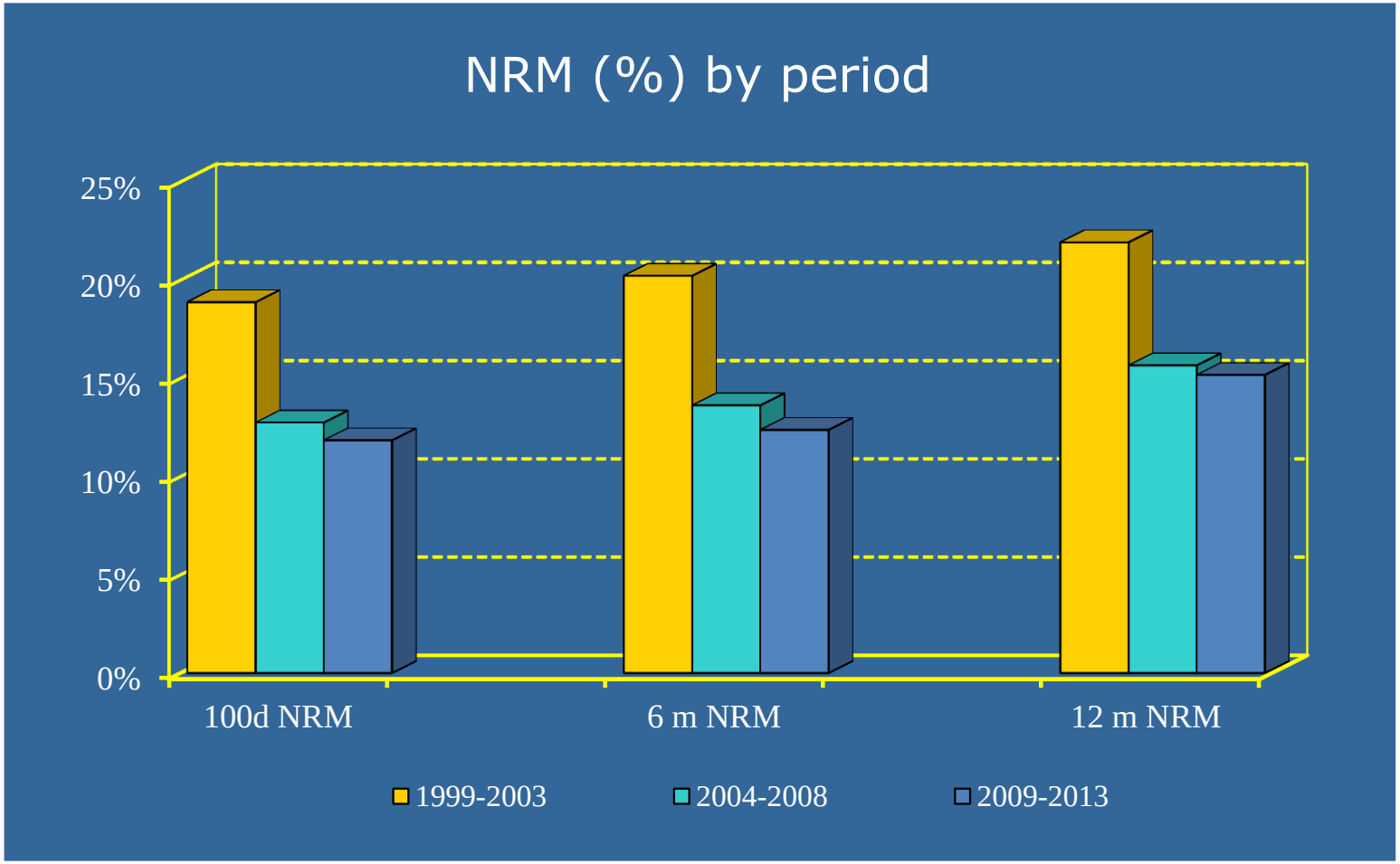


Michael L. Wang, JCO 2016

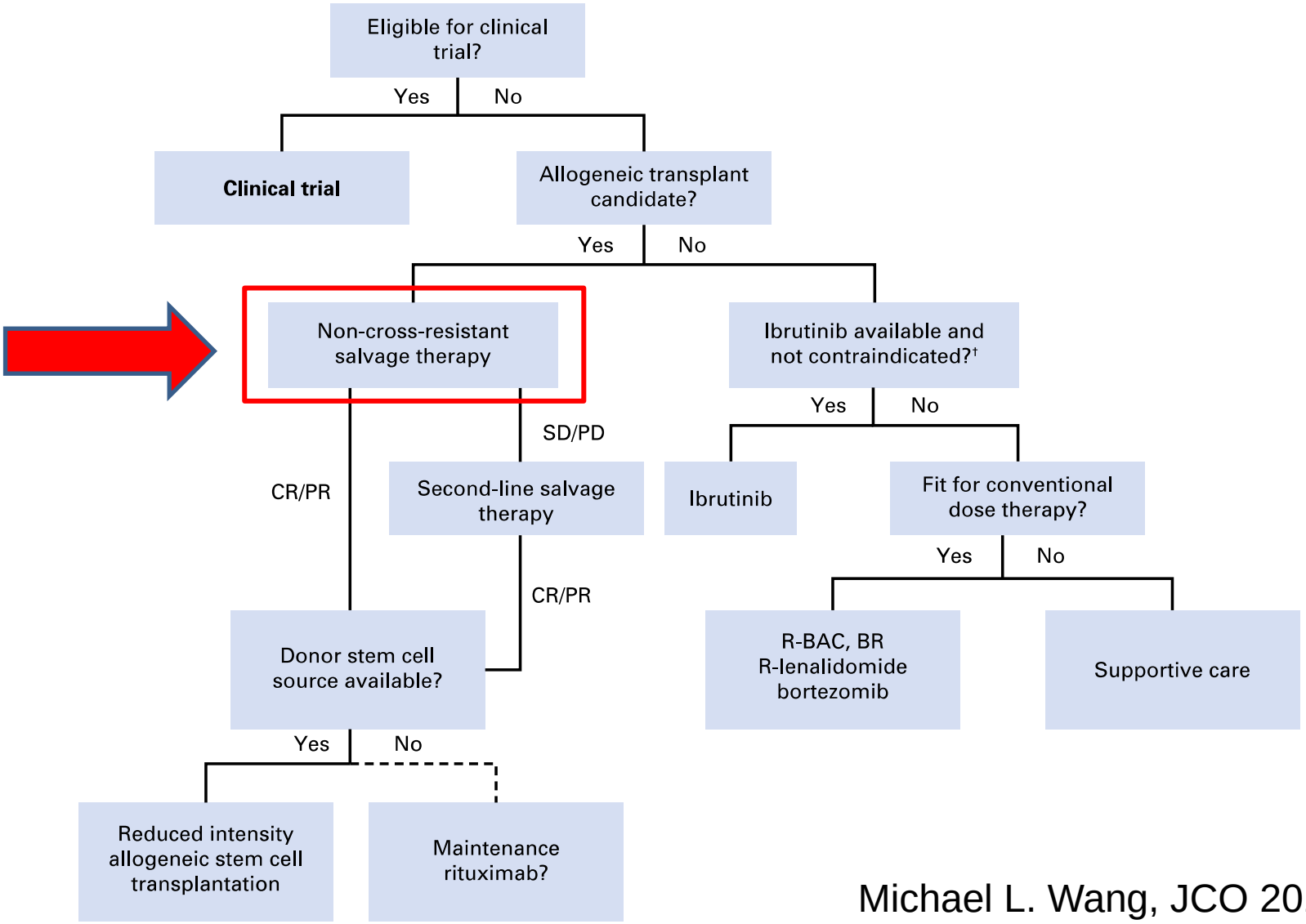
Lymphoma Registry: Allo-SCT adults 18-50 yo



Lymphoma Registry: Allo-SCT adults 51-70 yo



Mantle Cell Lymphoma: Relapse



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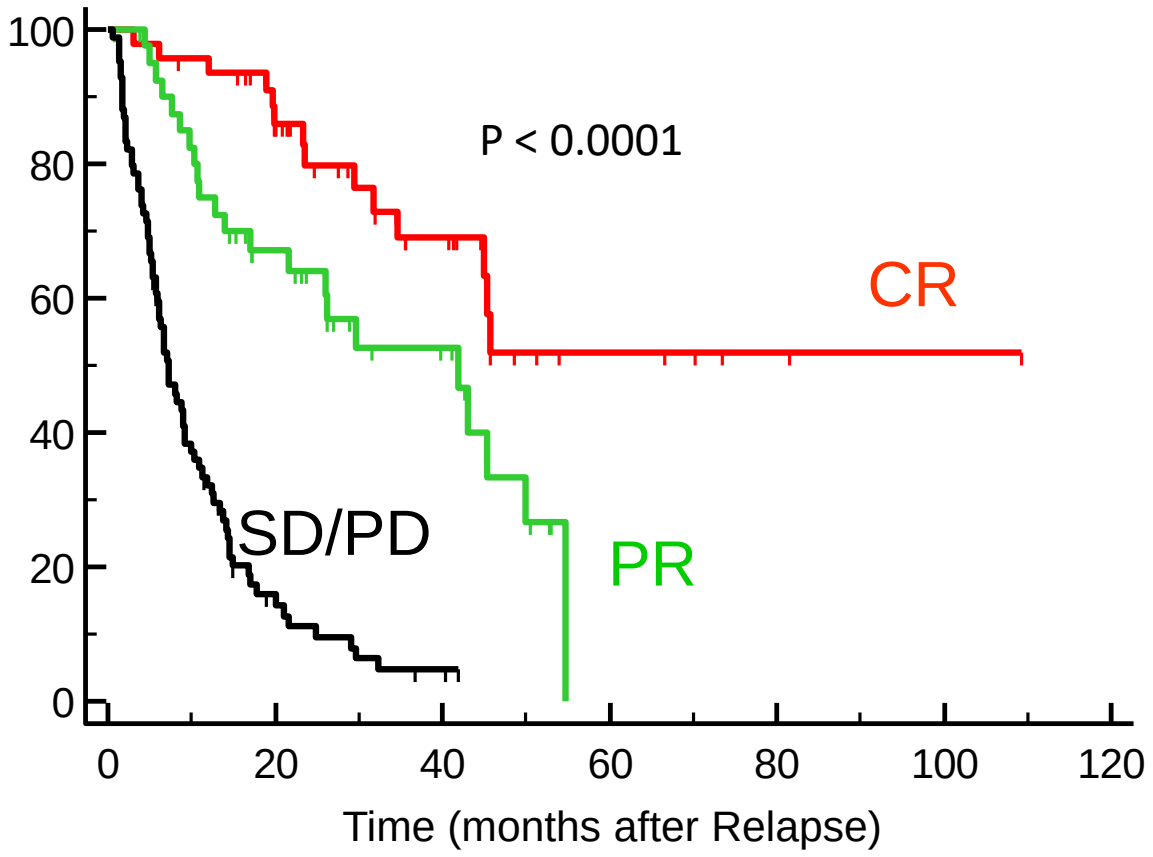
OS by response to 1st salvage therapy



