Management of Mantle Cell Lymphoma in the Era of Targeted Therapy

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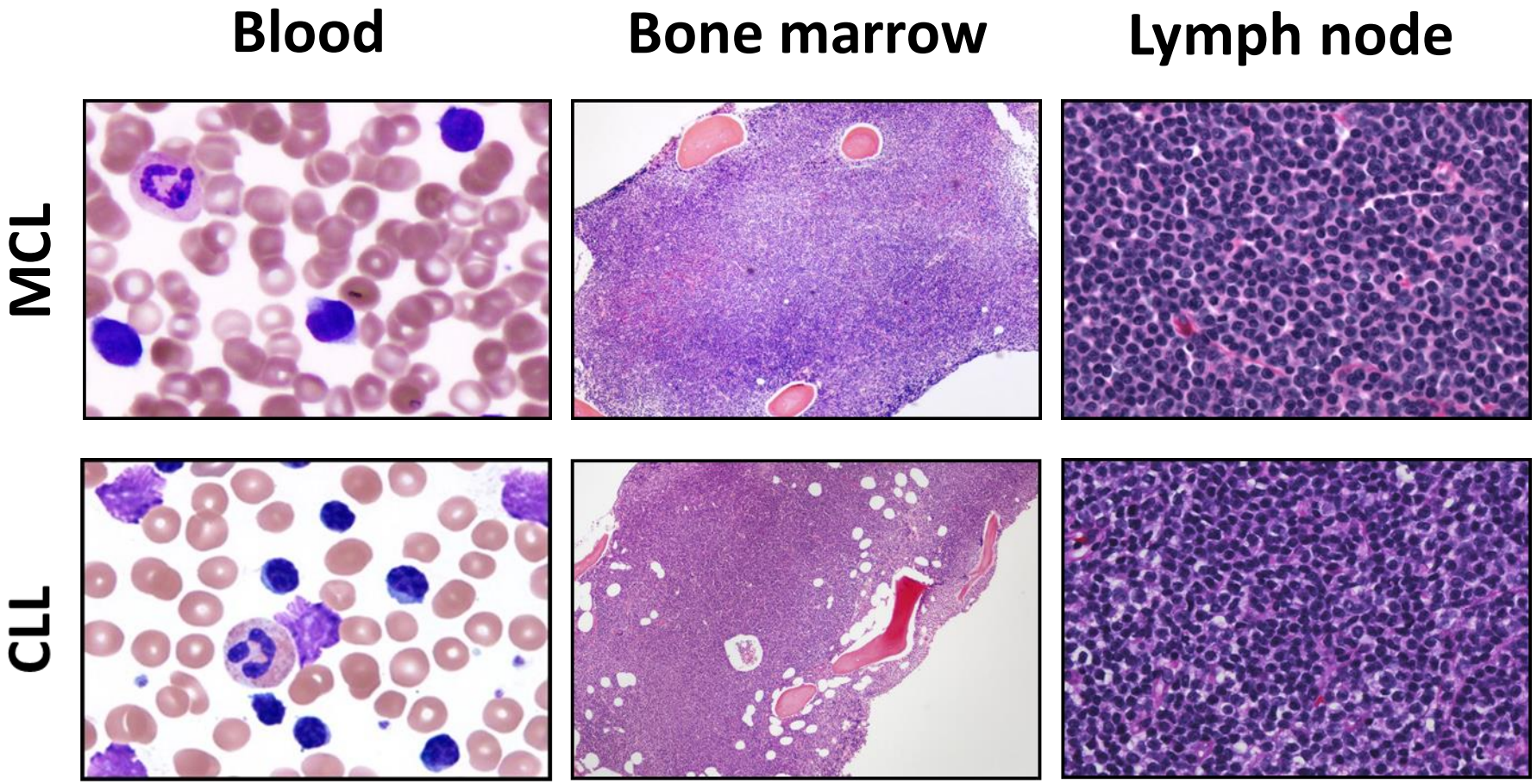
Disclosure of Conflicts of Interest

Nakhle Saba, MD has the following financial relationships to disclose:

- **Consultant**: AbbVie
- **Speaker's Bureau**: AbbVie; Janssen; Pharmacyclics
- **Advisory Board**: AbbVie; ADC Therapeutics,Janssen, Kyowa Kirin, Pharmacyclics

Accumulation of mature B-cells aberrantly expressing CD5

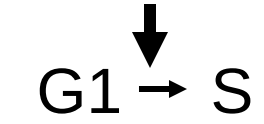


Saba *et al*. ASH 2013. Blood 2013; 122:82
Smedby *et al*. Semin Cancer Biol. 2011

Differential Diagnosis

	CD5	CD20	CD23	Other
CLL	+++	Weak	+++	
MCL	+++	+++	Weak	t(11;14)→ Cyclin-D1

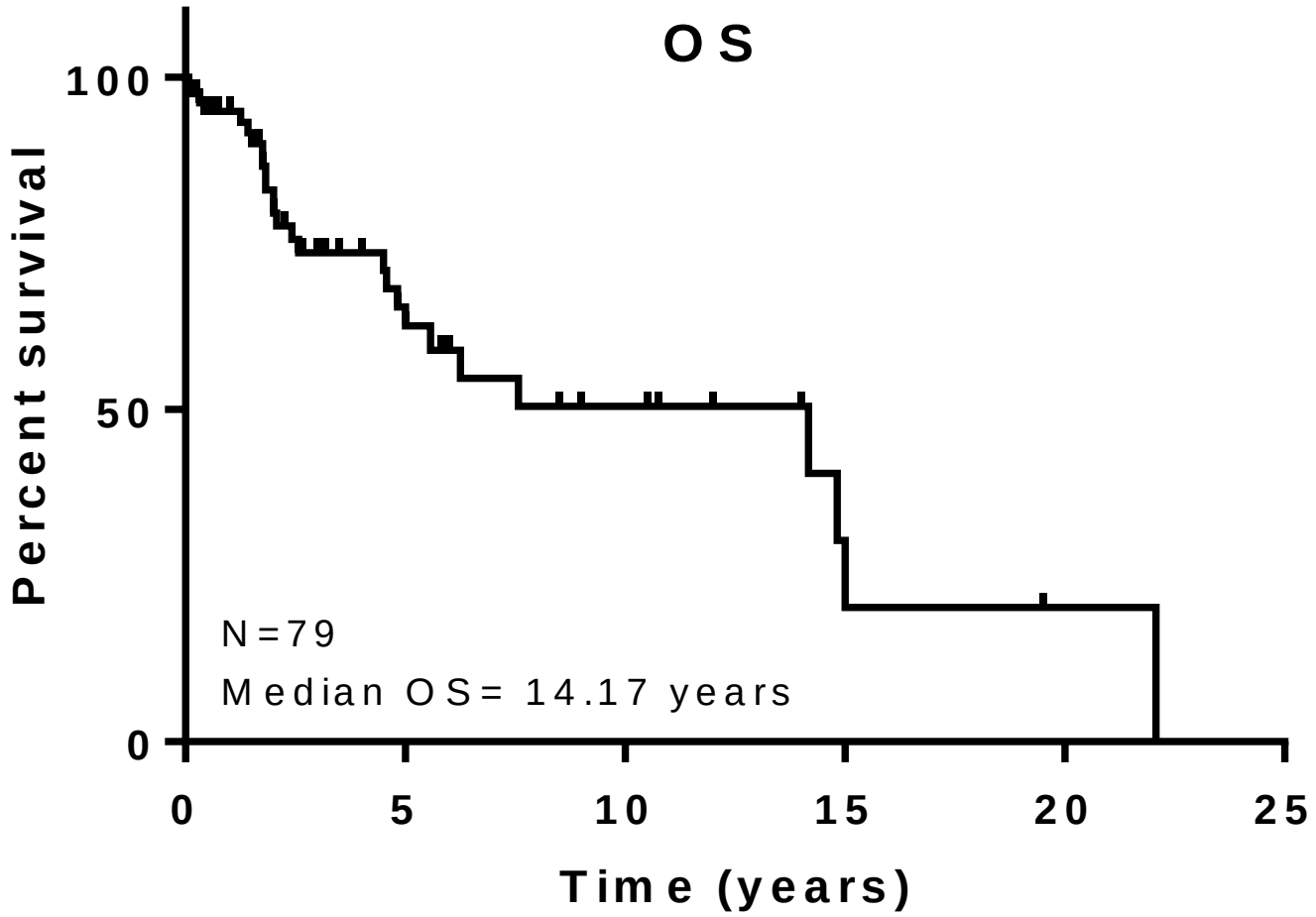
CLL, Chronic Lymphocytic Leukemia
MCL, Mantle Cell Lymphoma



MCL is an aggressive B-cell NHL

	Indolent (10%)	Aggressive (90%)
Leuk phase	Yes	Yes/No
LN	No	Yes
Spleen	Large	Large
SOX11	Neg	Pos
IGHV	Mutated	Mut/un-mut
Ki-67	<10%	< or ≥ 30%

Lack of CD5 predicts for a better OS in MCL



Soleimani… Saba. Leuk Lymphoma 2022

MCL is an aggressive B-cell NHL

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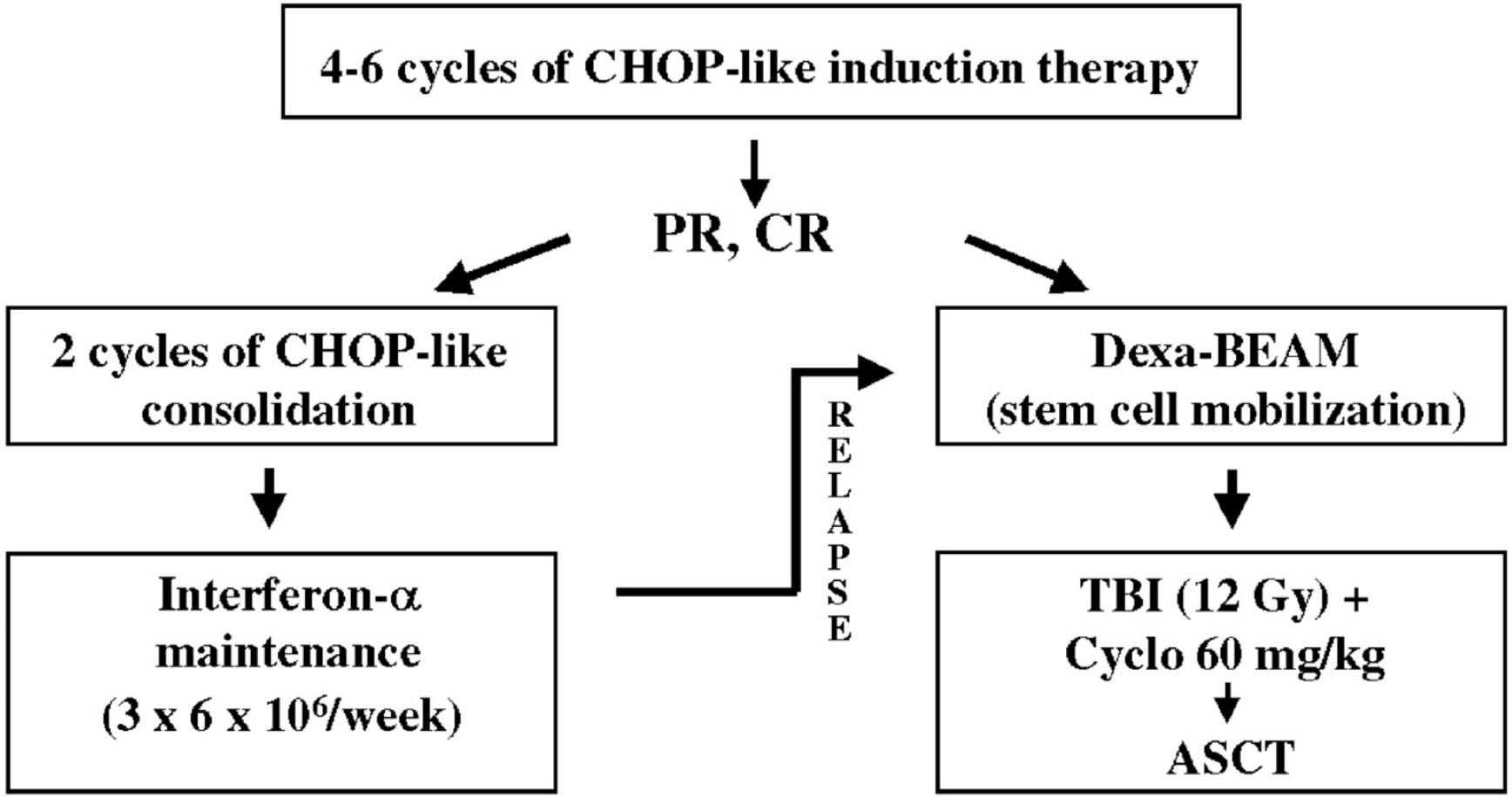
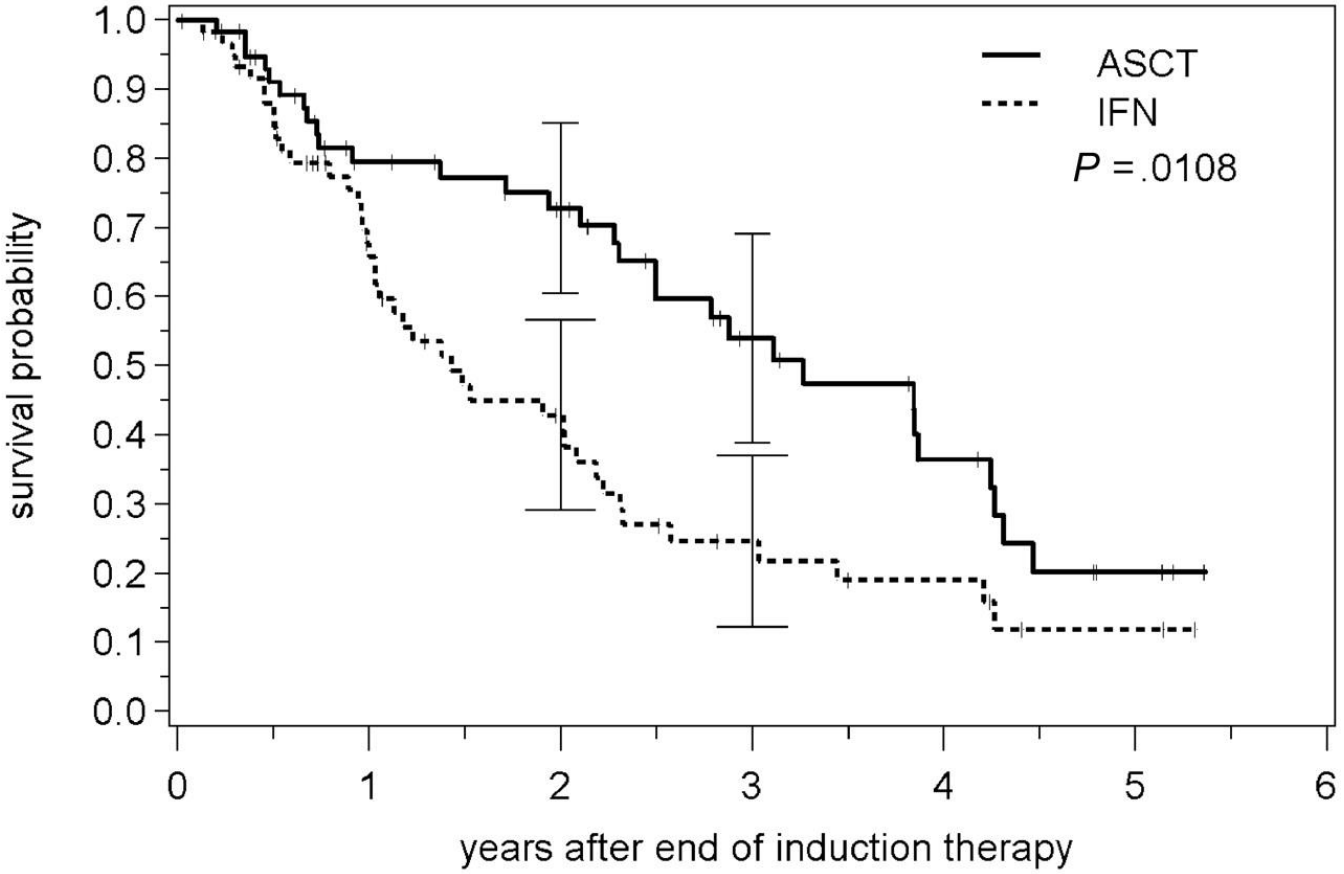
Yet incurable

CHOP in the front line setting, pre-Cytarabine and Pre-R era



Dreyling et al. Blood 2005

PFS benefit with ASCT



numbers of patients at risk						
ASCT	62	38	31	17	10	3
IFN	60	33	19	9	6	2

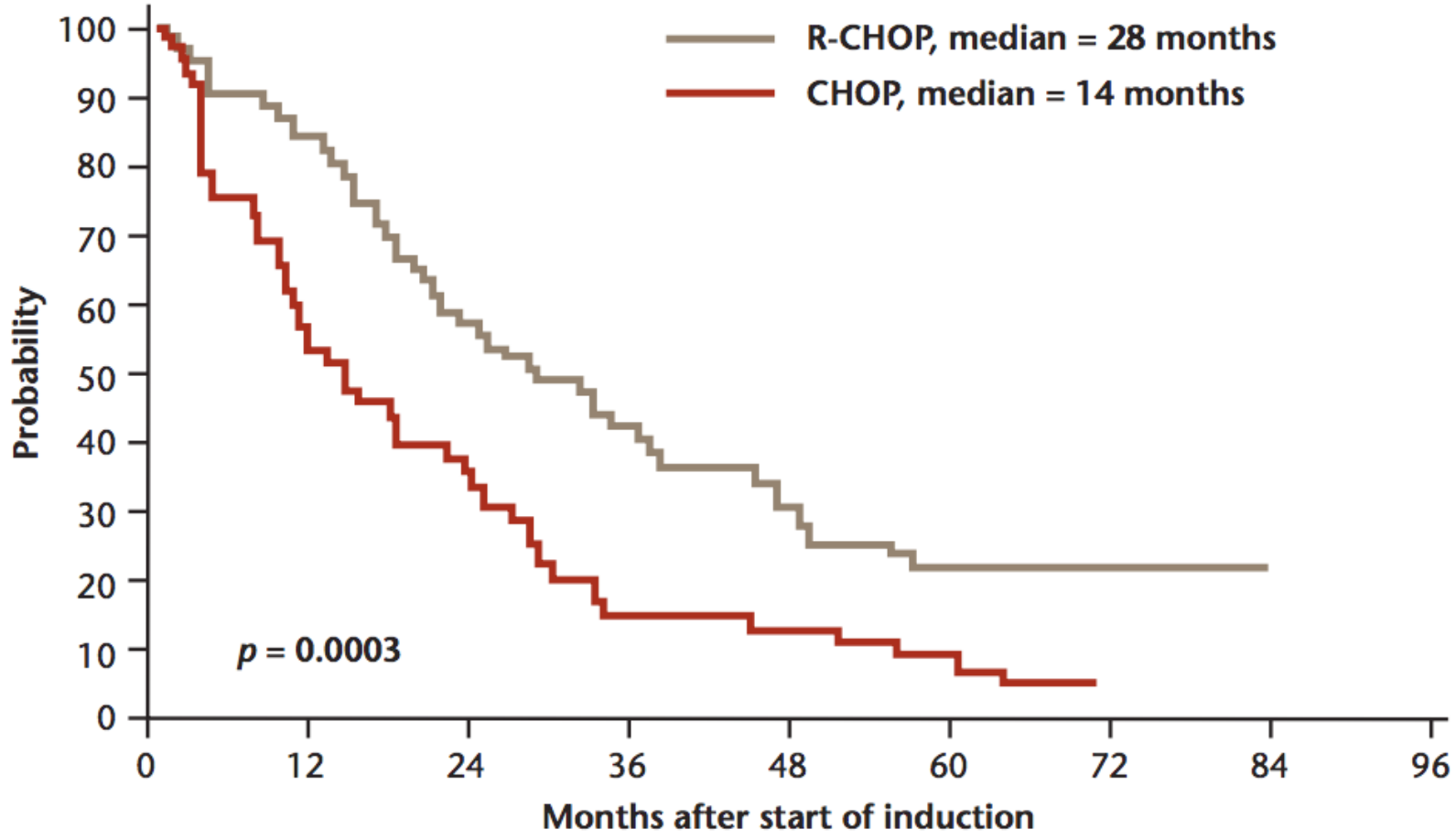
N=122.

mPFS = 39 vs. 17 months (*P* = .0108).

The 3-year OS 83% after ASCT versus 77% in the IFN group (*P* = .18).

Dreyling et al. Blood 2005

R improves both PFS and OS



Adapted from Hoster E, et al. Blood 2008;112(11):3049.

New standard:

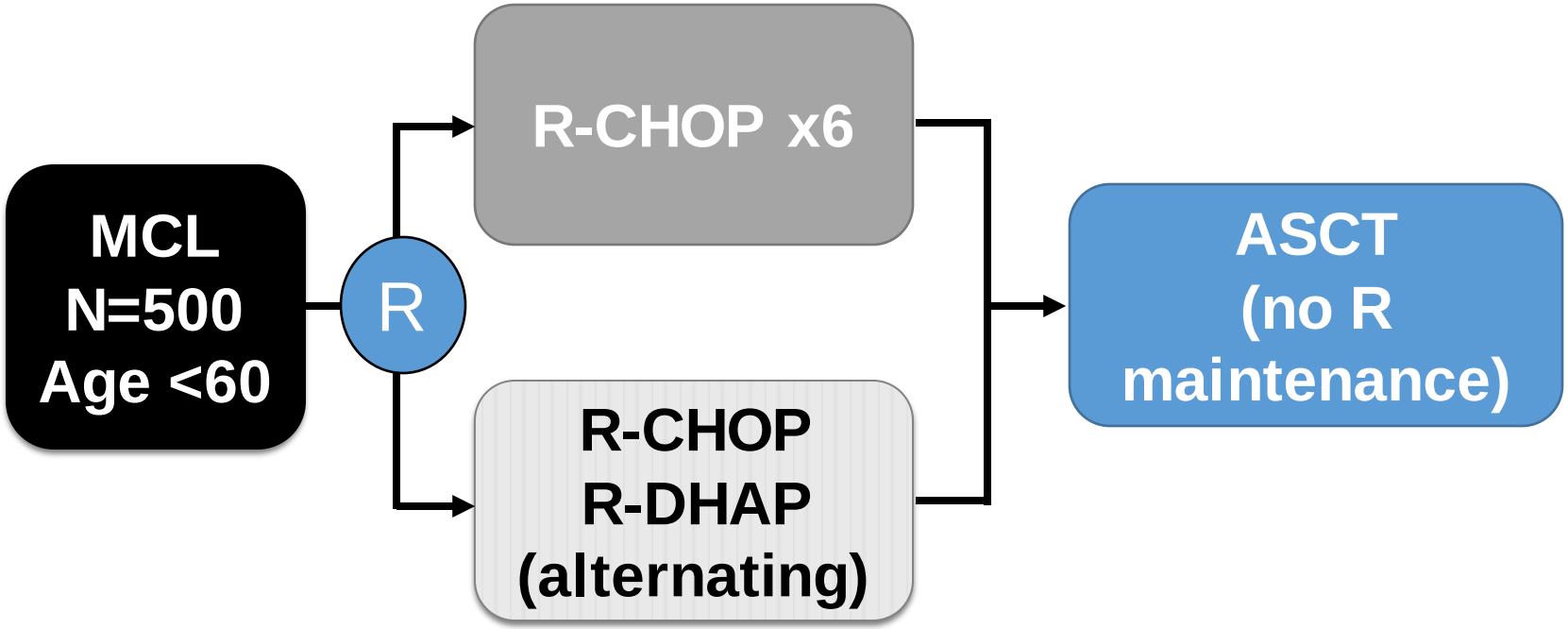
R-CHOP followed by ASCT.

What can we add to RCHOP to improve induction?

Era of Cytarabine:

- **DHAP/RCHOP: MCL YOUNGER Trial**
- **Hyper-CVAD: MDACC**
- **NORDIC: MCL2 trial**

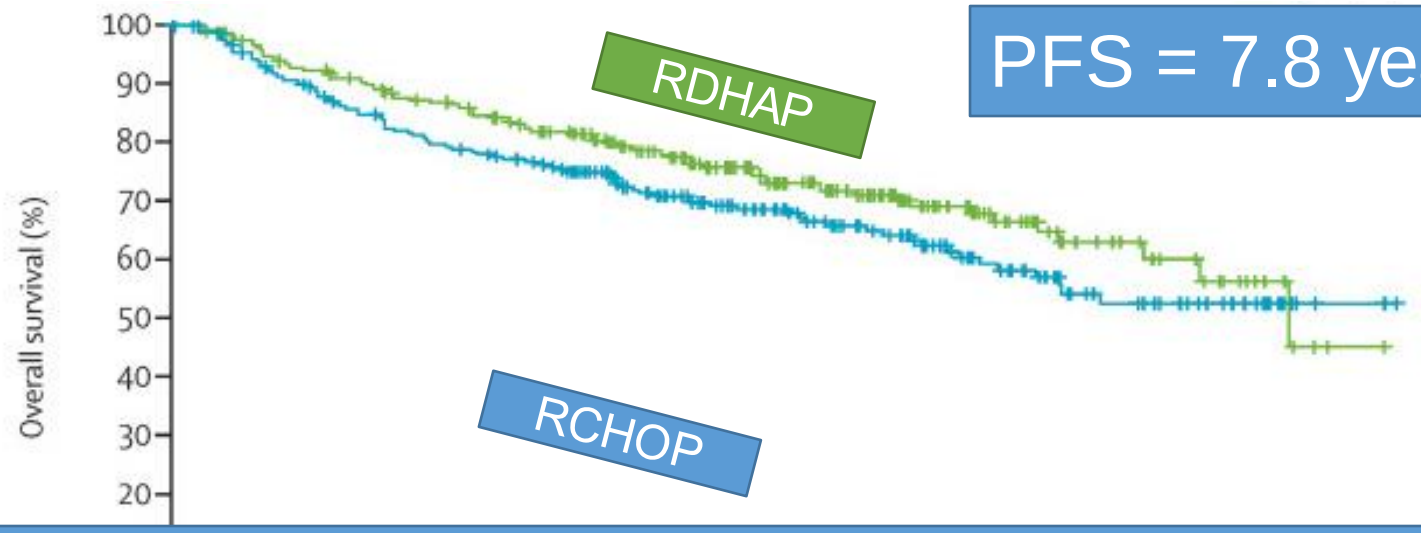
The era of Cytarabine: "MCL YOUNGER" trial



Primary endpoints: PFS and OS

Hermine et al. The Lancet, 2016

MCL YOUNGER, Outcomes



PFS = 7.8 years

Best durable responses are seen with ARA-C

ASCT does not compensate for the inferior response rates observed with R-CHOP alone

The new standard in young and fit:

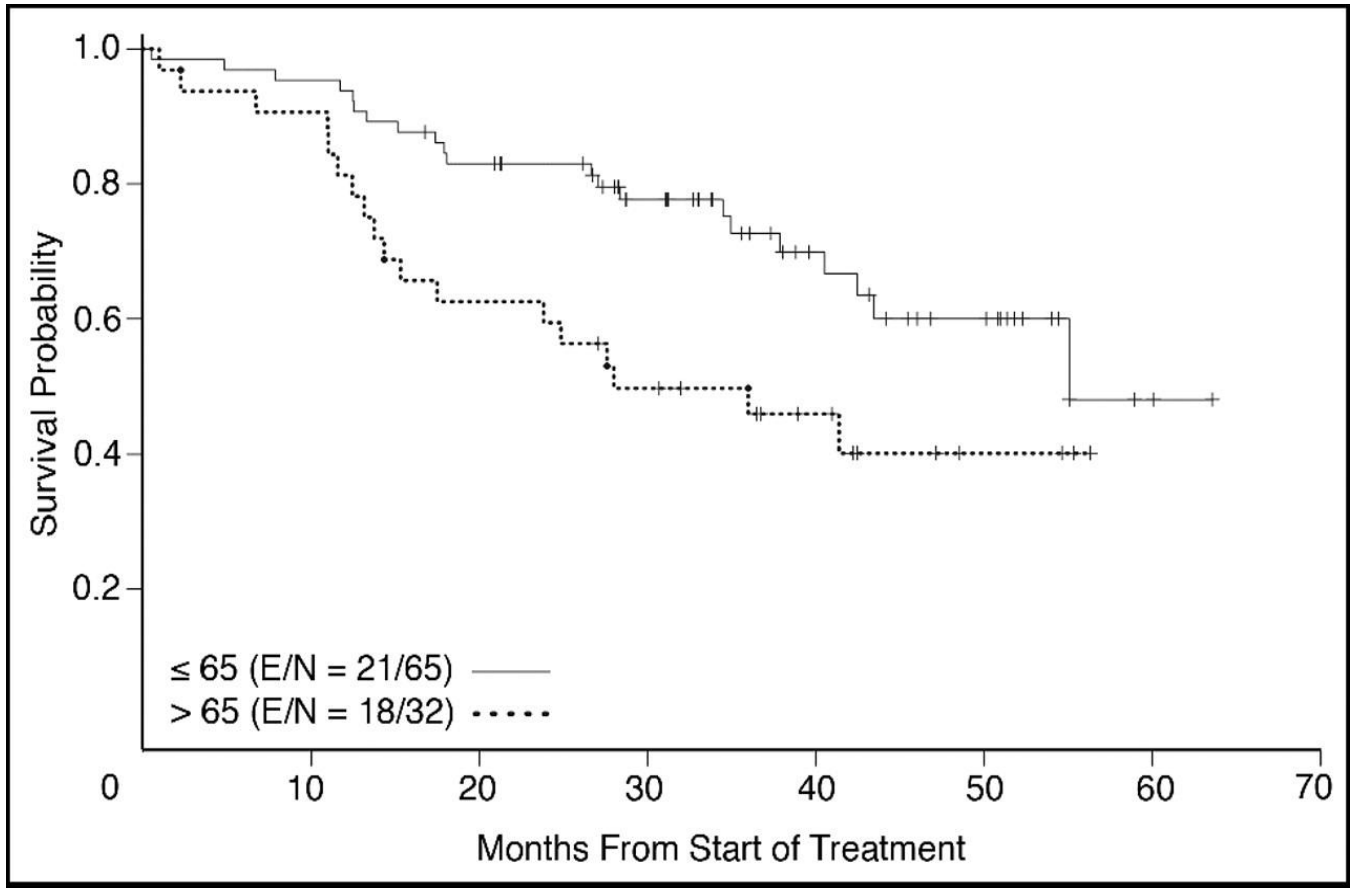
HiDAC containing induction regimen followed by ASCT

Hermine et al. The Lancet, 2016

What should we add to Cytarabine and Rituximab to improve outcomes, add MTX?

HyperCVAD/MTX-Ara-C?

mPFS = 4-5 years



Romaguera et al. JCO 2005

What should we add to Cytarabine and Rituximab to improve outcomes?

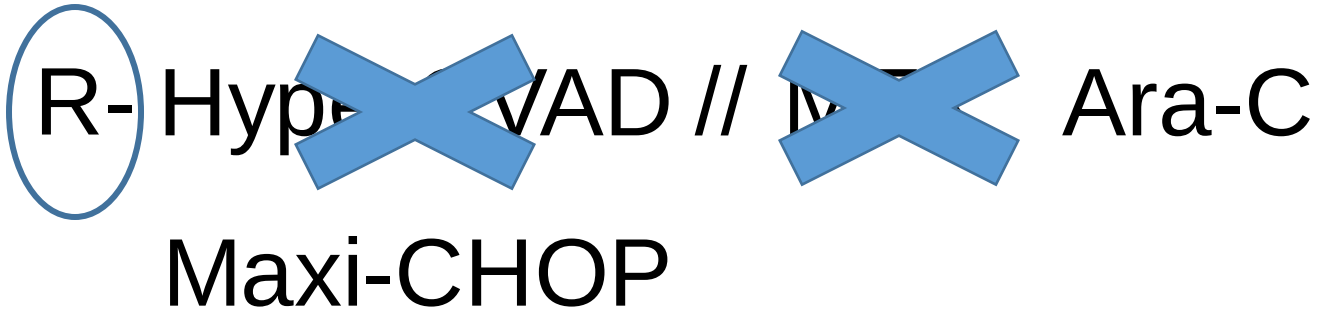
HyperCVAD?