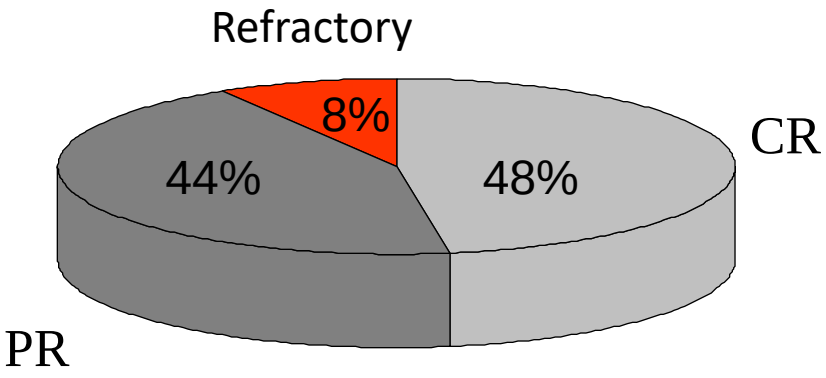
Chemotherapy salvage strategies

- No standard/ participation in clinical trials
- The salvage regimen used depends upon:

  - patient comorbidities
  - side effect profile of the selected regimen
  - prior therapies
  - clinical situation

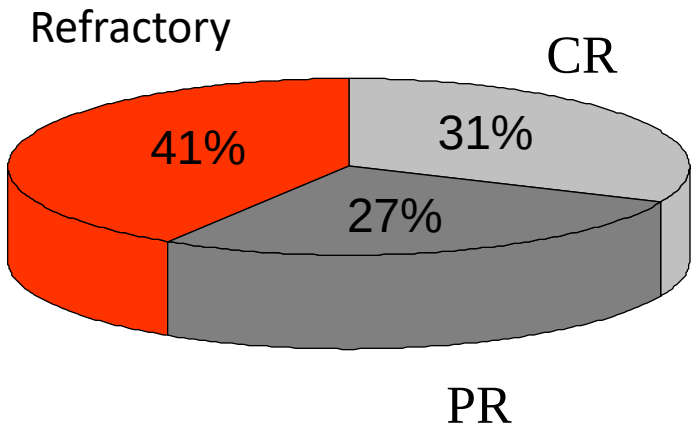
Response to salvage chemotherapy

Before 1st autoSCT



CR	48%
PR	44%
Refractory	**8%**

Salvage after autoSCT-relapse



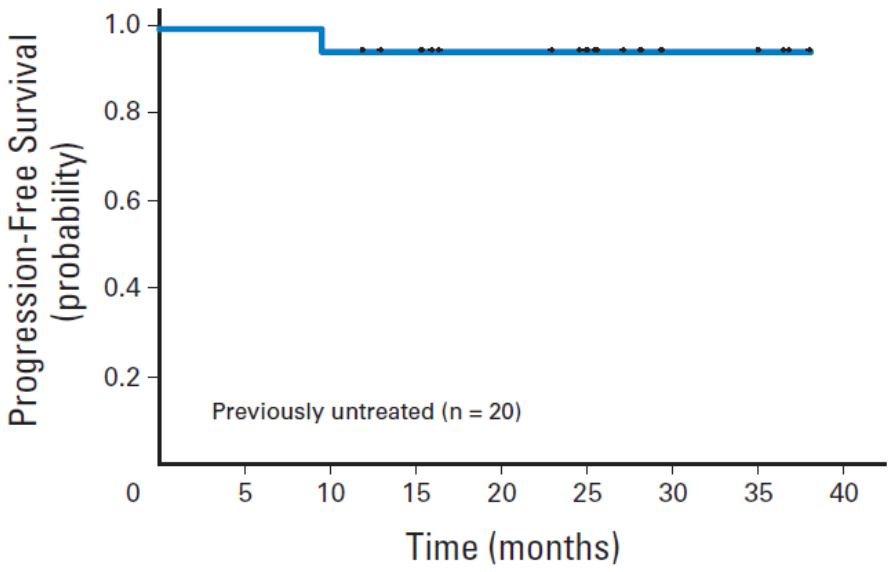
CR	31%
PR	27%
Refractory	**42%**

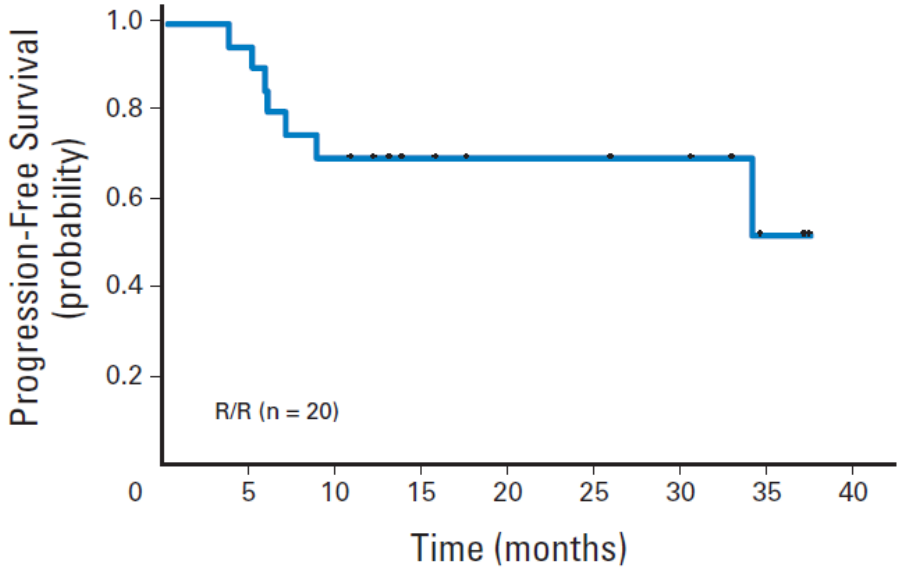
Treatment options for relapsed MCL

- ✓ Chemotherapy
  - ❑ Aracytine
  - ❑ Bendamustine combination
  - ❑ Anthracyclins/alkylating agents
- ✓ Novel drugs alone or in combinations
  - ❑ PI3K inhibitors
  - ❑ Temsirolimus
  - ❑ Ibrutinib
  - ❑ Lenalidomide
  - ❑ Bortezomib
  - ❑ Venetoclax

Mantle cell lymphoma
R-BAC

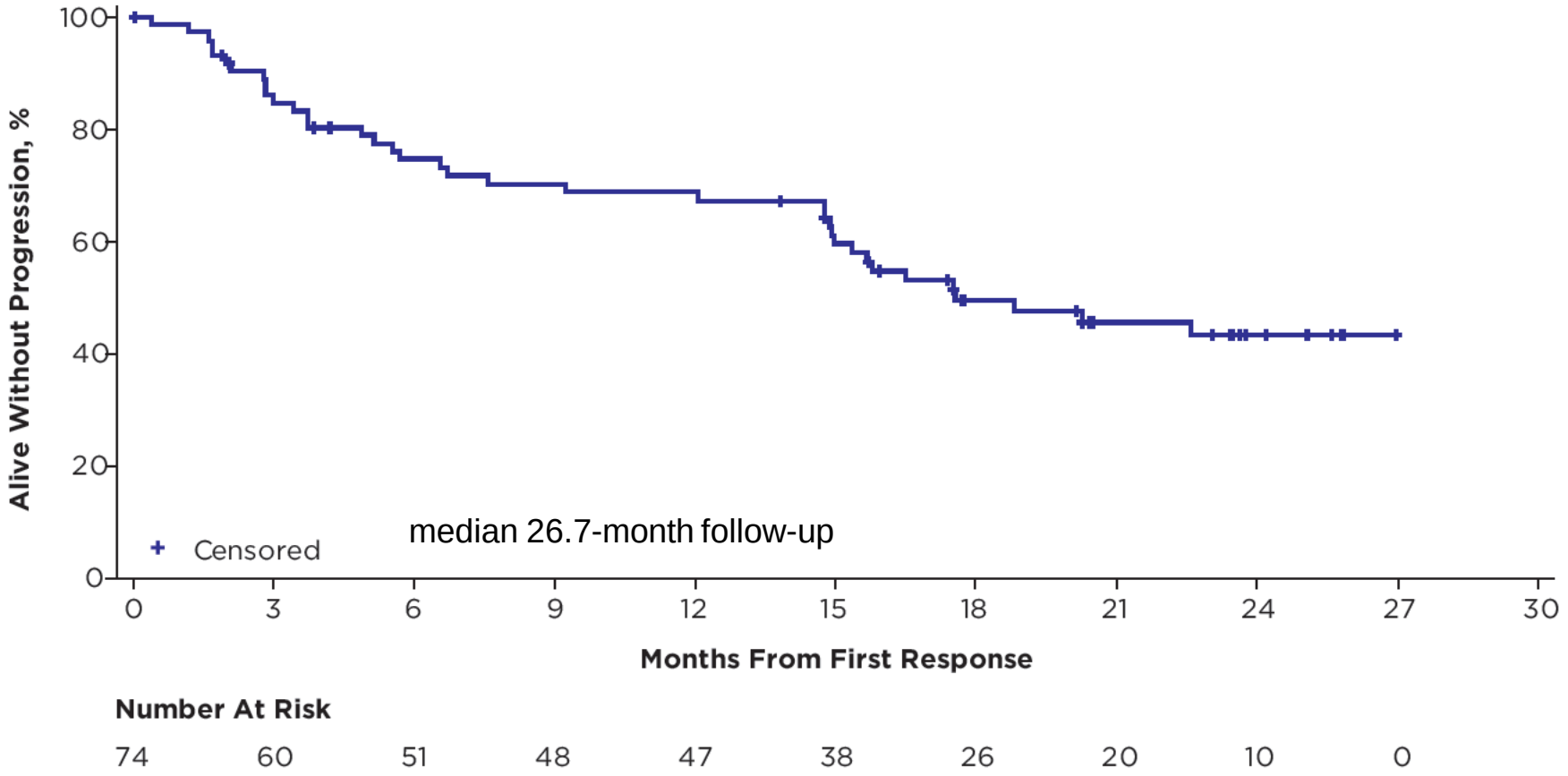
Characteristic	All Patients (N = 40)		Previously Untreated Patients (n = 20)		R/R Patients (n = 20)	
	No.	%	No.	%	No.	%
Response rates						
OR	36	90	20	100	16	80
CR	33	83	19	95	14	70
PR	3	7	1	5	2	10
NR	3	7	0	0	3	15
PD	1	3	0	0	1	5





Visco, JCO 2013

BTK inhibitor Ibrutinib
Duration of response



Wang, NEJM 2013, ASH 2014

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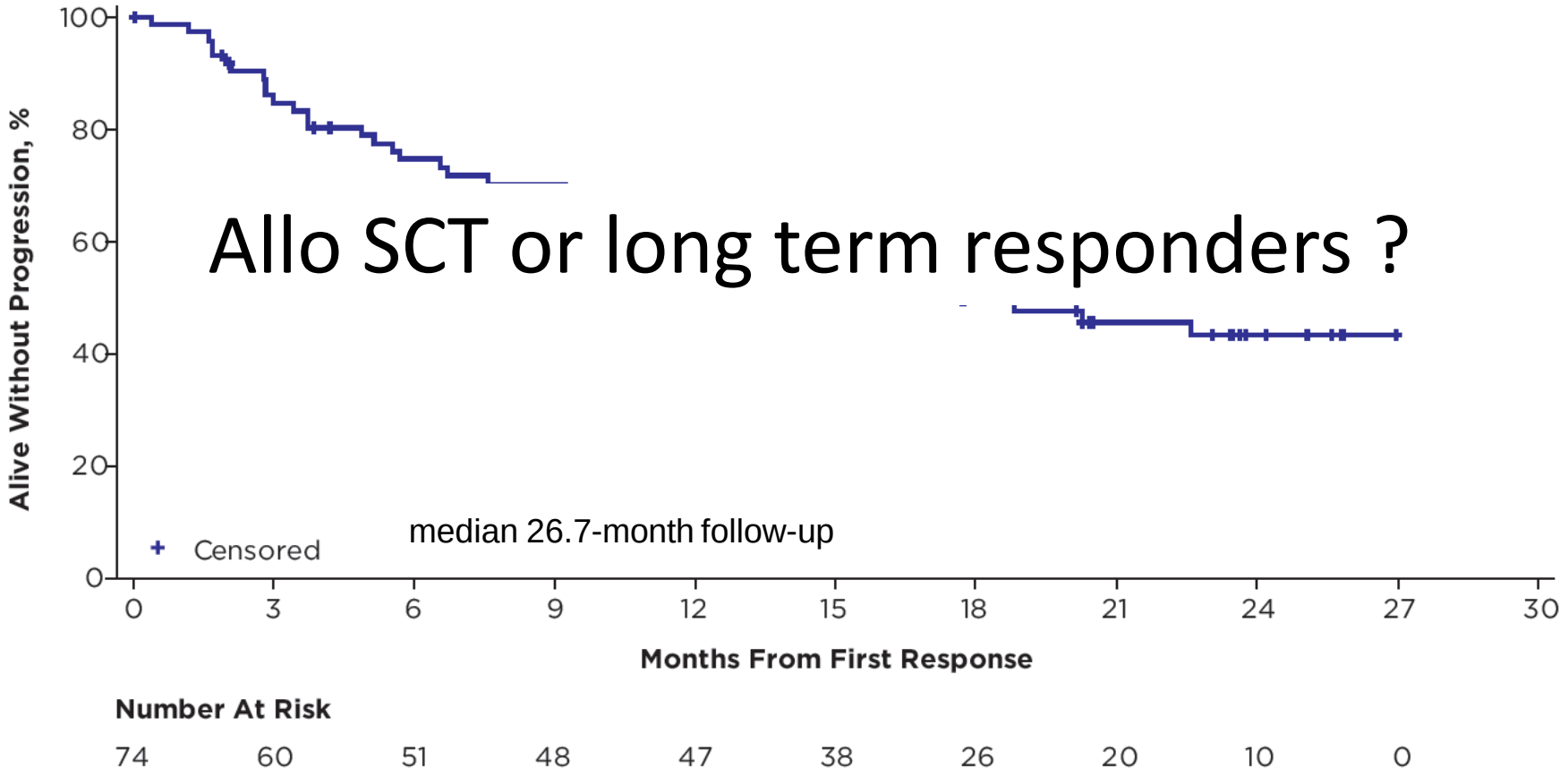
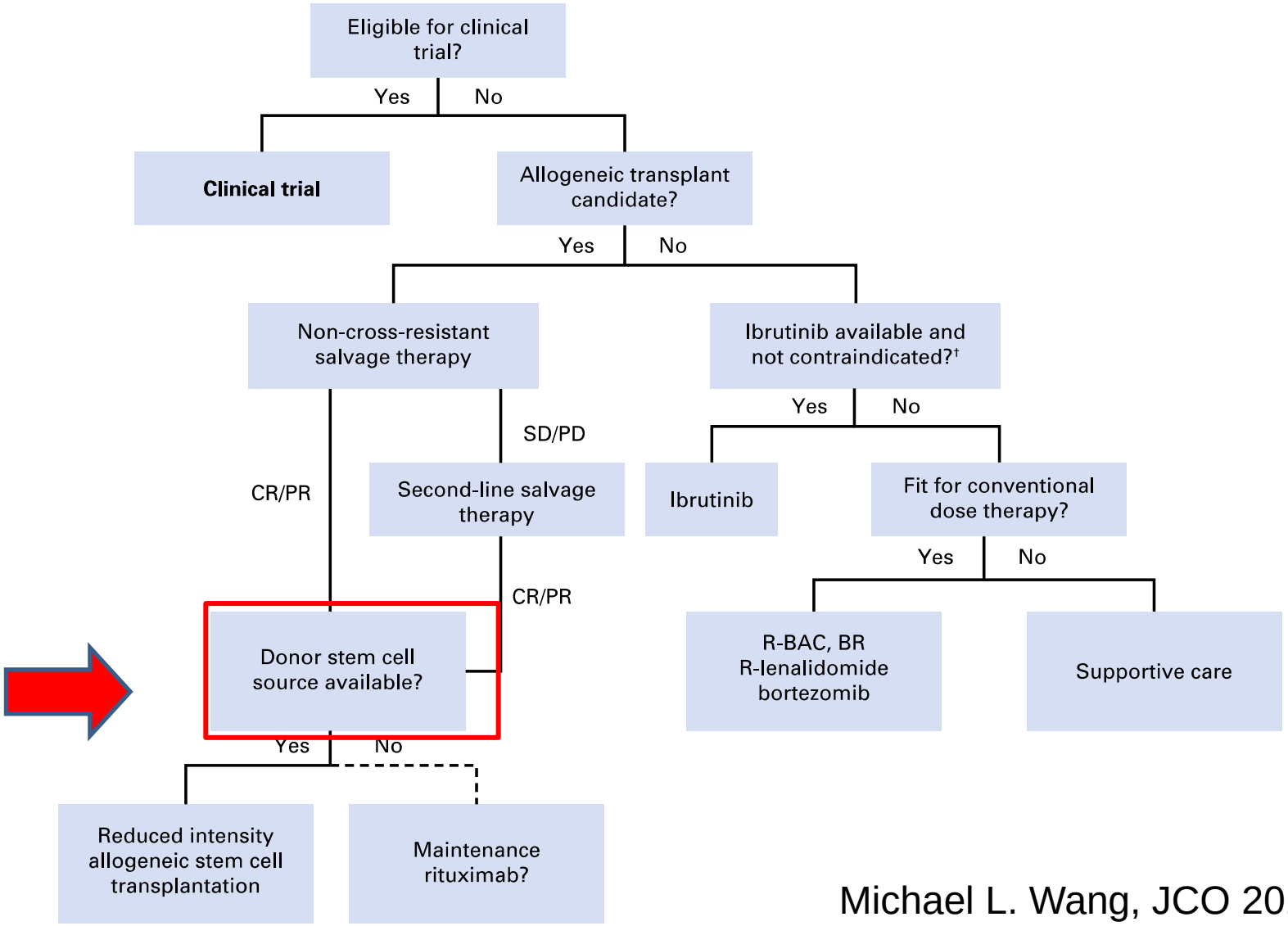


Allo SCT or long term responders ?