Table 1. Selective prospective studies of intensive frontline therapies in newly diagnosed MCL

Phase	Induction	Consolidation	N	OR (CR), %	Median response	Median OS	TRM	Reference
II (Single Centre)	R-Hyper-CVAD	—	97	97 (87)	22% 15 years FFS	33% 15 years	8%	Chihara et al[1]
II (Multi Centre)	R-Hyper-CVAD	—	60	83 (72)	61% 5 years PFS	73% 5 years	6.50%	Merli et al[6]
II (Multi Centre)	R-Hyper-CVAD	—	49	(86 (55)	4.8 years PFS	6.8 years	2%	Bernstein et al[7]
III (Randomized)	R-CHOP	Dexa BEAM ASCT	455	98 (63)	3.8 years PFS	6.8 years	4%	Hermine et al[5]
	vs			vs	vs	vs		
	R-CHOP/R-DHAP	ASCT		99 (61)	7.3 years PFS	NR		

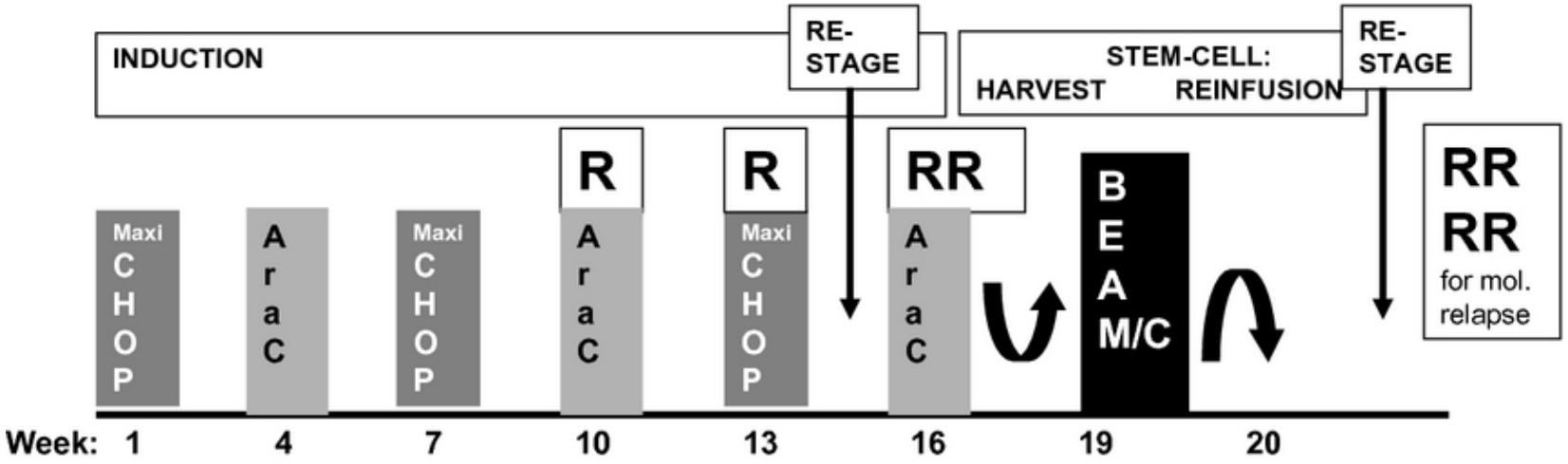
Non-reproducible
Non-randomized
High TRM, especially in >65
MTX is not needed for MCL

The Nordic group: MCL2 trial



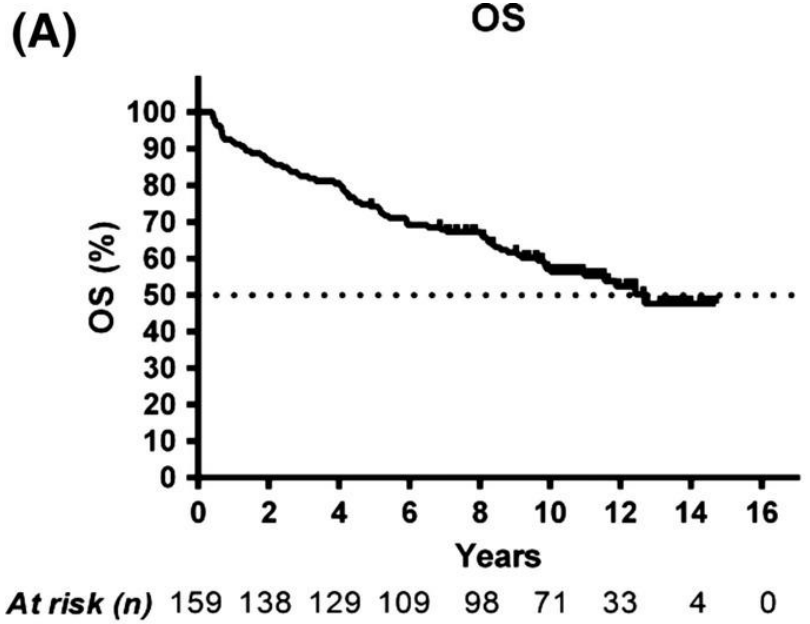
Eskelund et al. bjh 2016

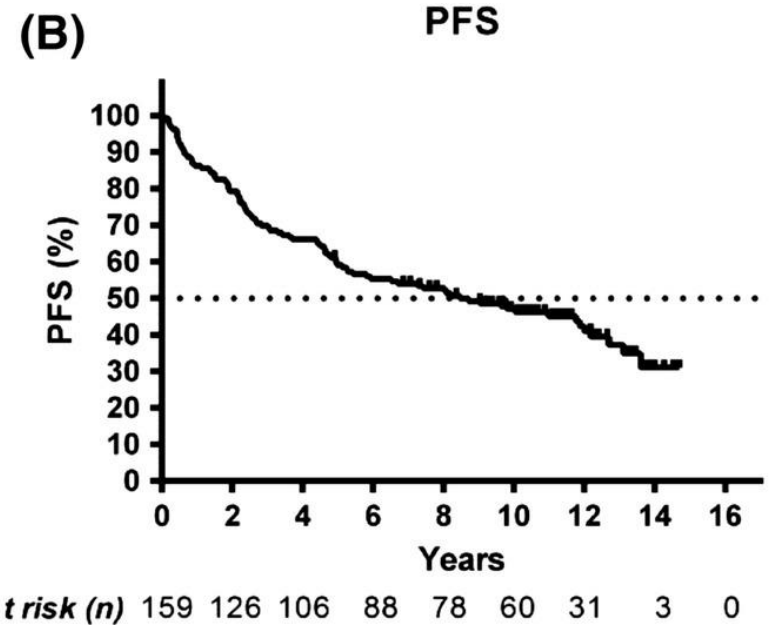
The Nordic group: MCL2 trial, N = 159

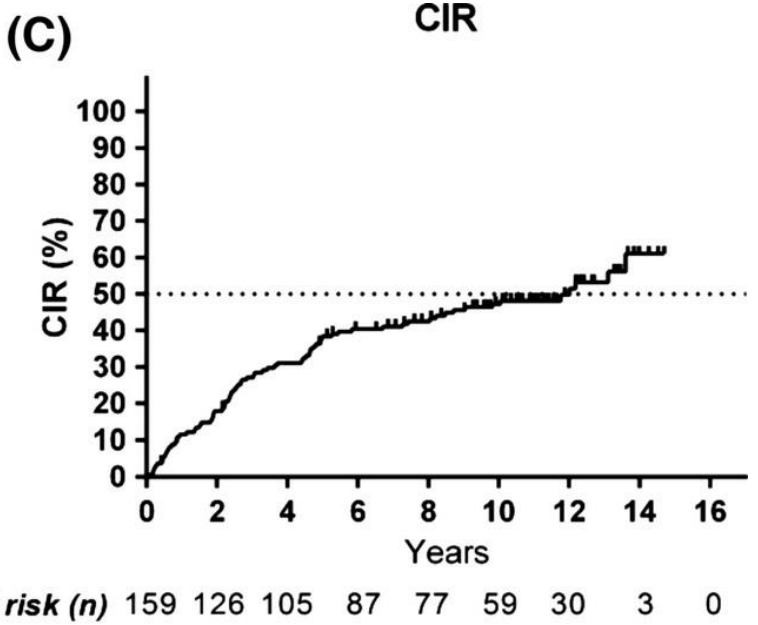


17 patients relapsed after 5 years or more in CR.

6 patients relapsed beyond 10 years in CR.





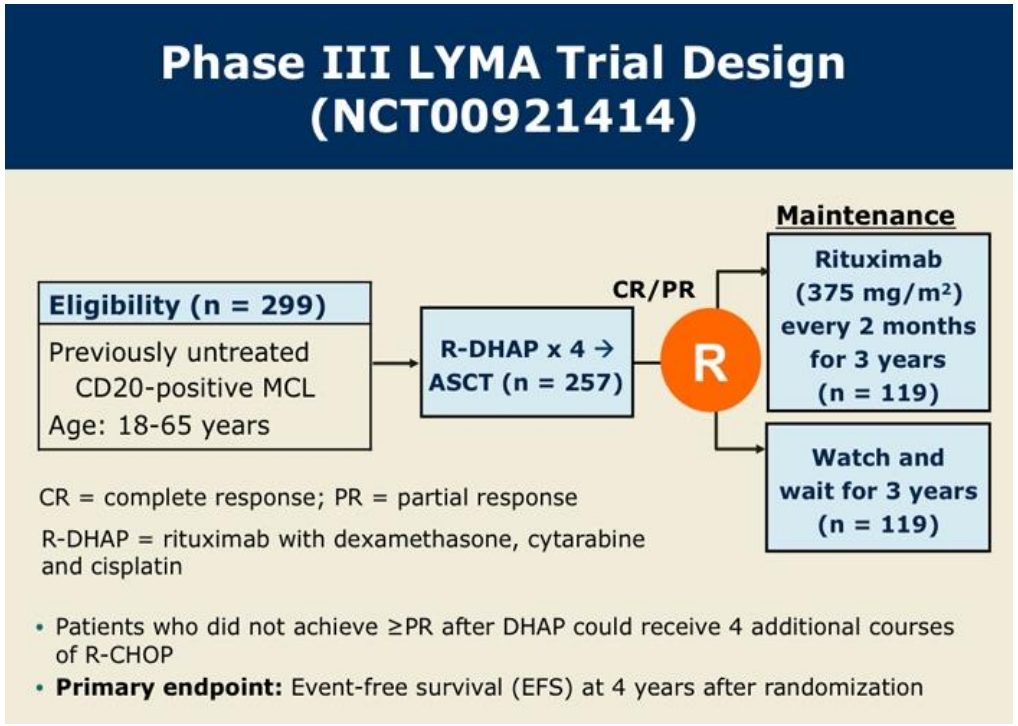


Eskelund et al. bjh 2016

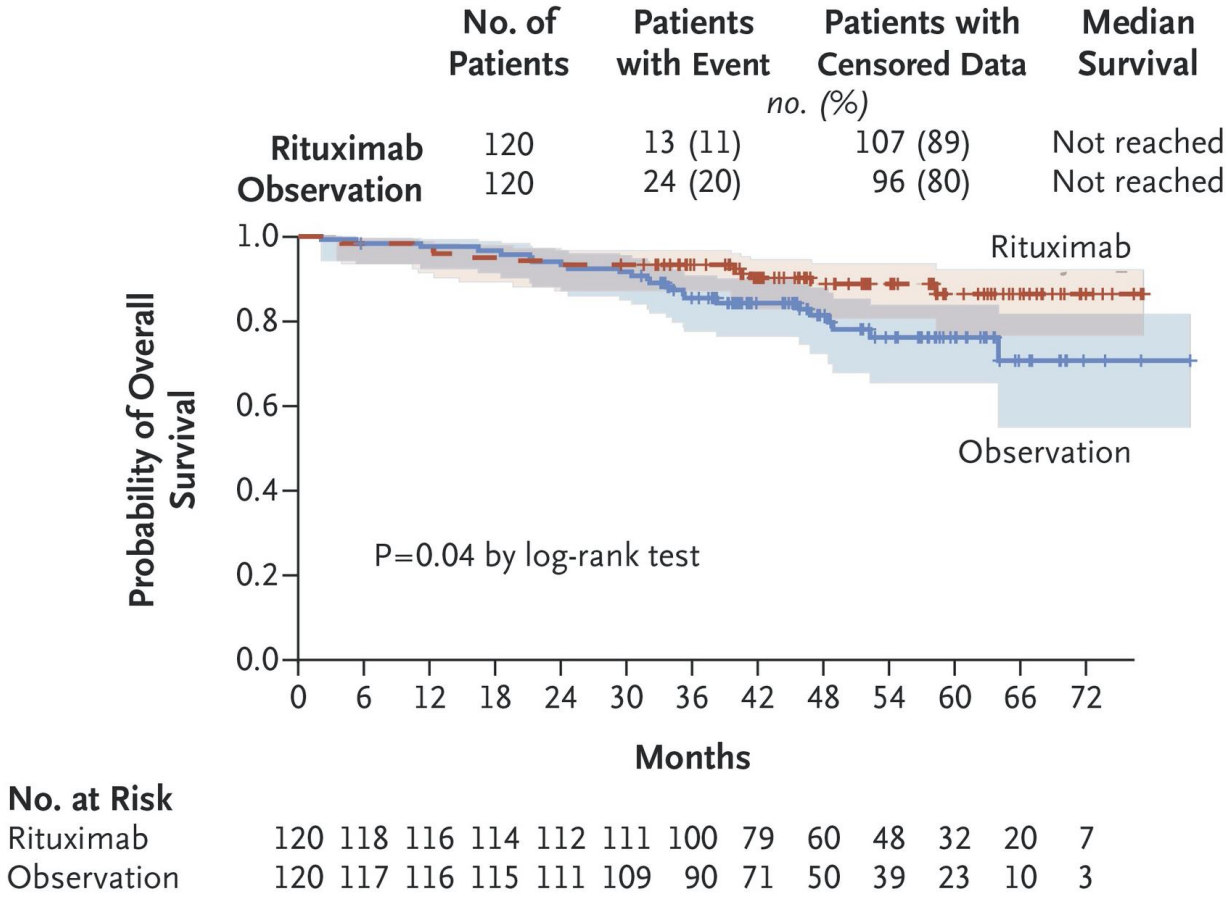
Cytarabine is a must, MTX is not needed. Do we need CHOP?

The LyMa trial

Since Cytarabine is a must, can we do RDHAP alone?
Does rituximab maintenance improve OS post ASCT?



R-CHOP was administered in 20 patients who had an insufficient response after R-DHAP, and 10 of these patients proceeded to transplantation

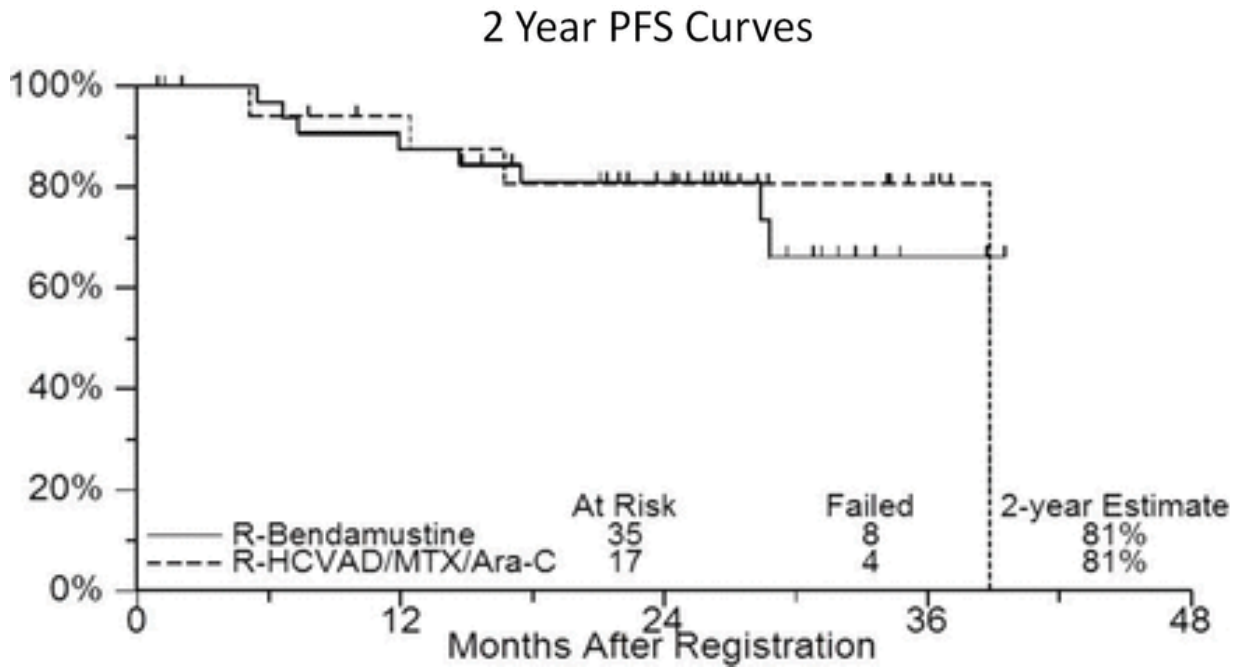


Le Gouill et al, NEJM 2017

BR Vs. HyperCVAD: S1106 trial

- Phase II, randomized,
- 6xBR or 4xRHyperCVAD, ASCT
- Terminated early due to poor mobilization with HyperCVAD
- N=53 (planned 160)