Wang, NEJM 2013, ASH 2014

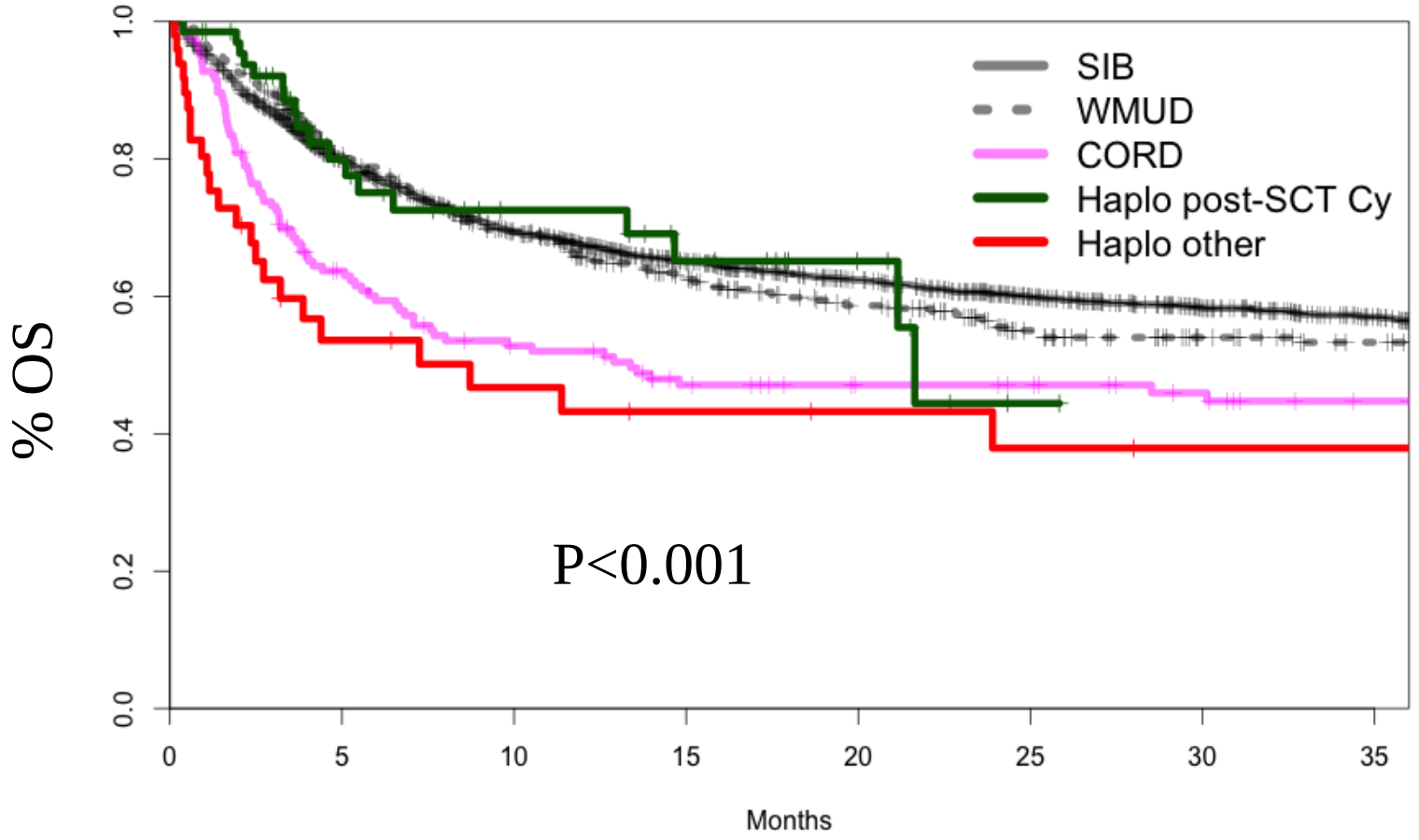
Mantle Cell Lymphoma: Relapse



Michael L. Wang, JCO 2016

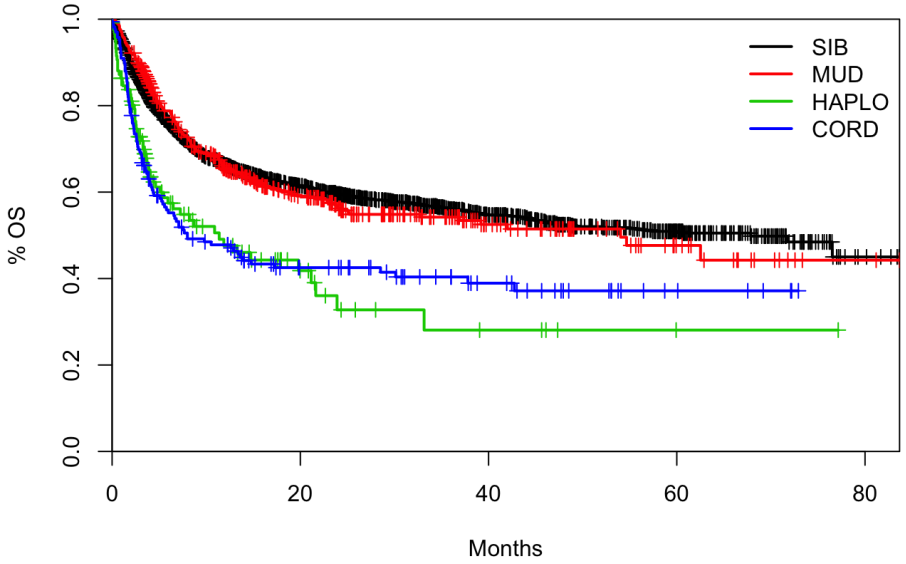
Donors for alloSCT in Lymphoma

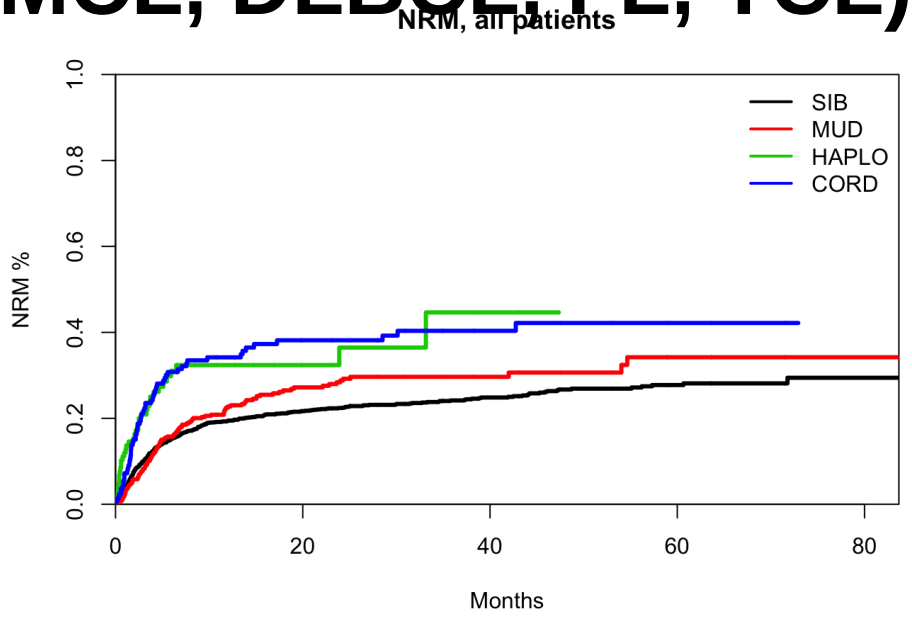
Adjusted for year of SCT, remission, performance status

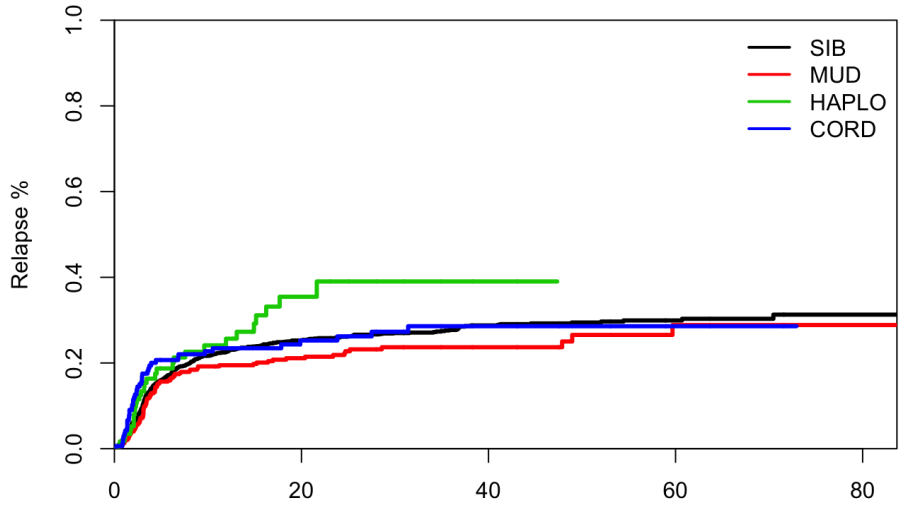


Dietrich et al, Leukemia 2016

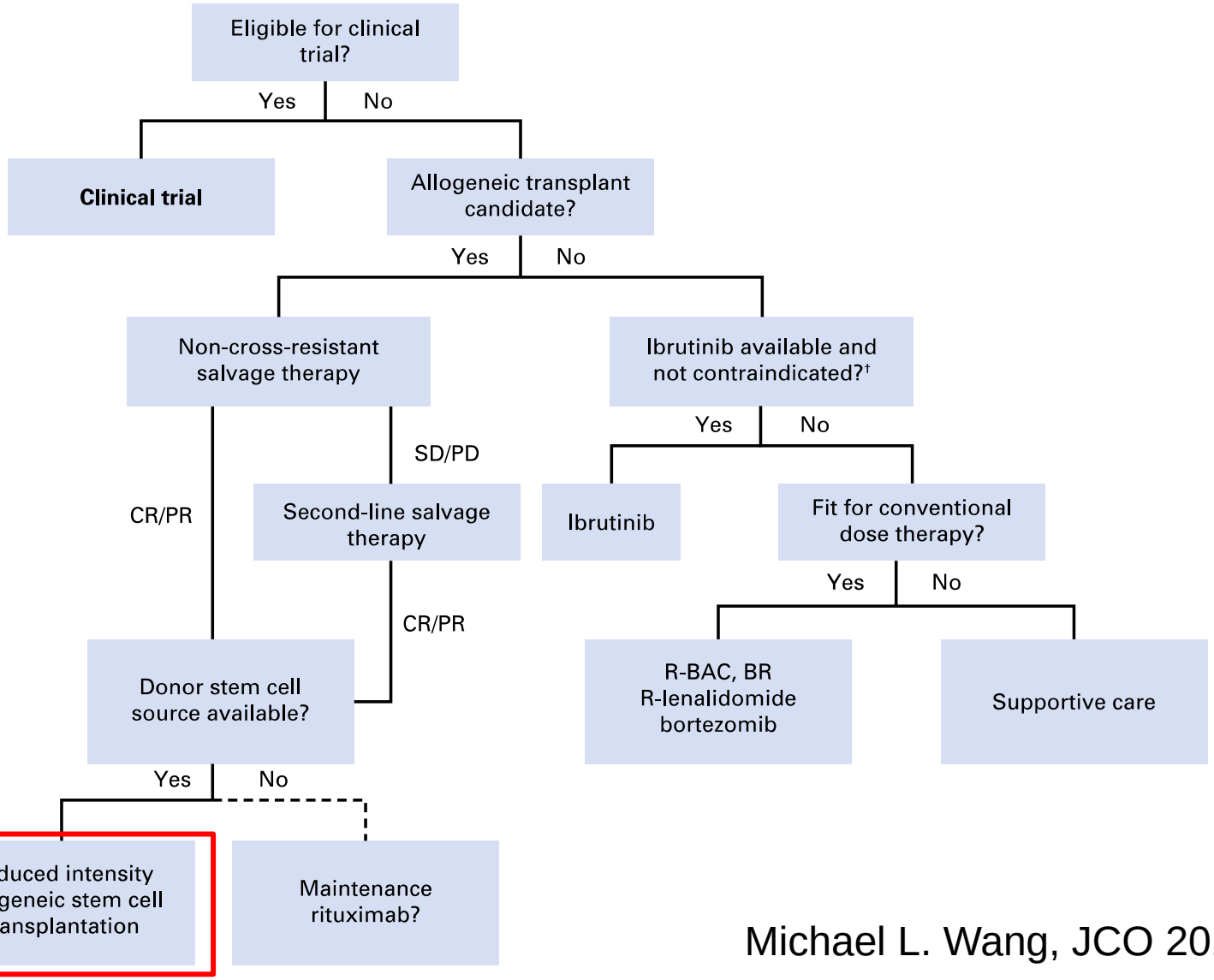
Donor Choice
(A pooled analysis of MCL, DLBCL, FL, TCL)







Mantle Cell Lymphoma: Relapse

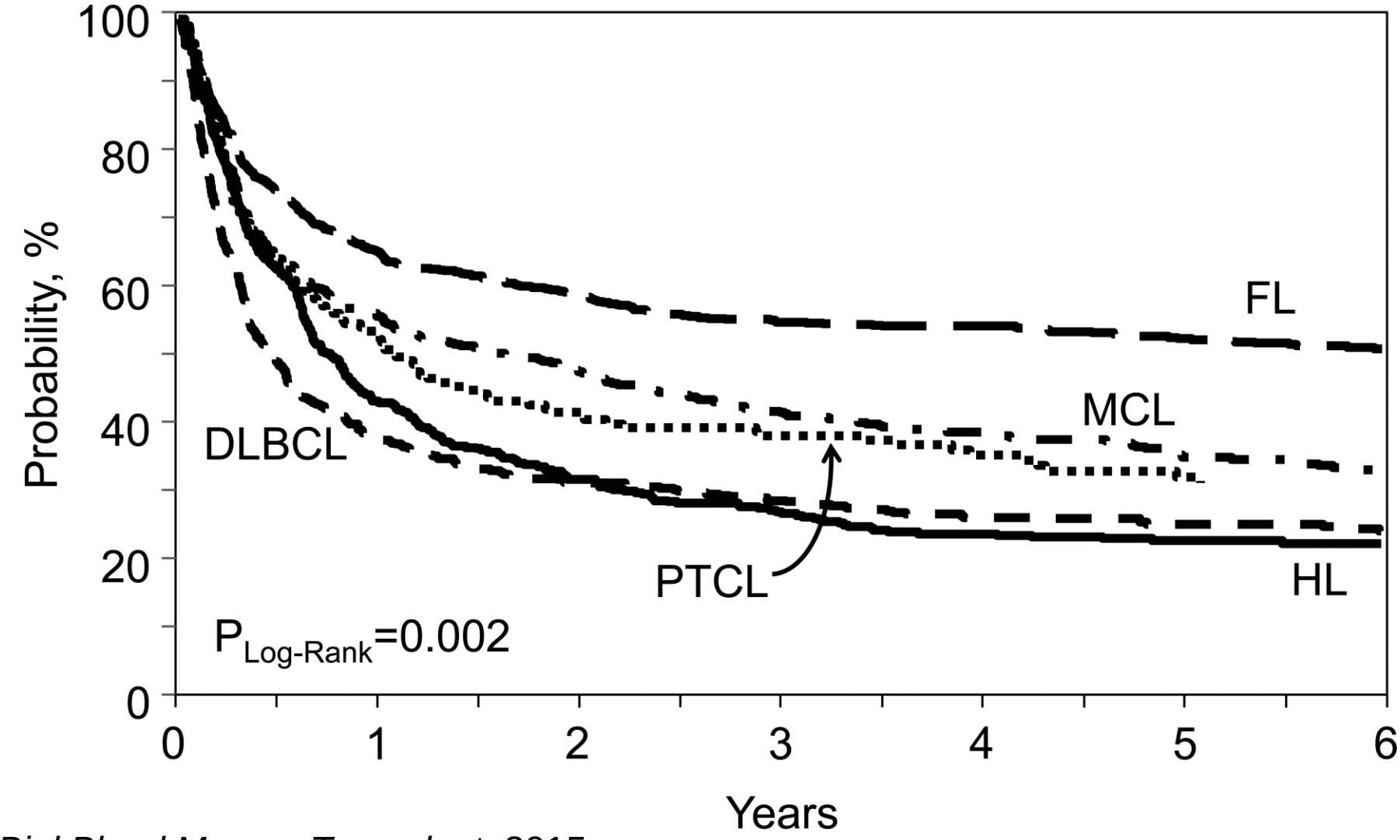


Michael L. Wang, JCO 2016

MAC vs. RIC alloSCT in MCL

Study	Design	n	Conditioning	2y-NRM	2y-DFS	2y-OS
Khouri	phase-II;	16	TBI/Cy	6 of 16	55% (3y)	55% (3y)
Laudi	phase-II	17	TBI/Cy	29%	50%	49%
Ganti	retrospective	17	TBI/Cy	19% (3m)	53%	58%
Maris	phase-II;	33	TBI2/F	24%	60%	65%
Khouri	phase-II	35	FC-R +/- CD52	9%	50% (4y)	54% (4y)
Morris	phase-II	10	F/Mel/CD52	20%	50% (3y)	60% (3y)

THE IMPACT OF GRAFT VERSUS HOST DISEASE ON RELAPSE RATE IN PATIENTS WITH LYMPHOMA DEPENDS ON THE HISTOLOGICAL SUB-TYPE AND THE INTENSITY OF THE CONDITIONING REGIMEN



Biol Blood Marrow Transplant. 2015

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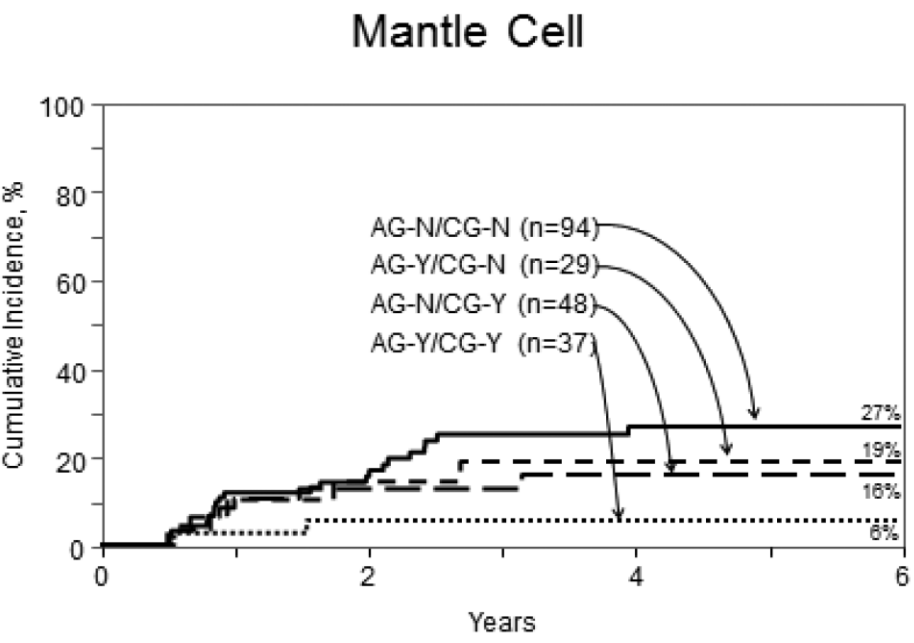
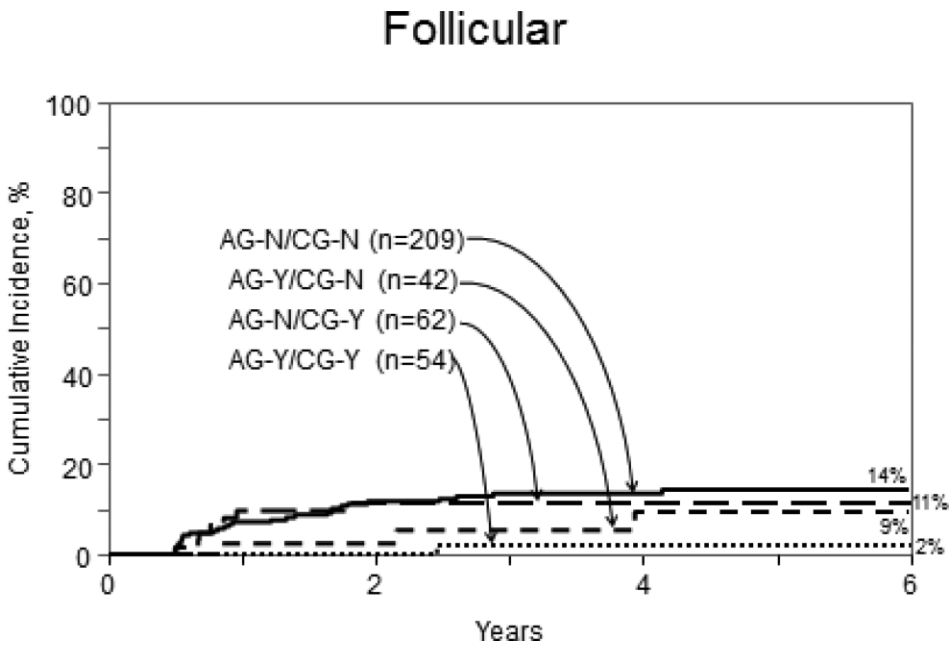
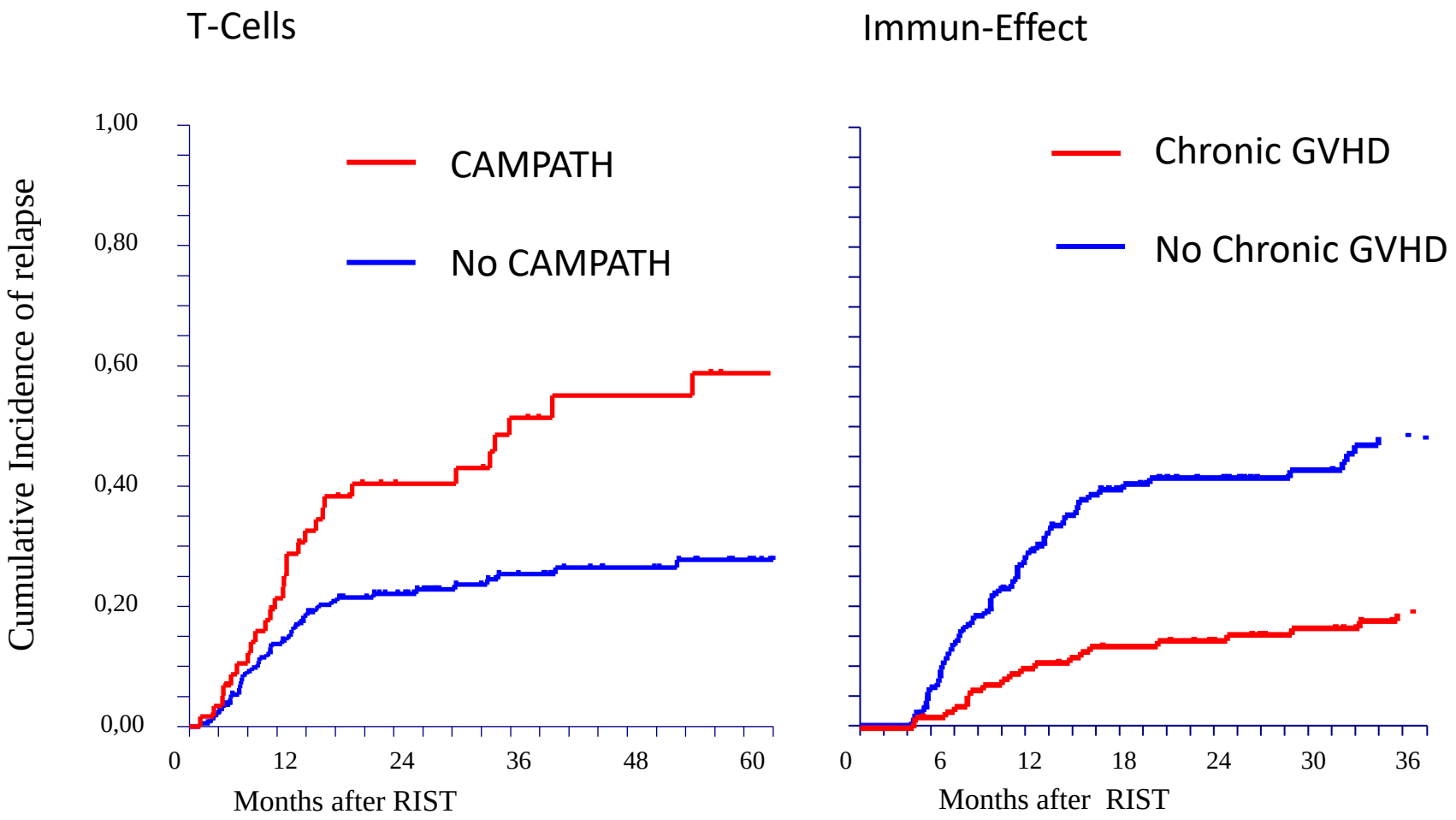