8/9 patients in BR converted to MRD-
2/2 HyperCVAD converted to MRD-



Chen et al, ASH 2015

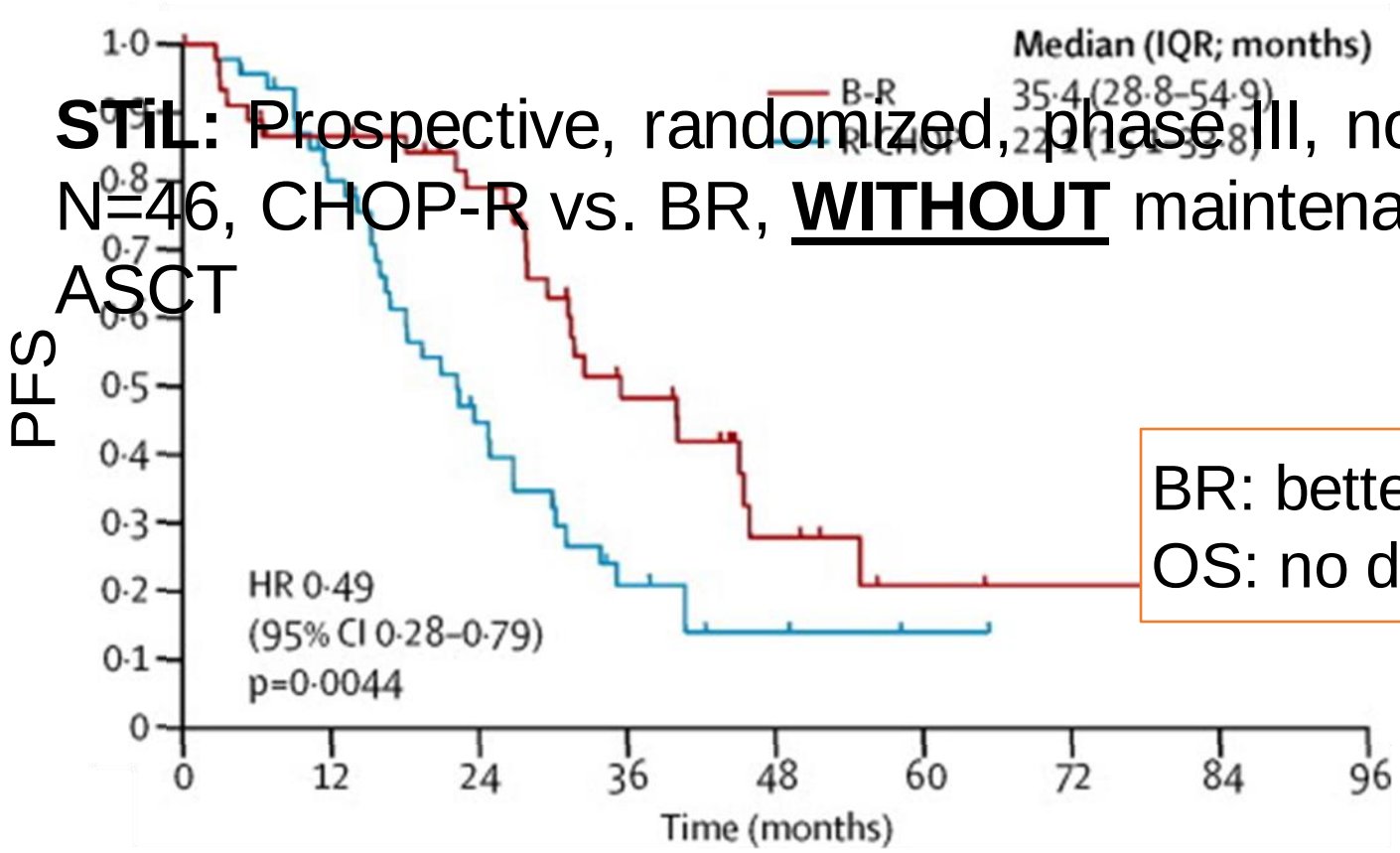
- **Cytarabine is a must, CHOP is needed with it**
- **MTX is not needed**
- **BR is very promising**

Frontline therapy for older patients

- CHOP-R
- BR
- R-BAC

CHOP-R vs. BR: STiL Trial

STiL: Prospective, randomized, phase III, non-inferiority, N=46, CHOP-R vs. BR, **WITHOUT** maintenance R or ASCT



BR: better tolerated
OS: no difference

Rummel et al. The Lancet 2013

CHOP-R vs. BR: BRIGHT Trial

BRIGHT: Prospective, randomized, phase III, non-inferiority, N=67, CHOP-R/CVP-R vs. BR, **WITHOUT** maintenance R or ASCT

	CR		CR + partial response	
Histologic subtype, n/N (%)	**BR**	**R-CHOP/R-CVP**	**BR**	**R-CHOP/R-CVP**
Indolent NHL	49/178 (28)	43/174 (25)	173/178 (97)	160/174 (92)
Follicular	45/148 (30)	37/149 (25)	147/148 (>99)	140/149 (94)
Marginal zone	5/25 (20)	4/17 (24)	23/25 (92)	12/17 (71)
Lymphoplasmacytic	0/5	1/6 (17)	3/5 (60)	6/6 (100)
MCL	17/34 (50)	9/33 (27)*	32/34 (94)	28/33 (85)*

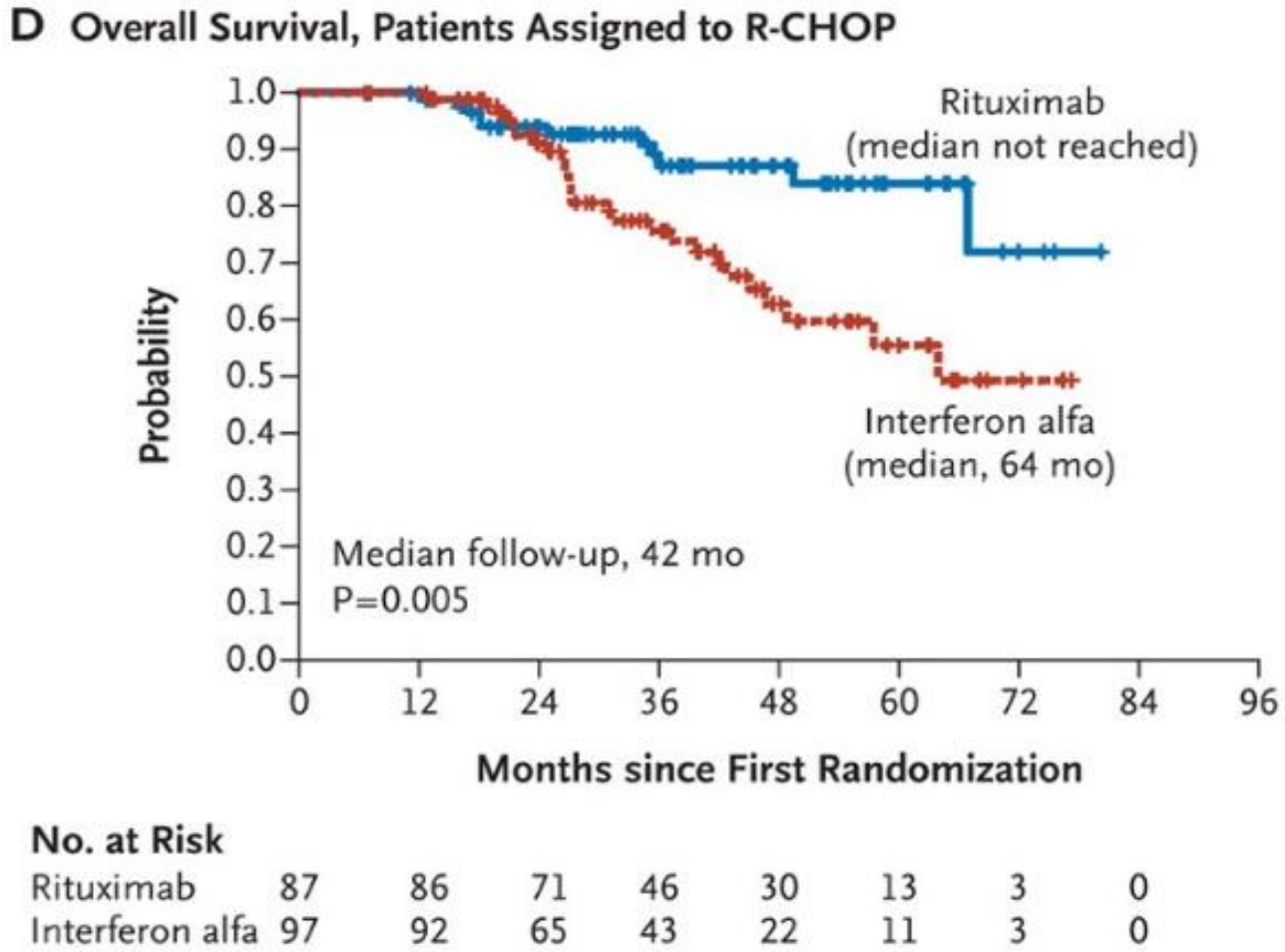
*R-CHOP, n = 22.

Small trials
No maintenance R, no consolidation ASCT
Difficult to definitively recommend R-CHOP or BR

Flinn et al. Blood 2014

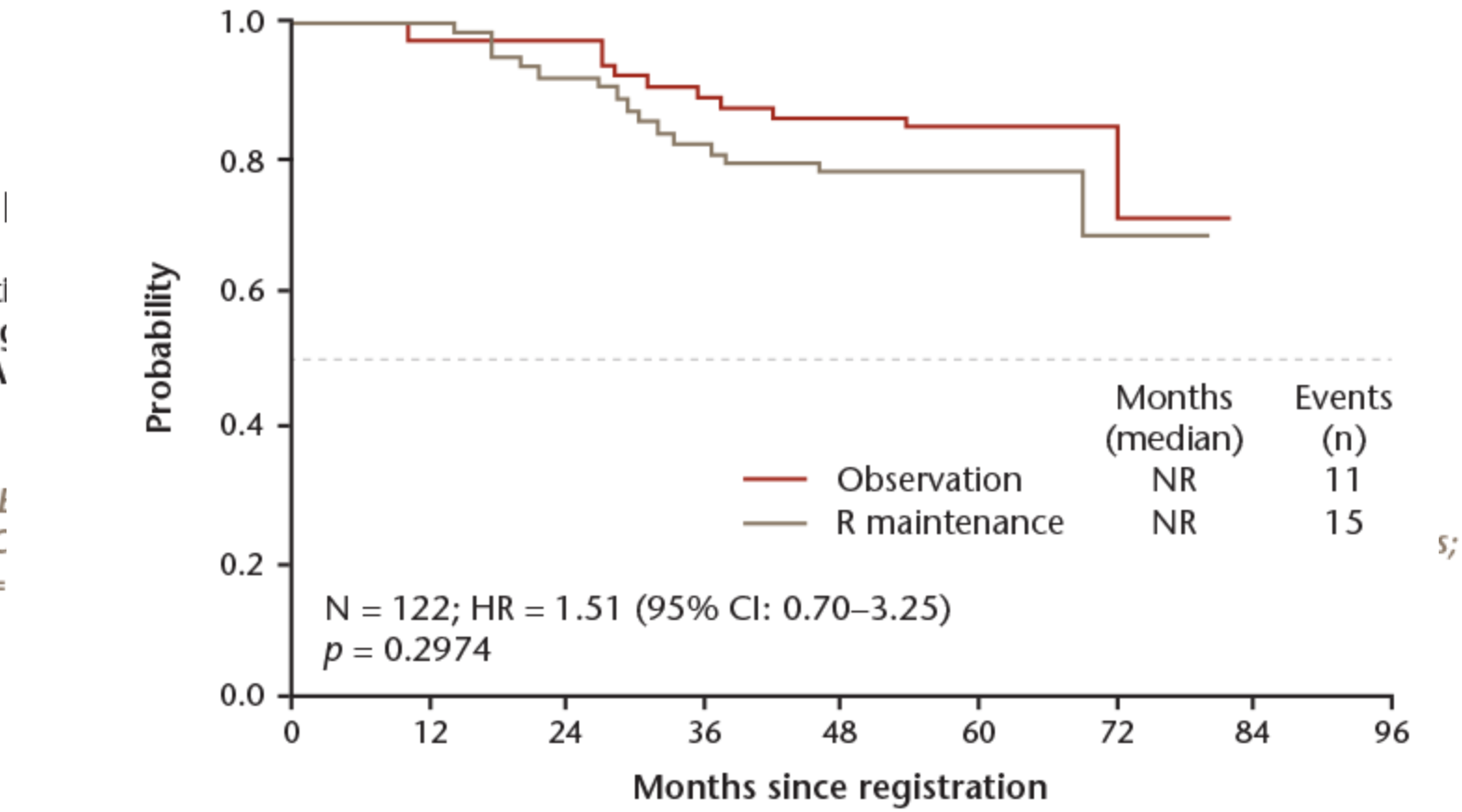
CHOP-R: R maintenance is effective

Prospective, randomized phase III, N=560, age>60, CR/PR followed by R or INF



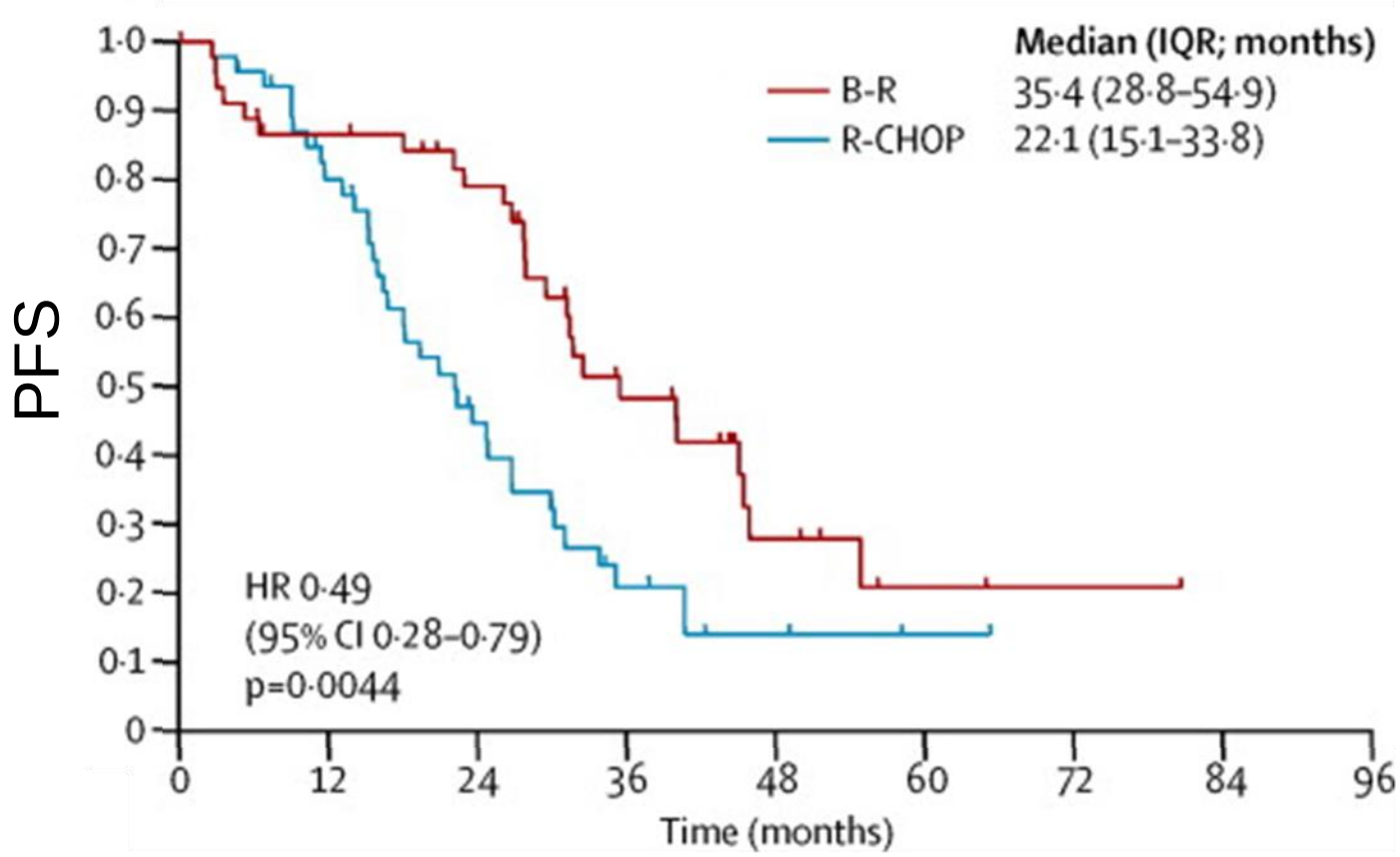
Kluin-Nelemans et al. NEJM 2012

R maintenance after BR?
StiL NHL7-2008 MAINTAIN trial



Rummel M, et al. ASCO 2016

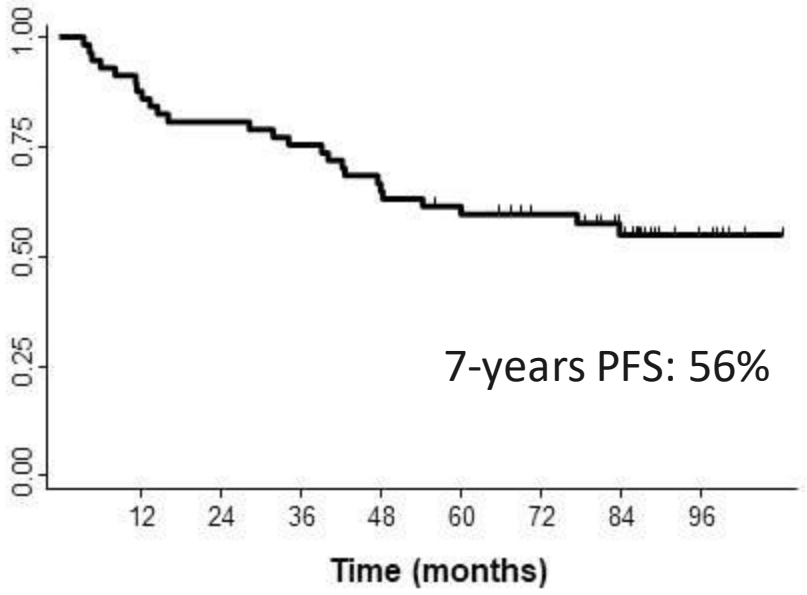
CHOP-R + R maintenance = BR???