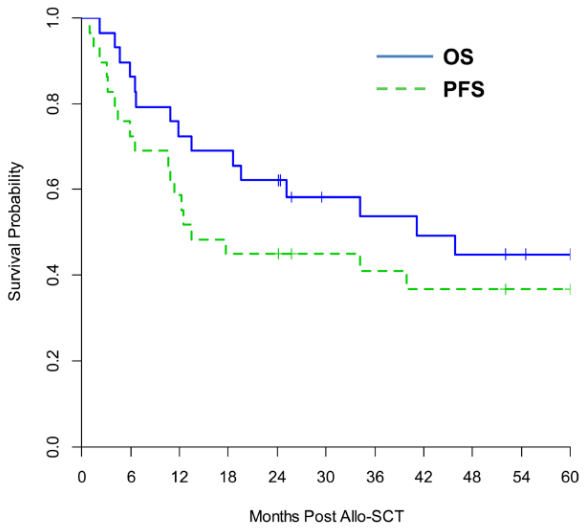


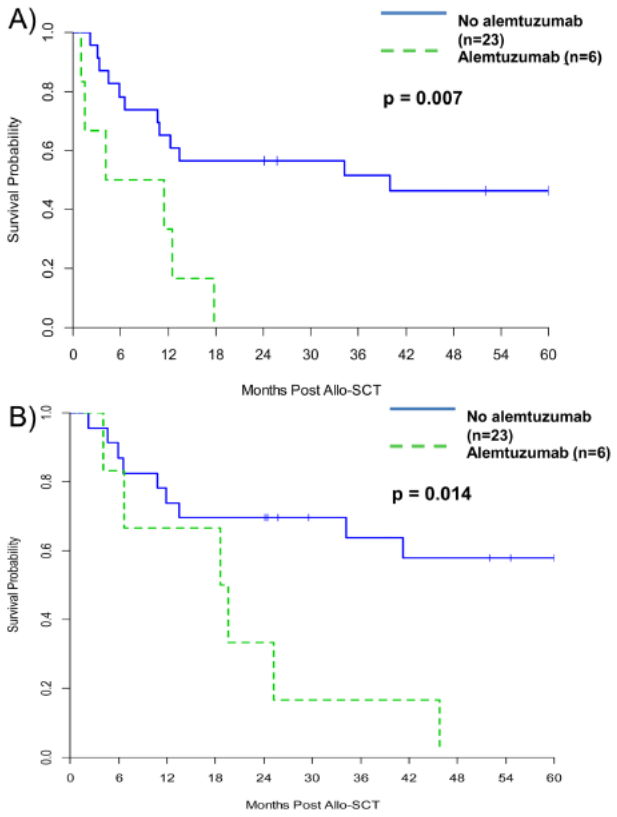
Biol Blood Marrow Transplant. 2015

Is there a Graft versus MCL (GV-MCL)?



Non-myeloablative Allogeneic Hematopoietic Stem Cell Transplantation for Adults with Relapsed and Refractory Mantle Cell Lymphoma: A Single Center Analysis in the Rituximab Era

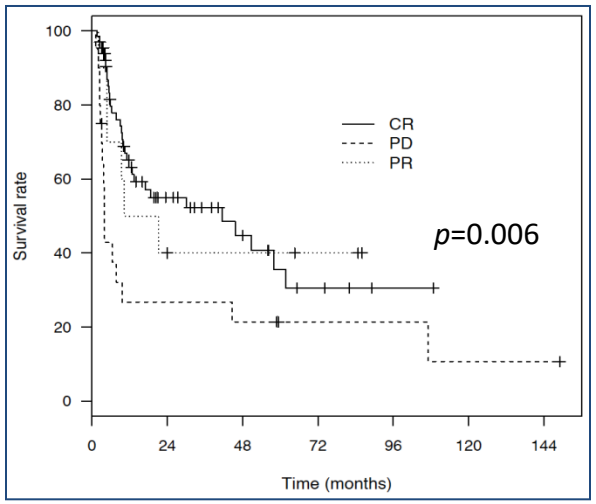




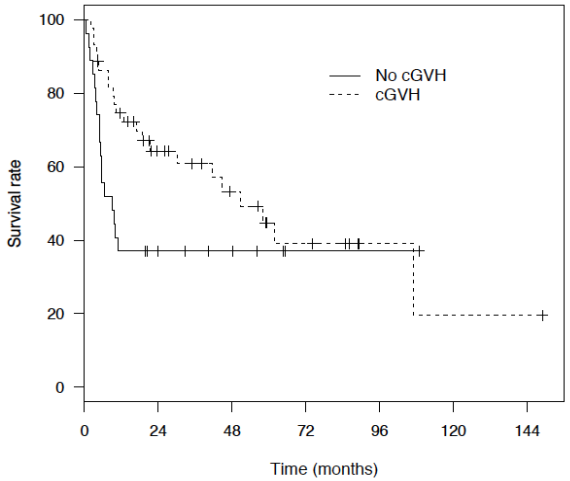
Bone Marrow Transplant. 2015 October ; 50(10): 1293–1298.

Response prior to RIC-Allo and role of cGvH

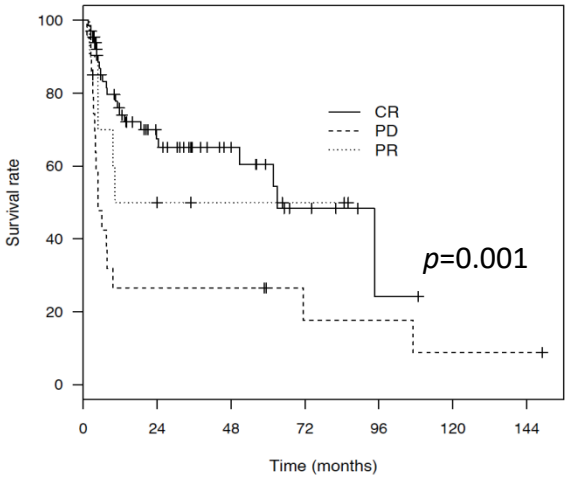
PFS



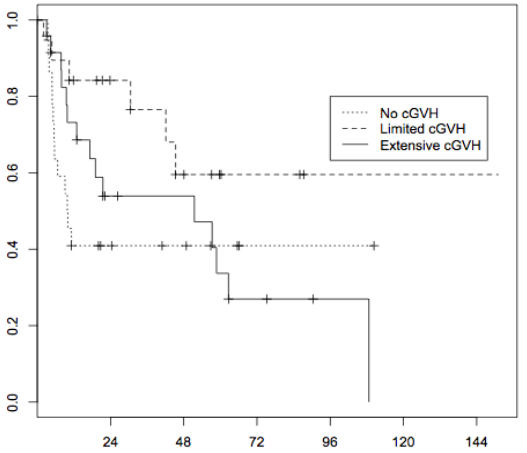
PFS



OS

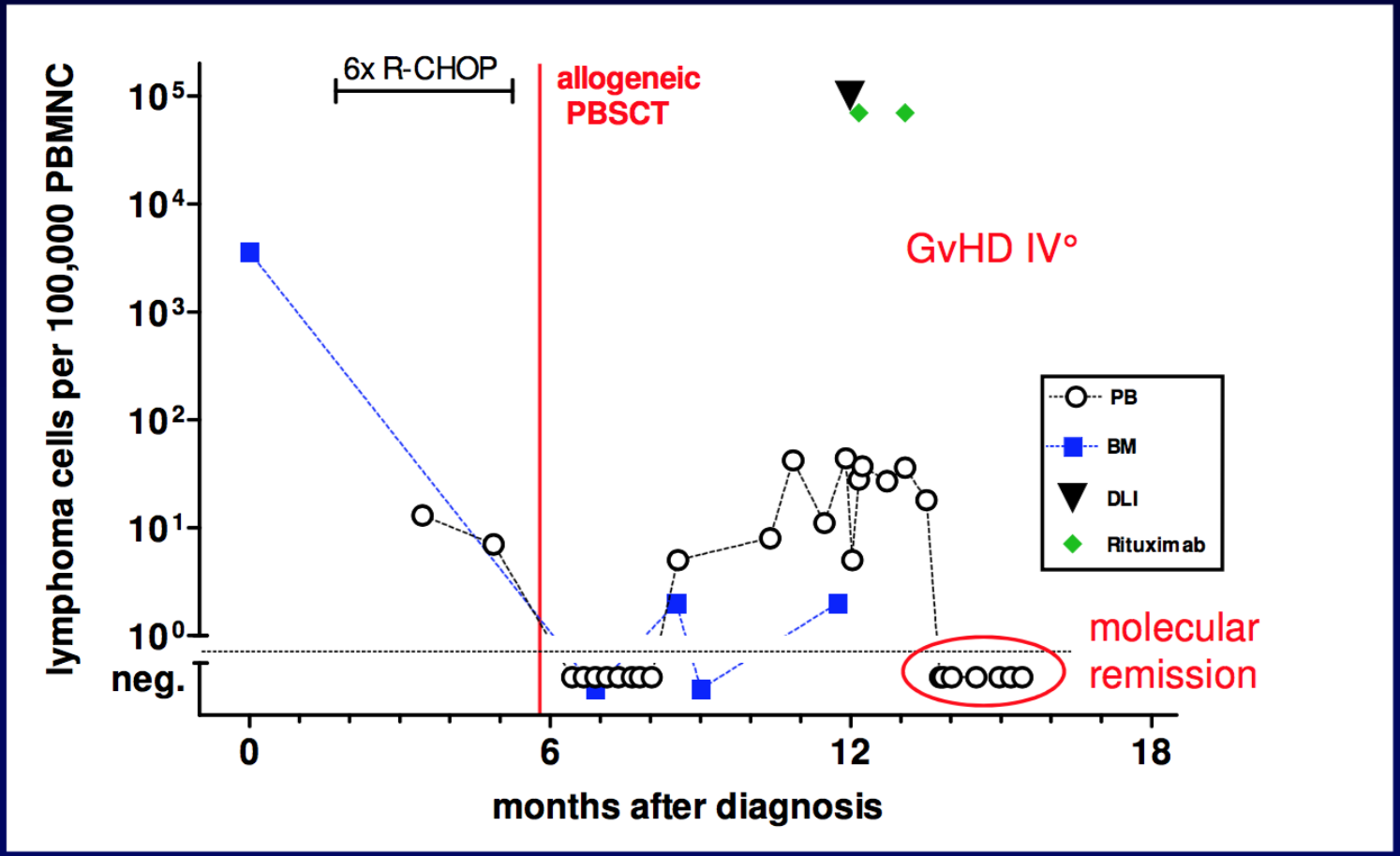


PFS



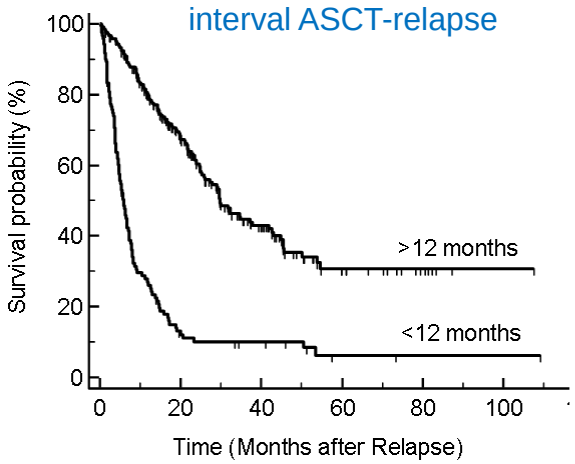
MCL_{BV}: relapse after alloSCT
➡ Rituximab + DLI

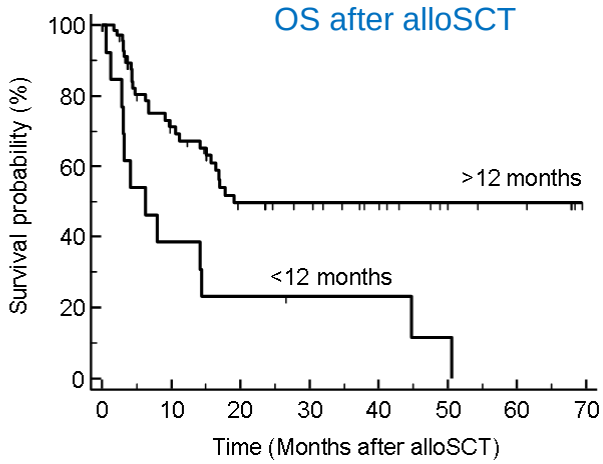
Molecular remission



Failure after ASCT

- ✓ 366 EBMT pts with MCL relapsed after ASCT (first line 64%; prior rituximab 68%; prior HD-ARAC 49%; 12% refractory to autoSCT).
- ✓ Salvage therapy: alloSCT in 23% and 2nd ASCT in 2%.
- ✓ Median f-up: 37 months.



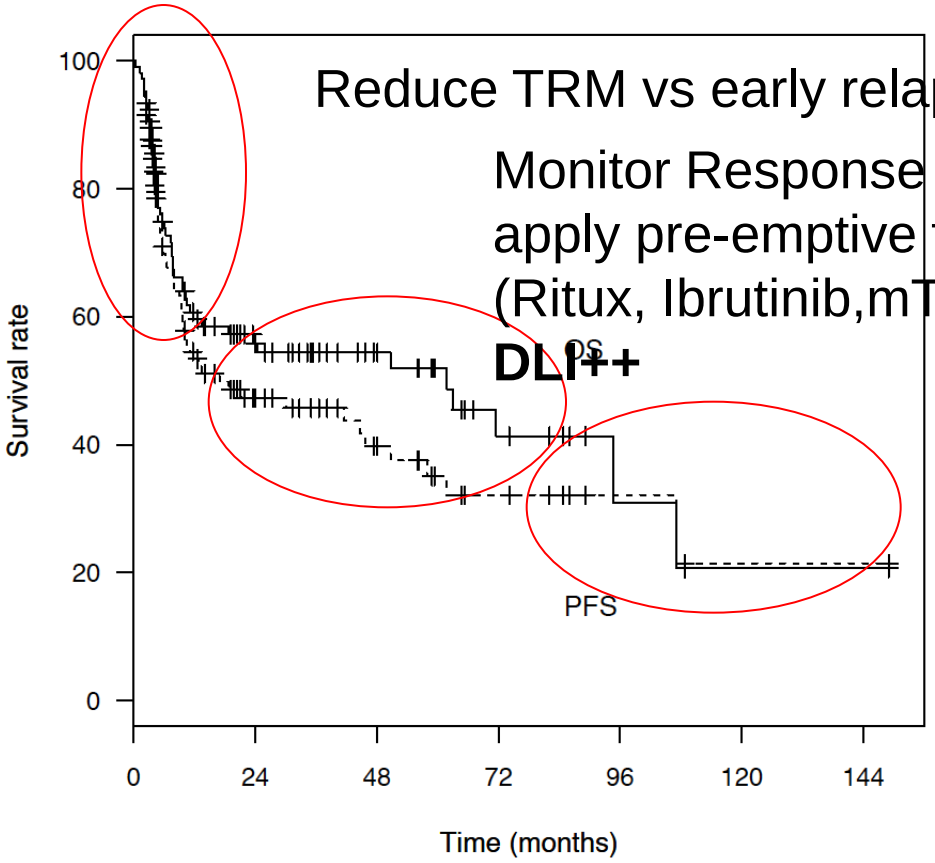


Median OS 20 mths

- ✓ OS for patients who received a 2nd ASCT was very poor.
- ✓ AlloSCT performed for late relapse (>12 mo after ASCT) was associated with superior OS.
- ✓ Donor source, T-cell depletion or conditioning intensity did not affect OS.

Diethich S, et al. Abstract #474 ASH 2012

How to improve these results?



Reduce TRM vs early relapses

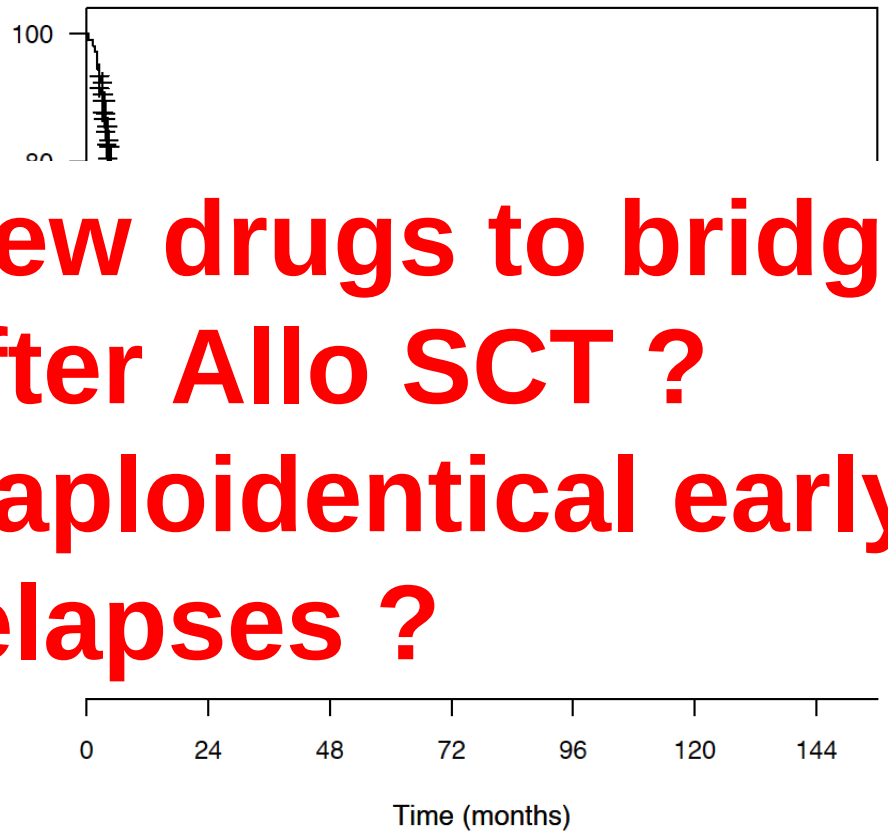
Monitor Response and apply pre-emptive therapies (Ritux, Ibrutinib,mTOR ?)

DLI++

Long term survivors
Maintenance therapy ?

Le Gouill, ICML 2013

How to improve these results?

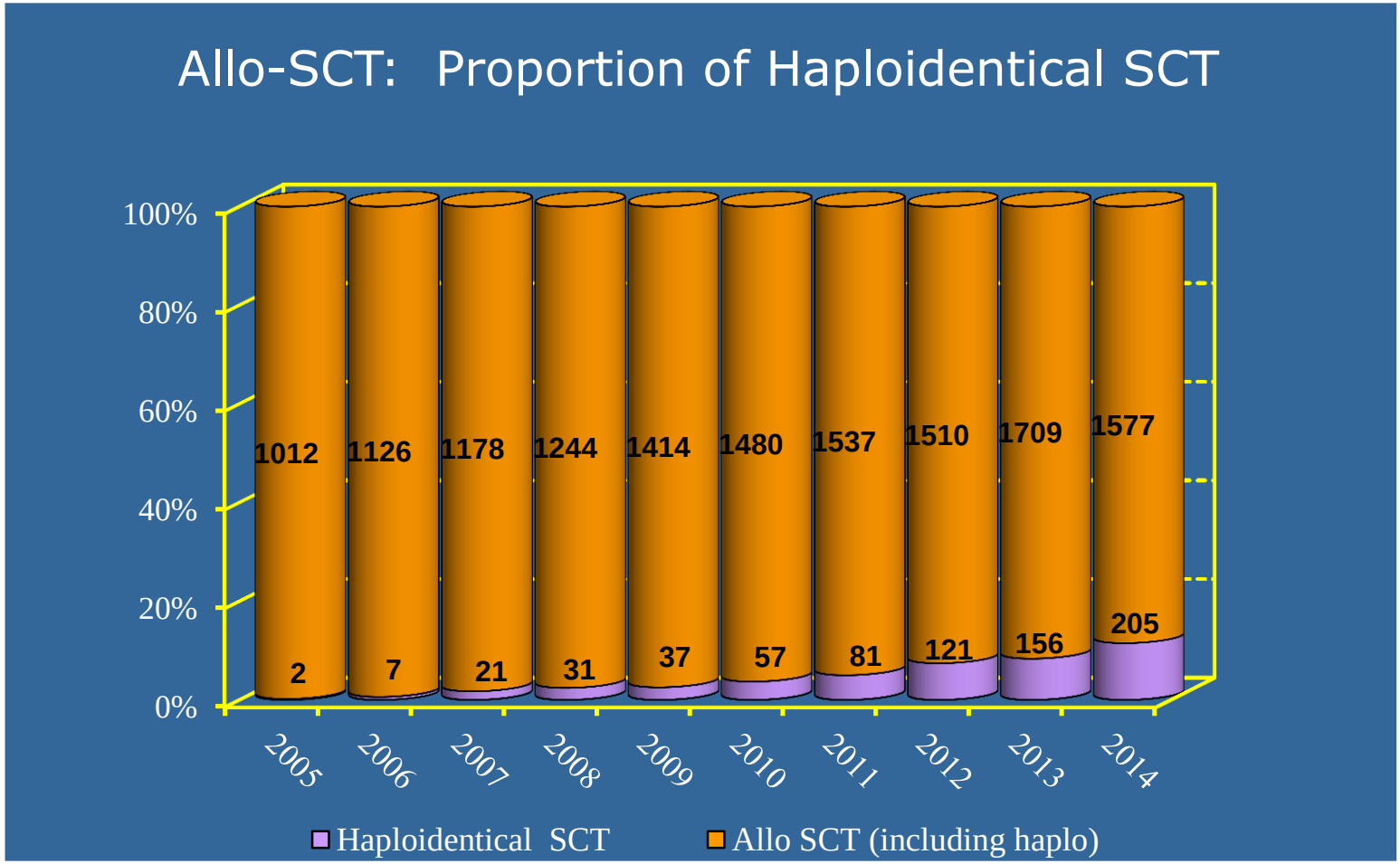


New drugs to bridge or after Allo SCT ?