Rummel et al. The Lancet 2013

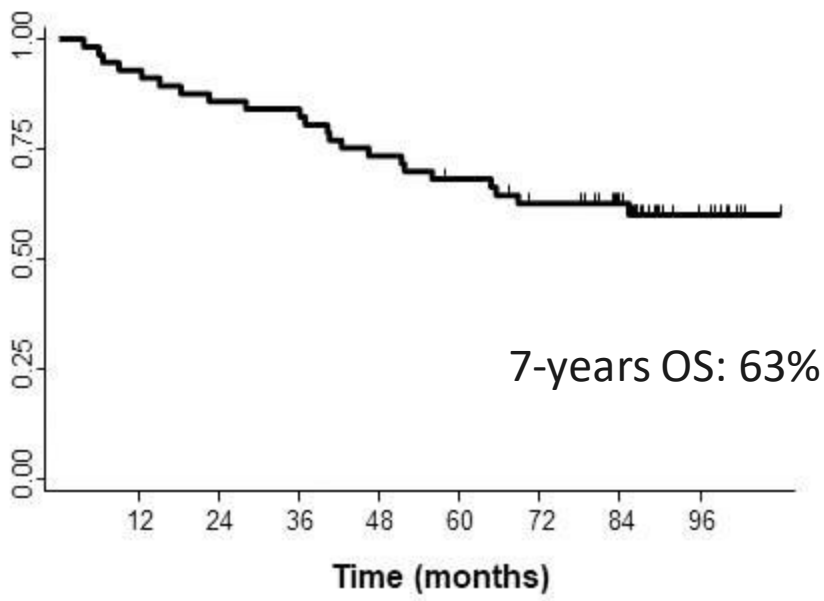
RBAC500: Phase 2 Study from the Fondazione Italiana Linfomi

Figure 1A: PFS



7-years PFS: 56%

Figure 1B: OS

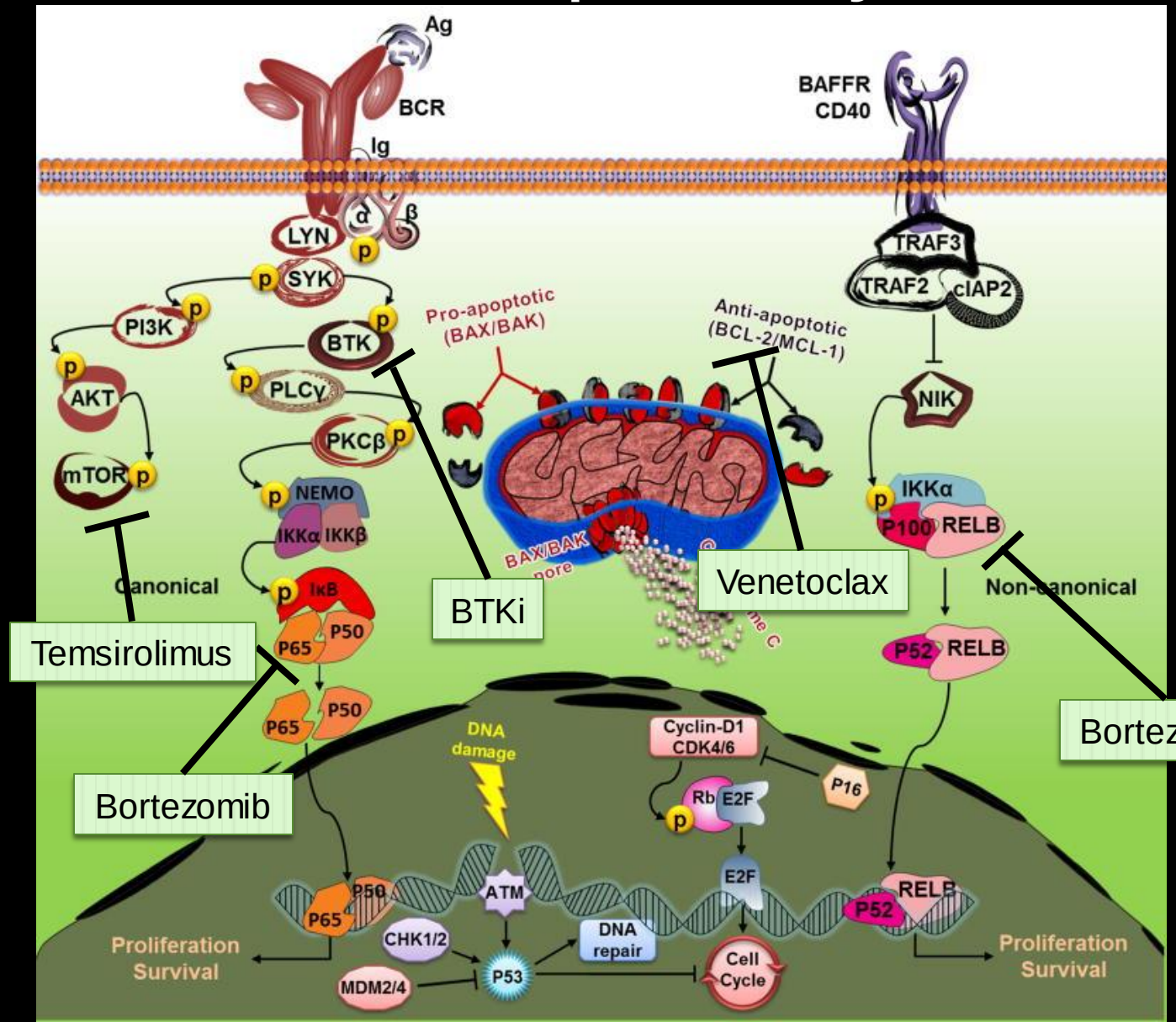


7-years OS: 63%

Visco et al. The Lancet Hematology 2017
Tisi et al. ASH 2021

Novel Agents

Survival pathways in MCL



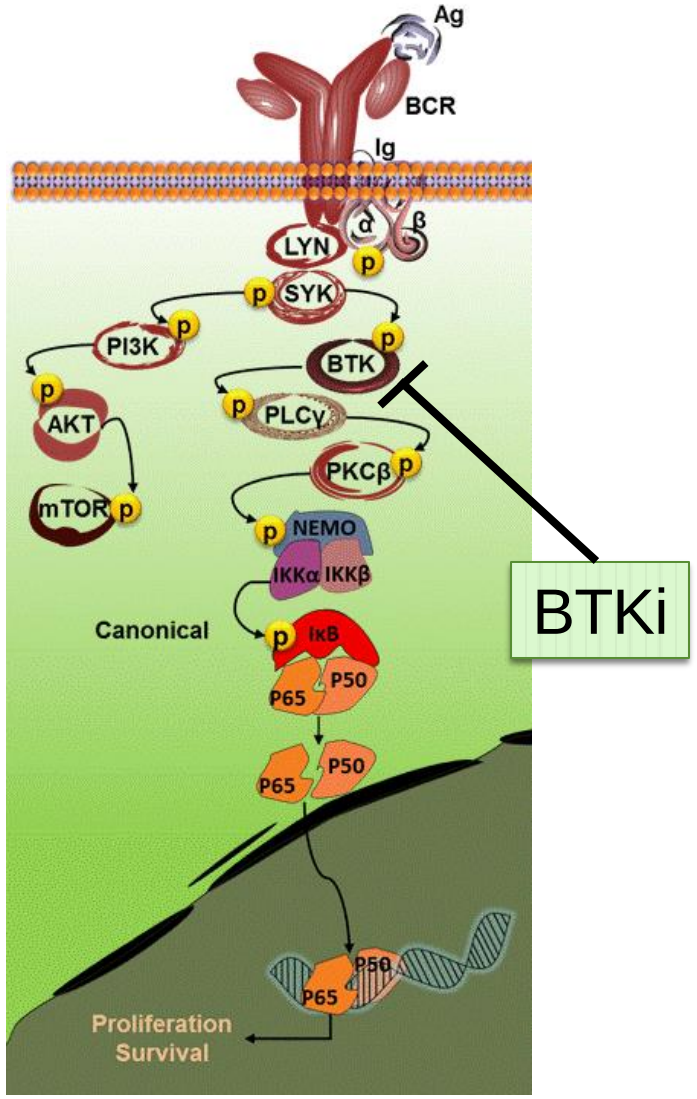
Saba & Wiestner.
Curr Opin Hematol. 2014

Novel Agents

Single Agent	ORR (%)	CR (%)
Bortezomib	33	8
Temsirolimus	22	2
Lenalidomide	28	8
Ibrutinib	68	21
Venetoclax	75	21

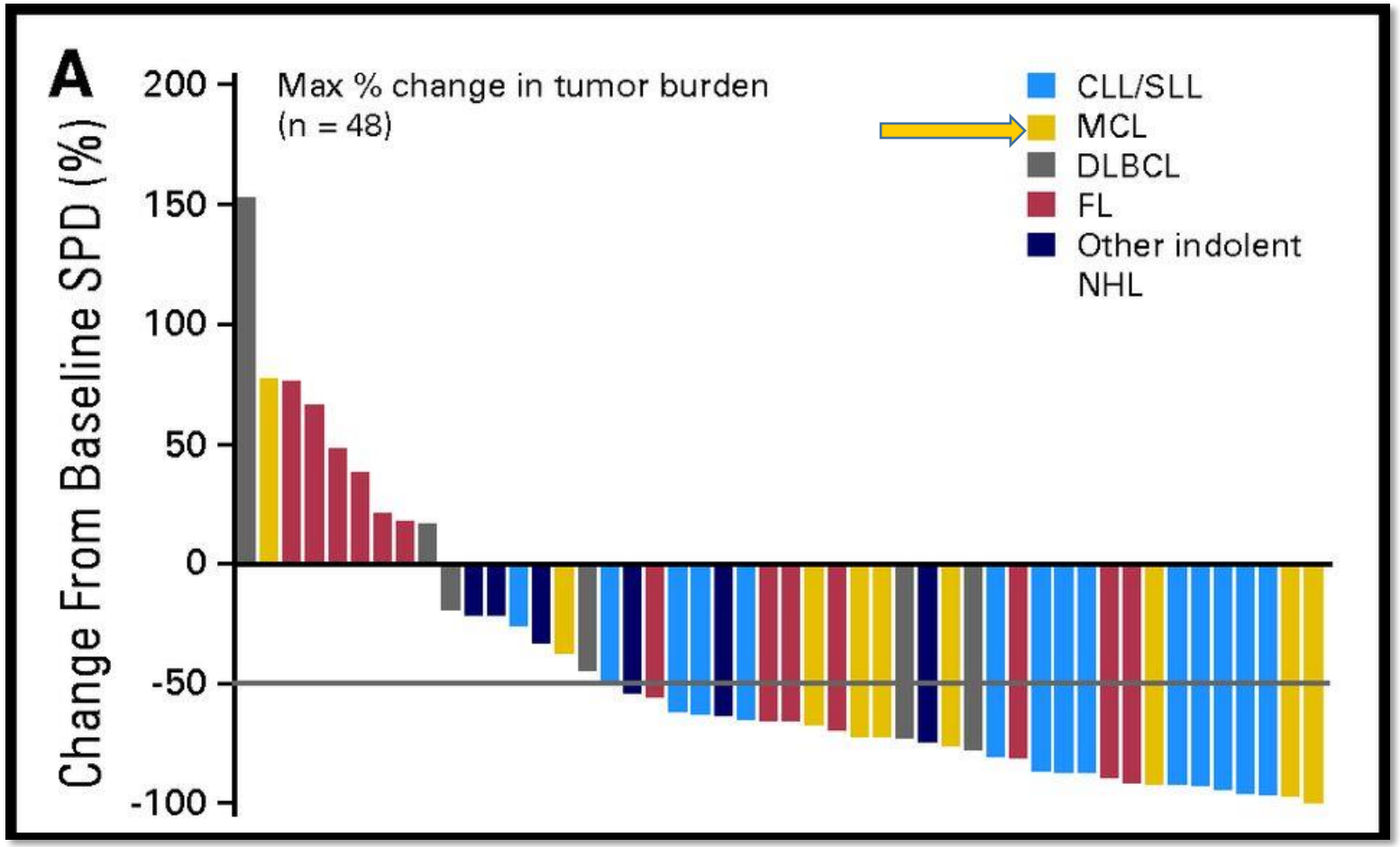
Head-to-head studies between these regimen are lacking. Therefore, direct comparisons cannot be made.

The BCR signaling pathway



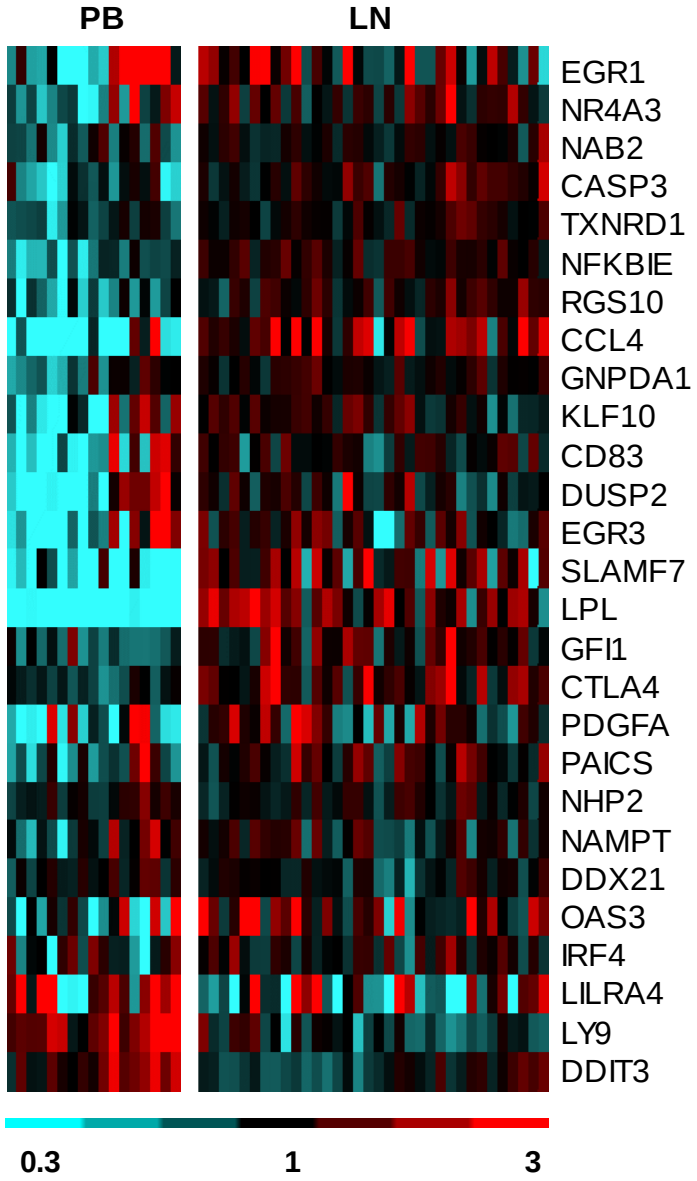
Saba & Wiestner.
Curr Opin Hematol. 2014

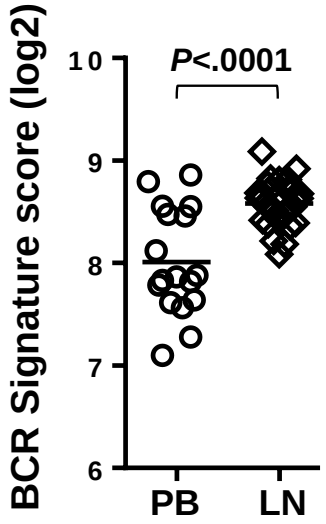
Ibrutinib, Phase 1 in Relapsed/Refractory Lymphomas

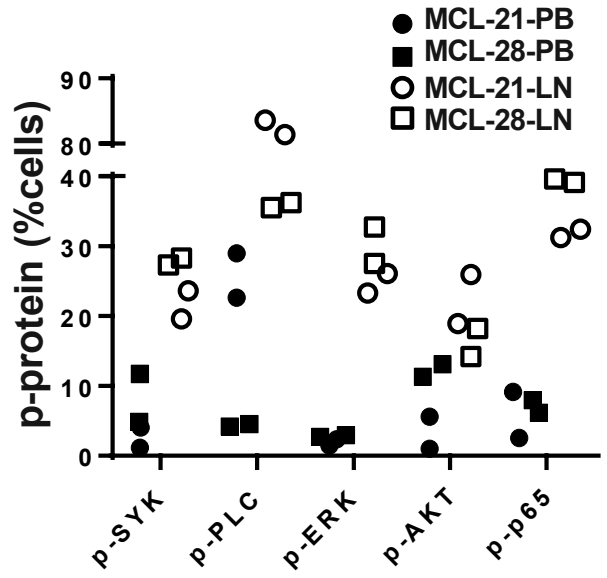


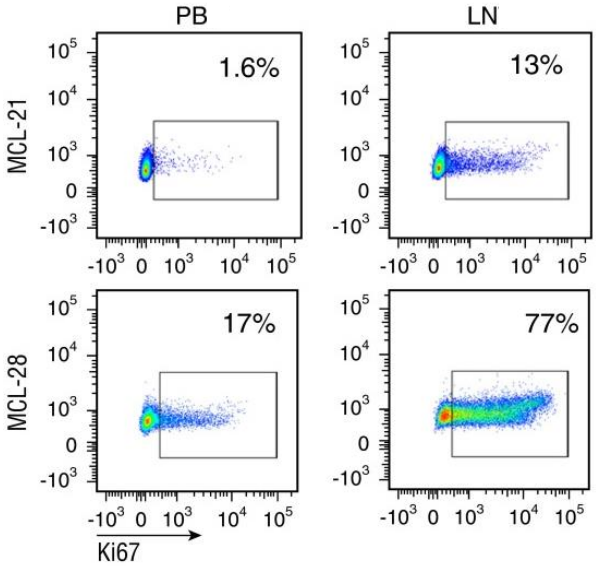
Advani et al, JCO 2012

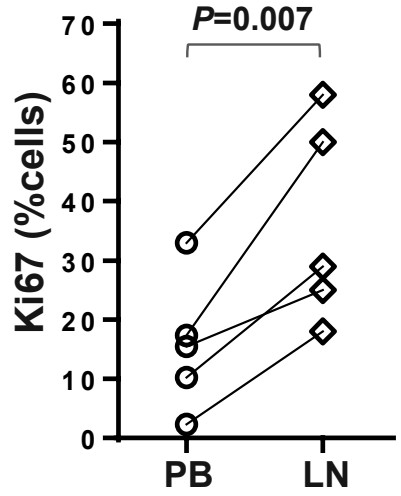
Lymph node-resident cells display higher BCR activity than cells in blood







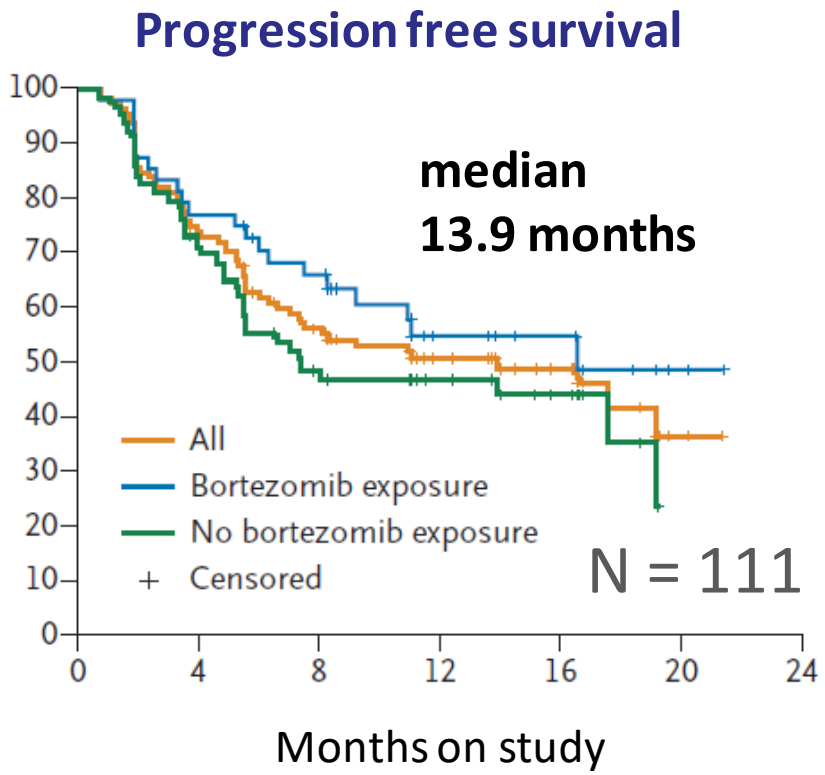




Saba et al. Blood 2016

Ibrutinib, Phase 2 in R/R MCL

- ORR 68%, CR 21%

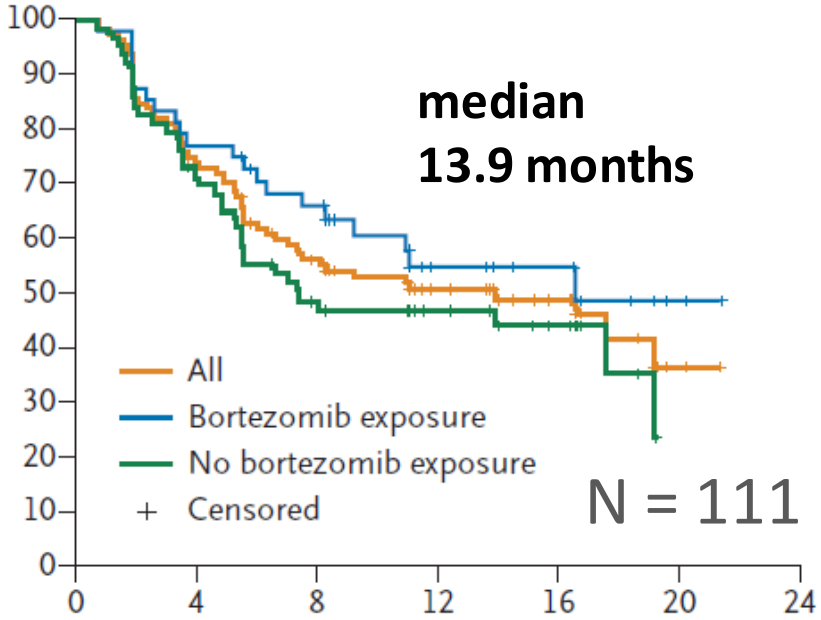


Wang et al, NEJM 2013

Ibrutinib, Phase 2 in R/R MCL

- ORR 68%, CR 21%

Progression free survival

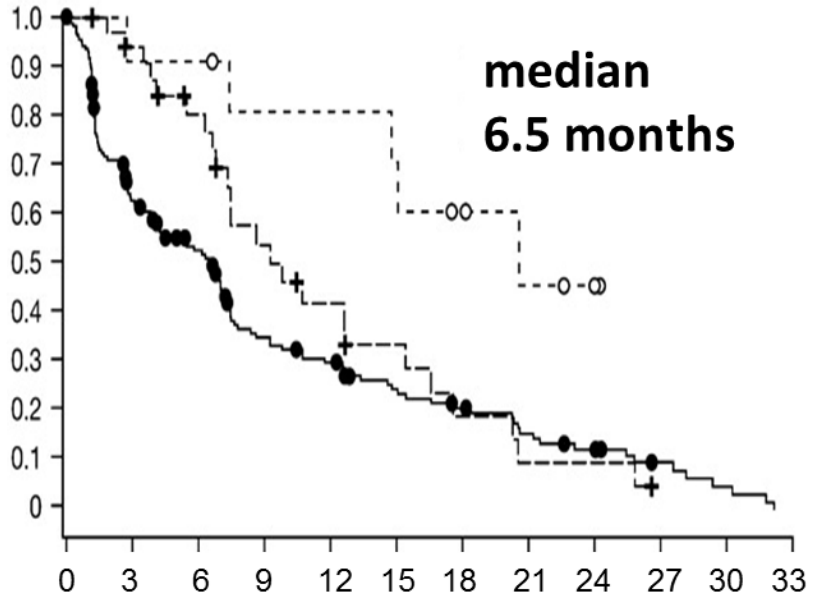


Months on study

Wang et al, NEJM 2013

- ORR 32%, CR 8%

Progression free survival

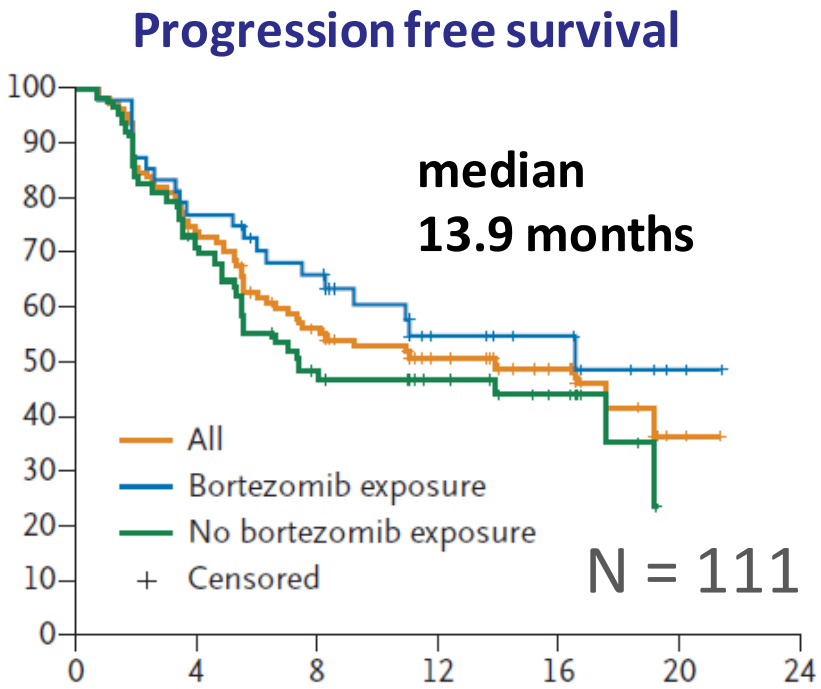


Bortezomib, months on study

Goy et al, Ann Oncol. 2009

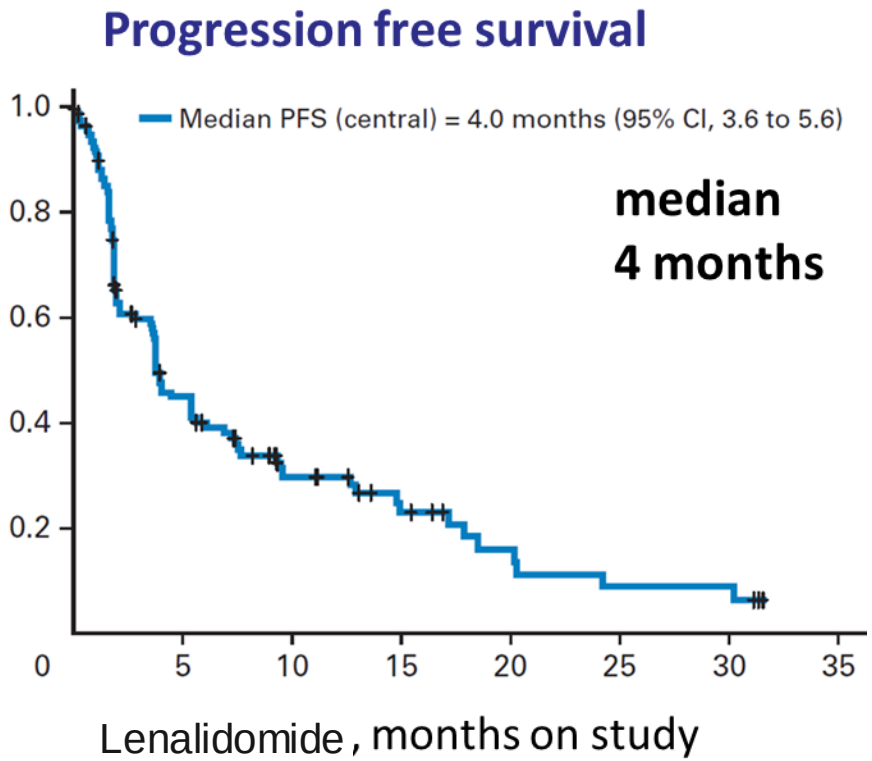
Ibrutinib, Phase 2 in R/R MCL

- ORR 68%, CR 21%



Wang et al, NEJM 2013

- ORR 28%, CR 7.5%



Goy et al, JCO 2013

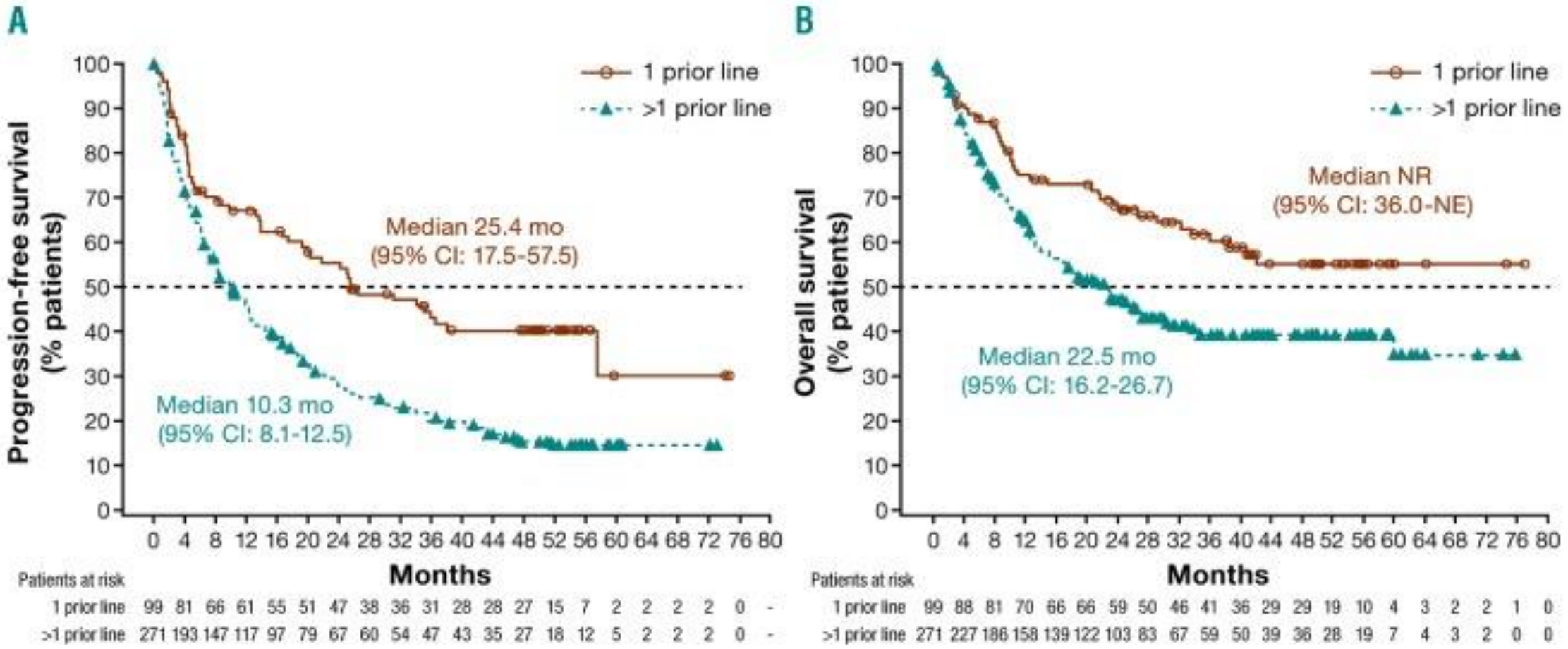
Covalent single agent BTKi activity in R/R MCL

BTKi	Phase	N	#PT	Resp. Criteria	ORR (CR)	mPFS (mo)	mOS (mo)
Ibr	2	111	3	Cheson (2007)	68 (21)	13.9	22.5
Acal	2	124	2	Lugano (2014)	81 (48)	22	59
Zanu	2	86	2	Lugano (2014)	84 (78)	33	N/R
Orela	2	106	NR	Lugano (2014)	88 (28)	NR	NR

Head-to-head studies between these regimen are lacking. Therefore, direct comparisons cannot be made.