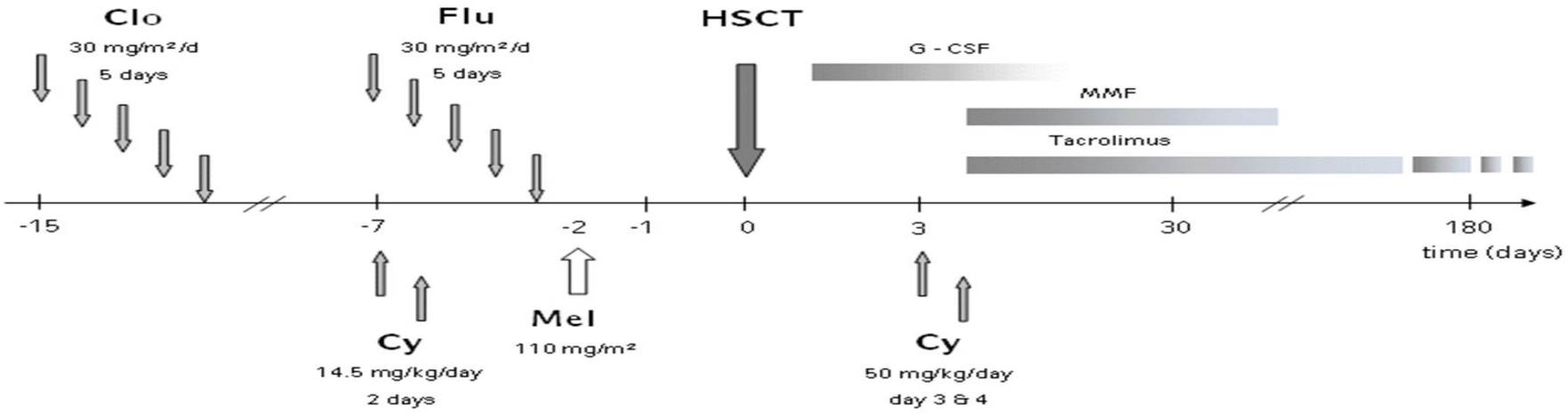
Haploidentical early relapses ?

Le Gouill, ICML 2013

Lymphoma Registry: SCT 2005-2014



Haplo-identical transplantation for MCL



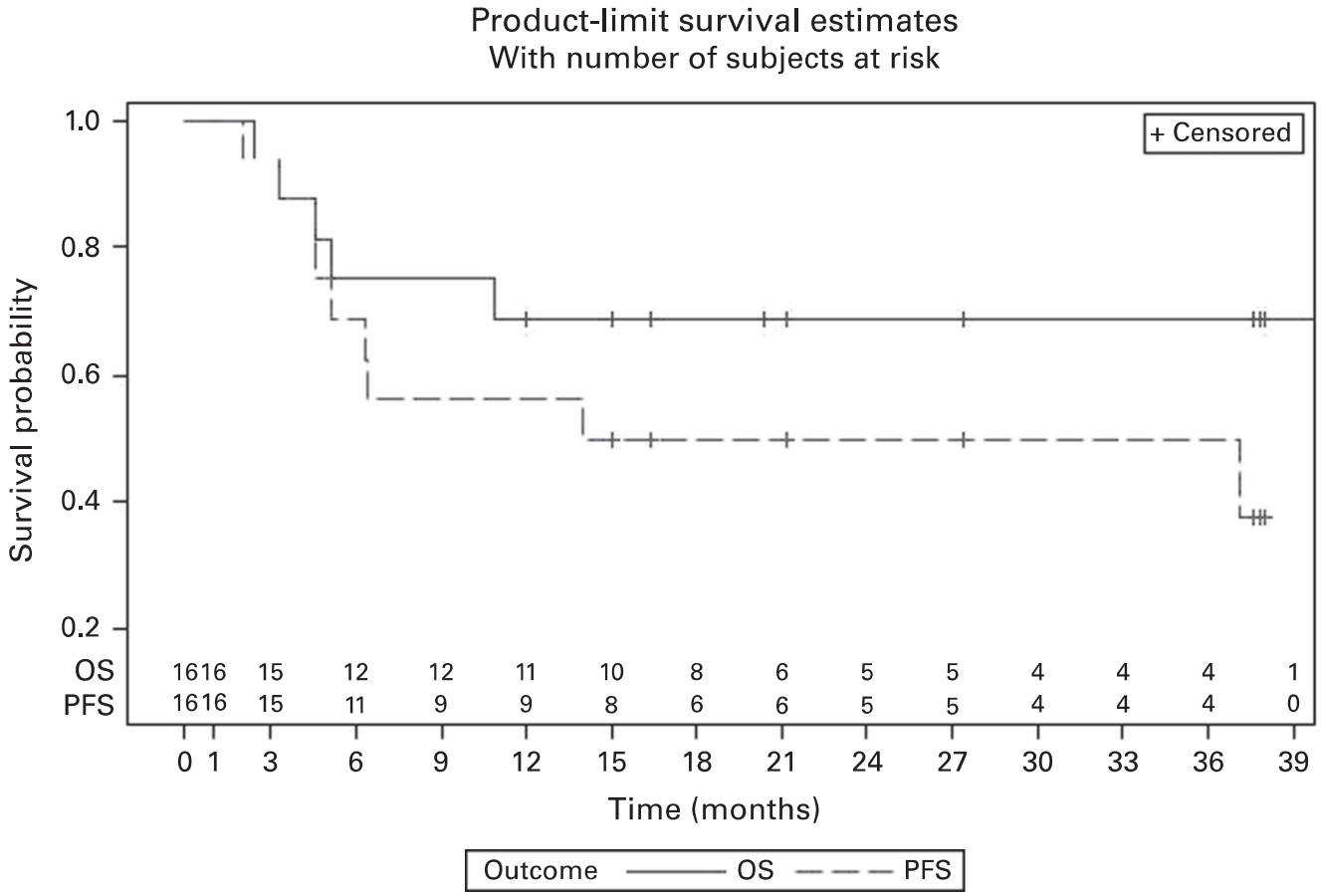
Sex	Age	HCI	Disease	Prior therapies	prior auto-SCT	Disease status pre allo-HSCT	Graft Source	Donor	CMV donor	CMV recipent
M	24	1	AILT	4	Yes	refractory	BM	brother	pos	pos
M	53	6	AILT	6	No	PR	BM	sister	neg	neg
M	51	3	MCL	5	Yes	PR	BM	sister	neg	neg
F	66	5	MCL	4	Yes	PD	BM	son	neg	neg
M	55	3	MCL	6	Yes	PD	PBSC	son	neg	neg
M	66	3	MCL	3	No	PD	BM	daughter	neg	neg
M	61	1	MCL	7	Yes	PD	BM	daughter	neg	neg
M	46	1	MCL	1	No	PR	BM	half brother	pos	pos
M	62	4	MCL	6	No	PD	BM	son	neg	pos
F	52	5	DLBCL	4	Yes	PR	BM	daughter	neg	neg
M	49	2	DLBCL	4	Yes	PD	BM	cousin	neg	neg
F	58	2	sDLBCL	3	Yes	PD	BM	son	neg	pos
M	46	2	sDLBCL	5	No	PR	BM	daughter	neg	pos
M	61	8	CLL	5	No	PR	BM	son	pos	pos
F	46	0	foll Lymphoma	3	No	PR	PBSC	mother	pos	pos
F	23	1	B-LBL	3	No	PD	BM	mother	pos	pos

Haematologica: Tischer, J

Haplo-identical transplantation for MCL

Patient	Day 30 Response	Full Donor Chimerism	Day 100 response	Full Donor Chimerism
1	CR	Y	CR	Y
2	CR	Y	PD	N
3	PR	Y	PR	Y
4	PR	Y	PR	Y
5	PR	Y	CR	Y
6	PR	Y	NA	NA
7	PR	Y	CR	Y
8	PR	Y	CR	Y
9	PR	Y	CR	Y
10	PR	Y	CR	Y
11	PR	Y	PR	Y
12	PD	Y	NA	NA
13	CR	Y	PD	Y
14	PR	Y	PR	Y
15	CR	Y	CR	Y
16	PR	Y	CR	Y

Haematologica: Tischer, J


Product-limit survival estimates
With number of subjects at risk
+ Censored
Survival probability
1.0
0.8
0.6
0.4
0.2
OS 16 16 15 12 12 11 10 8 6 5 5 4 4 4 1
PFS 16 16 15 11 9 9 8 6 6 5 5 4 4 4 0
0 1 3 6 9 12 15 18 21 24 27 30 33 36 39
Time (months)
Outcome OS PFS

Allogeneous Stem Transplantation in MCL

- GVL effect occurs (DLI)
- Curative procedure
- In relapsing setting in responding patients (CR or PR)
- Role of a new targeted therapies remains to be define (before to bridge and after) ?
- Haploidentical (sequential ?) in R/R pts ?
- CAR-T cells ?

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ORIGINAL ARTICLE

The EBMT/EMCL consensus project on the role of autologous and allogeneic stem cell transplantation in mantle cell lymphoma

S Robinson[1], P Dreger[2], D Caballero[3], P Corradini[4], C Geisler[5], M Ghielmini[6], S Le Gouill[7], E Kimby[8], S Rule[9], U Vitolo[10], M Dreyling[11] and O Hermine[12] on behalf of the European MCL Network and the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation

Relapse Therapy For MCL

Patients relapsing after an autoSCT should be considered for an allogeneic stem cell transplant following reinduction therapy.

Patients undergoing an allogeneic SCT should receive reduced intensity conditioning regimens

Patients with evidence of MRD should, in the absence of graft versus host disease, be considered for rapid withdrawal of immunesuppression and

Patients undergoing alloSCT should be screened for MRD post transplant