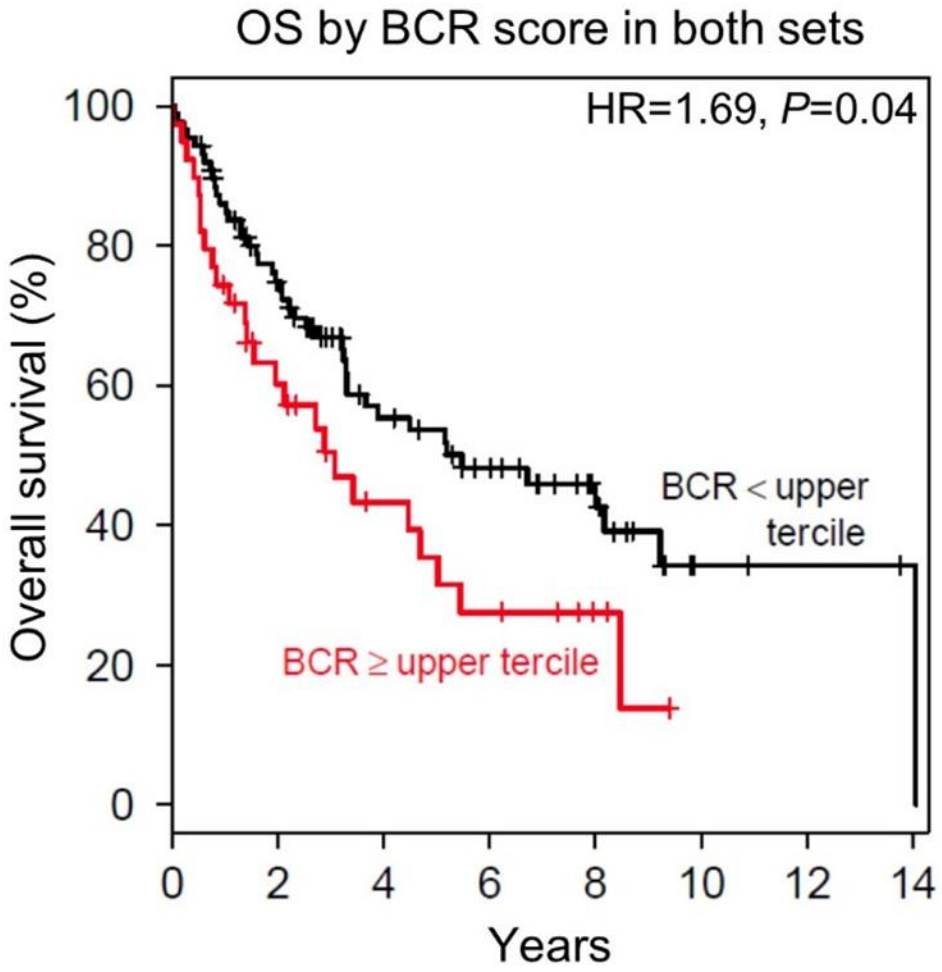
Wang et al. NEJM 2013; Le Gouill et al. EHA 2022; Song Y, et al. Blood. 2022; Song et al. ASH 2020

Ibrutinib in R/R MCL: 3.5-year follow-up, N=370 pooled from phase II PCYC-1104 and SPARK, phase III RAY: Line of therapy matters.



Rule et al. Hematologica 2019

Strength of BCR signaling is associated with resistance to chemotherapy in MCL



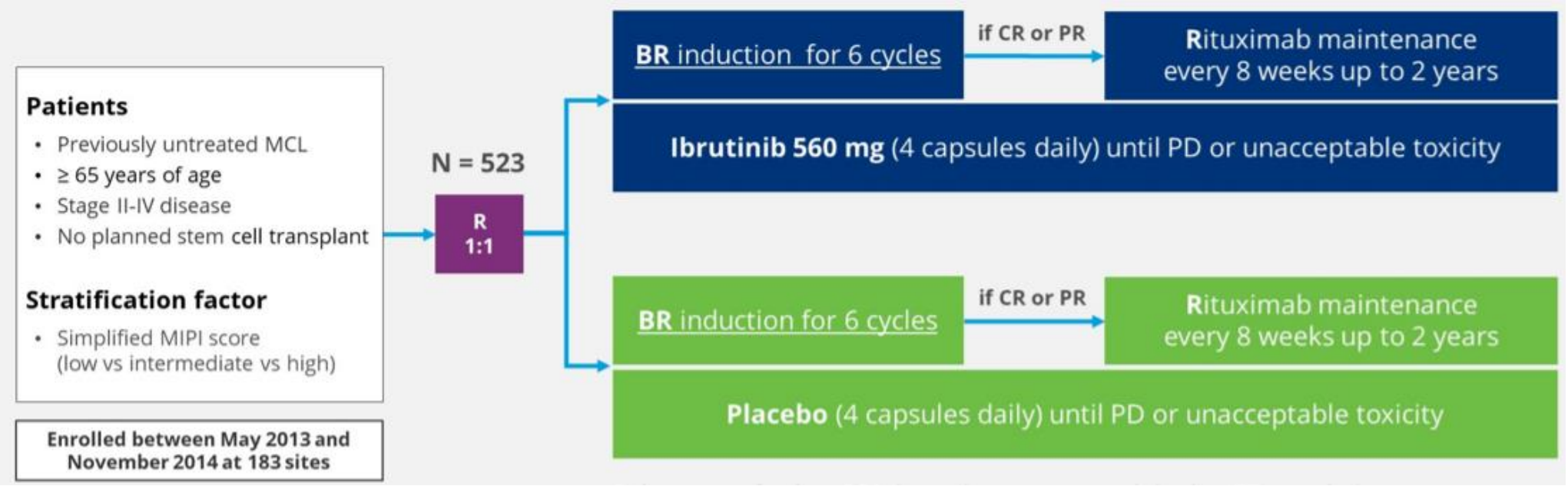
Saba et al. Blood 2016

Ibrutinib in combination with chemotherapy in frontline MCL

Patient status/trial name	Phase	N	Treatment	First outcome	ClinicalTrials.gov
Transplant eligible					
TRIANGLE	3	870	R-CHOP/R-DHAP → ASCT R-CHOP + ibrutinib/R-DHAP → ASCT + ibrutinib maintenance R-CHOP + ibrutinib/R-DHAP → ibrutinib maintenance	EFS	NCT02858258
EA4151	3	689	Rituximab chemotherapy → MRD MRD positive: ASCT + rituximab maintenance MRD negative: ASCT + rituximab maintenance vs rituximab maintenance	OS	NCT03267433
Transplant ineligible					
E1411	2	332	Bendamustine-rituximab → rituximab maintenance Bendamustine-rituximab → rituximab-lenalidomide maintenance Bendamustine, rituximab, and bortezomib (Velcade) → rituximab maintenance Bendamustine, rituximab, and bortezomib (Velcade) → rituximab-lenalidomide maintenance	PFS	NCT01415752
SHINE	3	523*	Bendamustine-rituximab → rituximab maintenance Bendamustine-rituximab-ibrutinib → rituximab-ibrutinib maintenance	PFS	NCT01776840

SHINE: First-line Ibrutinib + BR Followed by R Maintenance in Older Patients With MCL

- Multicenter, randomized, double-blind, placebo-controlled phase III trial



- **Primary endpoint:** investigator-assessed PFS (in ITT)
- **Key secondary endpoints:** ORR, time to next treatment, OS, safety

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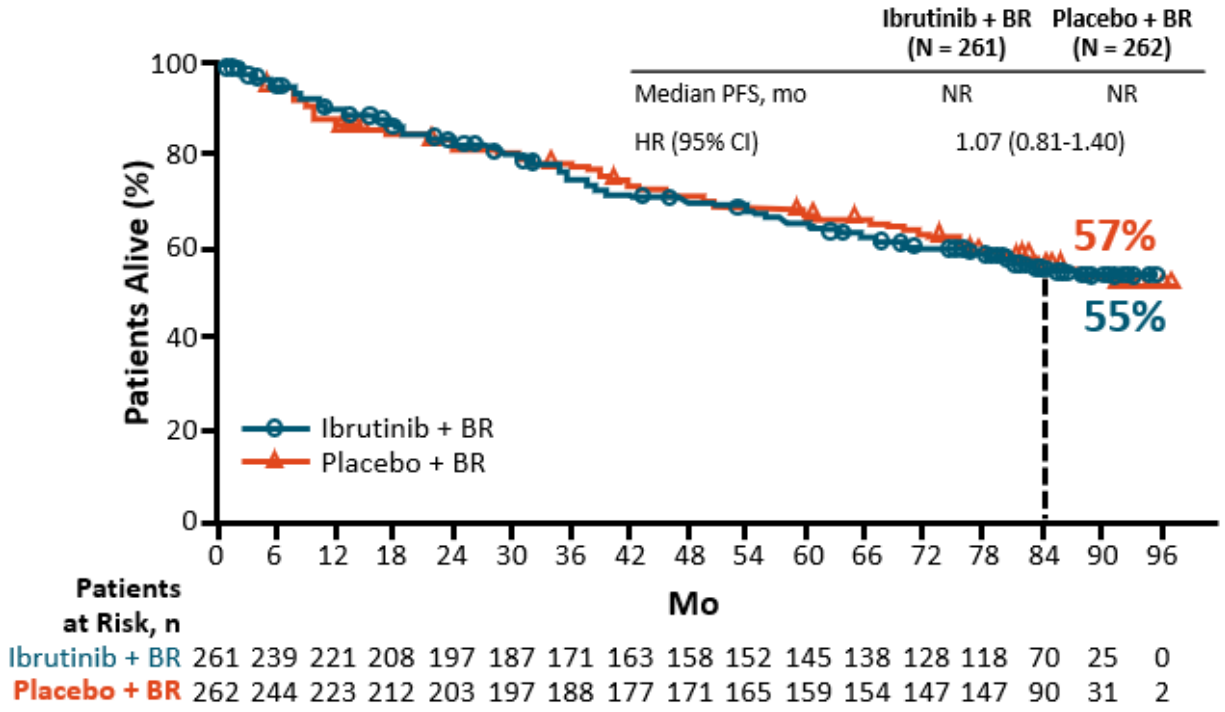
SHINE: Primary Endpoint of Improved PFS was met



Median PFS, Mo	Ibrutinib + BR	Placebo + BR	HR (95% CI)
Patients with blastoid/ pleiomorphic histology	25.6	10.3	0.66 (0.32-1.35)
Patients with *TP53* mutation†	28.8	11.0	0.95 (0.50-1.80)

Efficacy Outcome	Ibrutinib + BR (n = 261)	Placebo + BR (n = 262)
ORR, %	**89.7**	**85.5**
▪ CR	65.5	57.6
▪ PR	24.1	30.9

- **Median follow-up**: **84.7 mo (7.1 yr)**
- Ibrutinib + BR and R maintenance showed:
  - Significant improvement in median PFS by 2.3-yr for ibrutinib arm vs the placebo arm (6.7 vs 4.4 years)
  - 25% reduction in risk of PD or death

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SHINE: TEAEs of Clinical Interest

TEAEs of Interest With BTK Inhibitors, %	Ibrutinib + BR (n = 259)		Placebo + BR (n = 260)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any bleeding	42.9	3.5	21.5	1.5
Major bleeding	5.8	--	4.2	--
Atrial fibrillation	13.9	3.9	6.5	0.8
Hypertension	13.5	8.5	11.2	5.8
Arthralgia	17.4	1.2	16.9	0

- TEAEs of interest with BTK inhibitors typically not treatment limiting
- Other events similar with ibrutinib vs placebo: SPMs, 21% vs 19%; MDS/AML, 2 vs 3 patients

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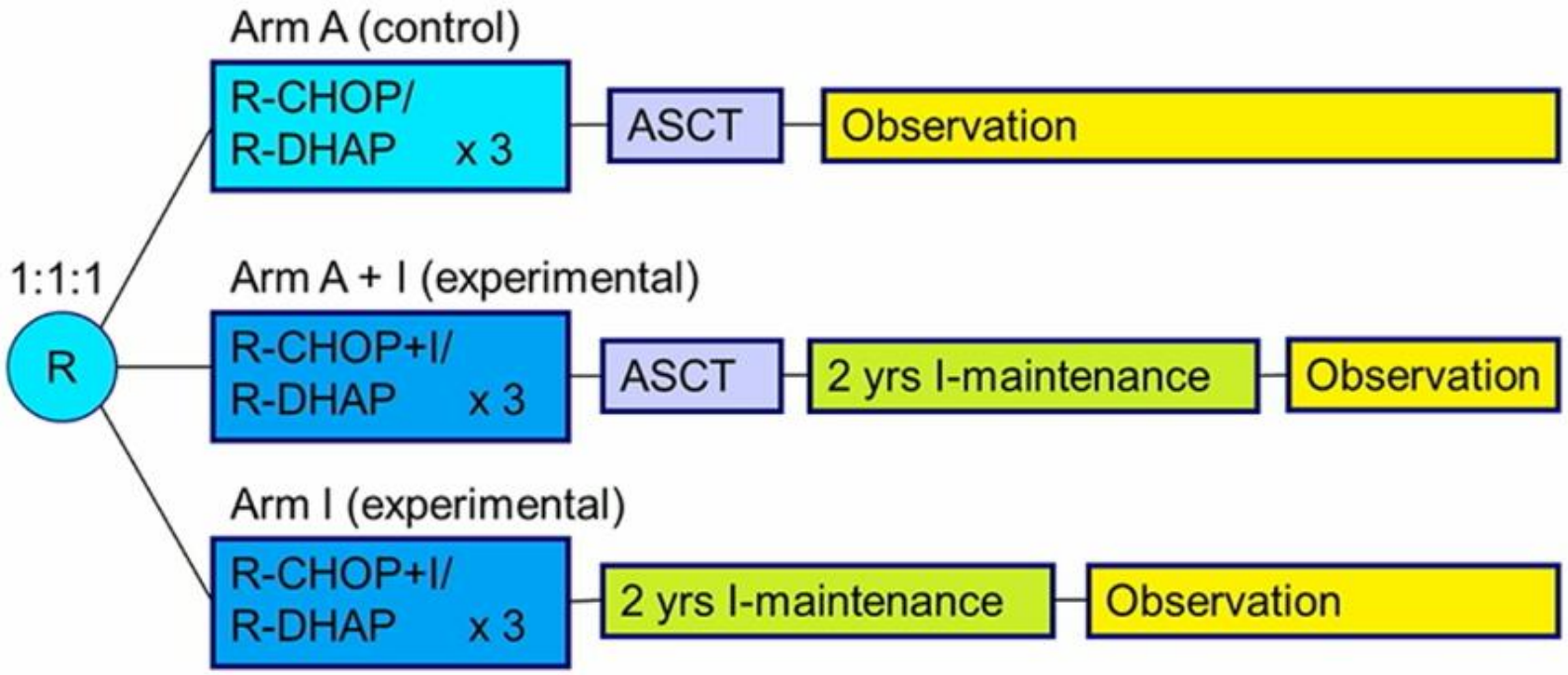
TRIANGLE: Study Design



- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

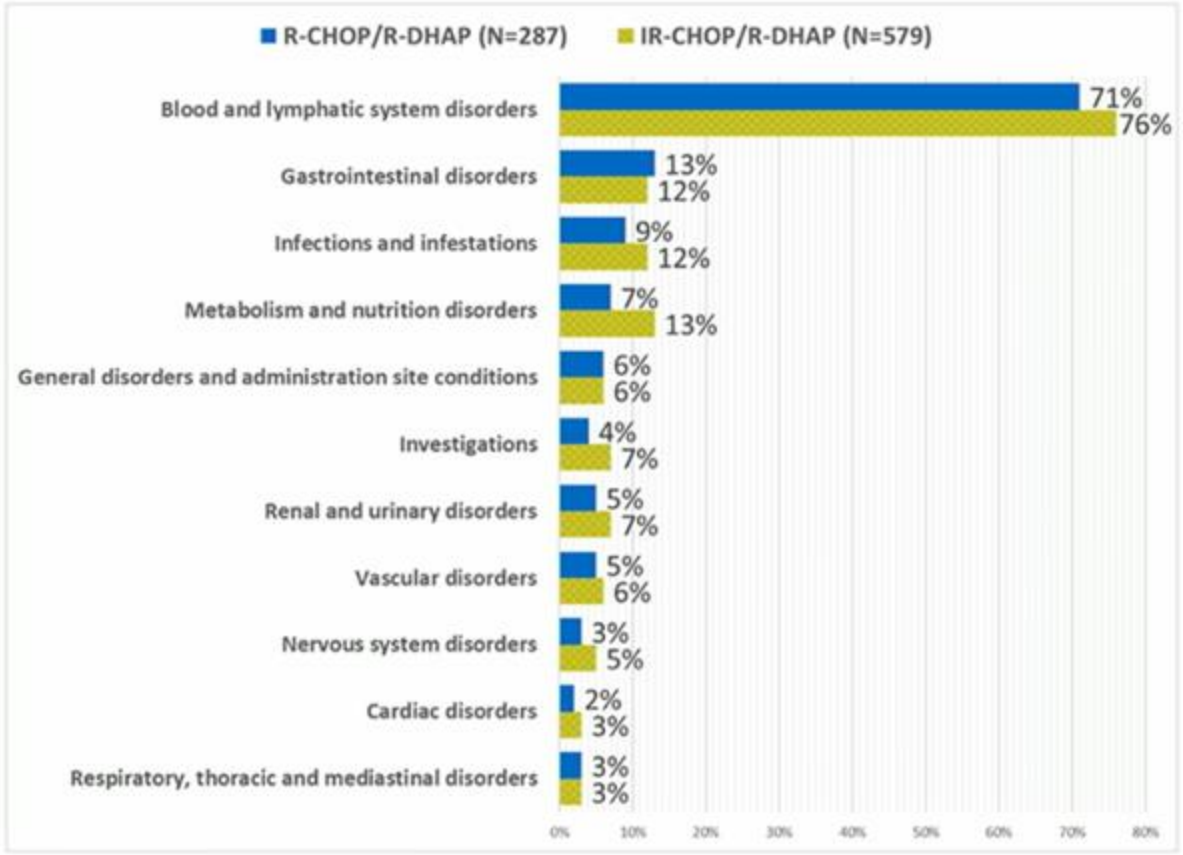
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety

- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

Dreyling et al. ASH 2022

Induction Response and Toxicity

Grade 3-5 AEs (induction period)



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

The inclusion of Ibrutinib was associated with a modest increase in toxicity during induction, but was associated with a significant improvement in ORR and CR

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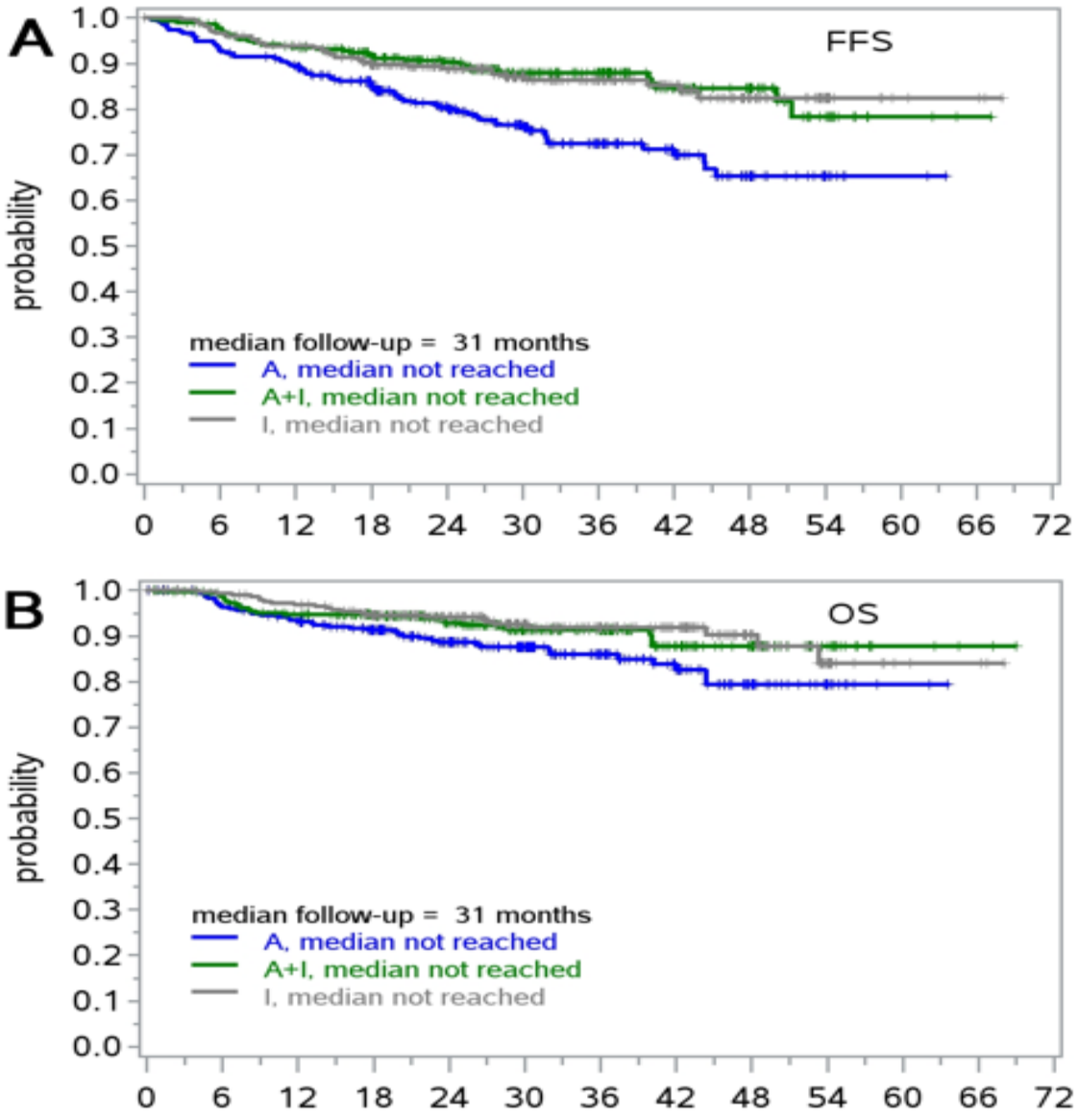


	Ibrutinib + AutoSCT (n=292)	AutoSCT (n=288)	P-Value
3y FFS	88%	72%	HR 0.52, p=0.0008
3y OS	91%	86%	-

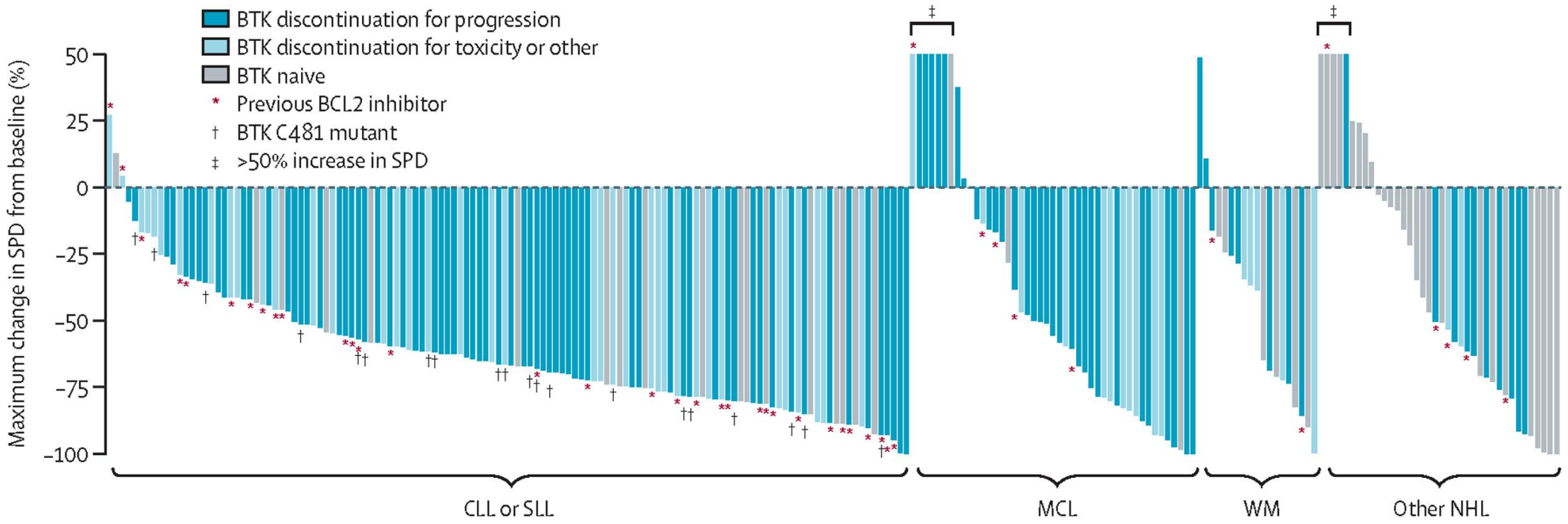
	AutoSCT (n=288)	Ibrutinib (n=290)	P-Value
3y FFS	72%	86%	HR 1.77, p=0.9979
3y OS	86%	92%	-

- AutoSCT failed to show superiority over Ibr
- AutoSCT+Ibr is superior to AutoSCT
- Statistical monitoring for the FFS comparison of Auto-SCT+Ibr vs. Ibr is still ongoing

Dreyling et al. ASH 2022

Looking Forward: Exciting Agents in Relapsed and Refractory MCL

Pirtobrutinib in R/R B-cell malignancies (BRUIN): a Phase 1/2 study



- N=90, all BTKi exposed
- Median on treatment time: 12 months
- ORR 58% (CR 20%)

Low rates of Grade ≥3 TEAEs:

- HTN (3%), hemorrhage (2%), a-fib/flutter (1%)
- Discontinuation due to a TRAE: 2%

Wang et al. ASH 2022
Mato et al. Lancet 2021

ZUMA-2 Phase 2 Brexu-Cel in R/R MCL: Study Design

Key Eligibility Criteria

- ≥18 years of age
- Histologically confirmed MCL that was relapsed/refractory to 1-5 prior regimens
- Received prior anthracycline-containing or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and BTKi therapy

Enrollment/Leukapheresis

↓

Optional Bridging Therapy

Dex 20-40 mg PO or IV daily for 1-4 days, or ibrutinib 560 mg PO daily, or acalabrutinib 100 mg PO twice daily

↓

Conditioning Chemotherapy

Flu 30 mg/m^2 IV and Cy 500 mg/m^2 IV on days -5, -4, -3

↓

CAR T-Cell Dose

2×10^6 KTE-X19 cells/kg on day 0

↓

First Tumor Assessment on Day 28

Primary endpoint: ORR as assessed by IRC

Secondary endpoints: DOR, PFS, OS, AE incidence, blood CAR T-cell levels, and serum cytokine levels

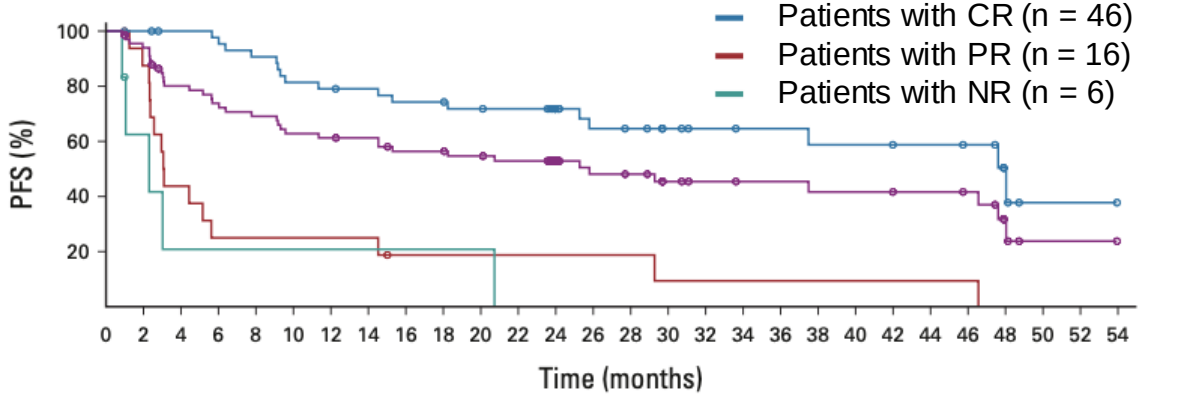
Patient Characteristics		N=68
Median age, years (range)		65 (38-79)
Intermediate or high risk according to Simplified MIPI, n (%)		38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL, n (%)		21 (31)
Median no. of previous therapies		3 (1-5)
Previous BTKi therapy, n (%)	Ibrutinib	58 (85)
	Acalabrutinib	16 (24)
	Both	6 (9)
Relapsed or refractory disease, n (%)	Relapse after ASCT	29 (43)
	Refractory to most recent prior therapy	27 (40)
	Relapse after most recent prior therapy	12 (18)
Disease that relapsed or was refractory to BTKi, n (%)	Refractory to BTKi therapy	42 (62)
	Relapse during BTKi therapy	18 (26)
	Relapse after BTKi therapy	5 (7)
	Could not take BTKi because of AEs	3 (4)

Wang M, et al. ASH 2019; Wang M, et al. J Clin Oncol. 2022

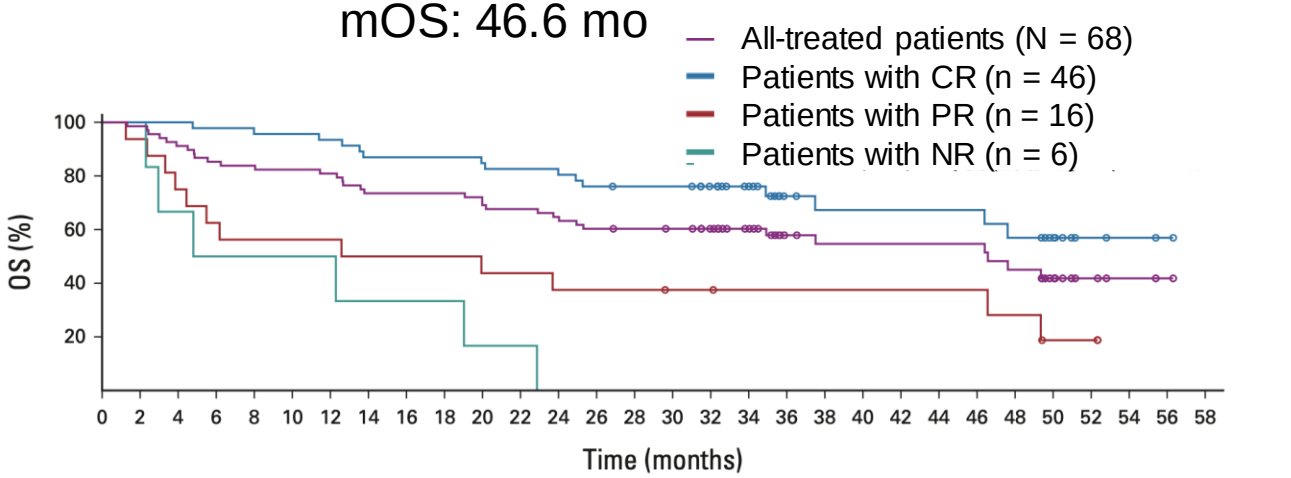
ZUMA-2 Phase 2 Brexu-Cel in R/R MCL: Efficacy

All Treated Since Previous Report		N=68
ORR, n (%)		62 (91)
Best response, n (%)	CR	46 (68)
	PR	16 (24)
	SD	3 (4)
	PD	3 (4)

mPFS: 25.8 mo



mOS: 46.6 mo



Wang M, et al. ASH 2019; Wang M, et al. J Clin Oncol. 2022

Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated R/R MCL

Phillips et al., ASH. 2022

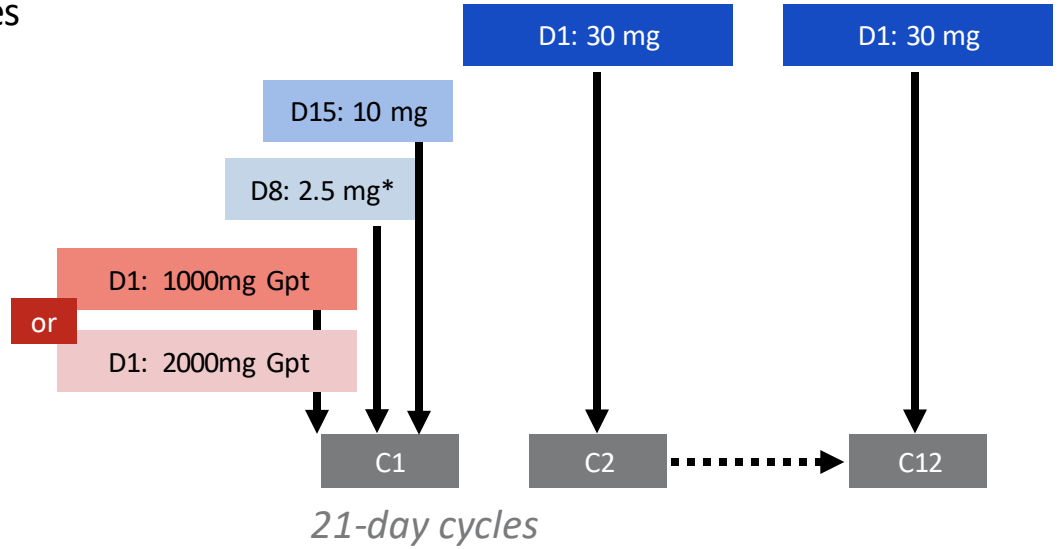
Study schema

Glofitamab IV administration
- Fixed-duration treatment: maximum 2 cycles

CRS mutation
- Obinutuzumab pretreatment
- (1 x 1000mg or 1 x 2000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

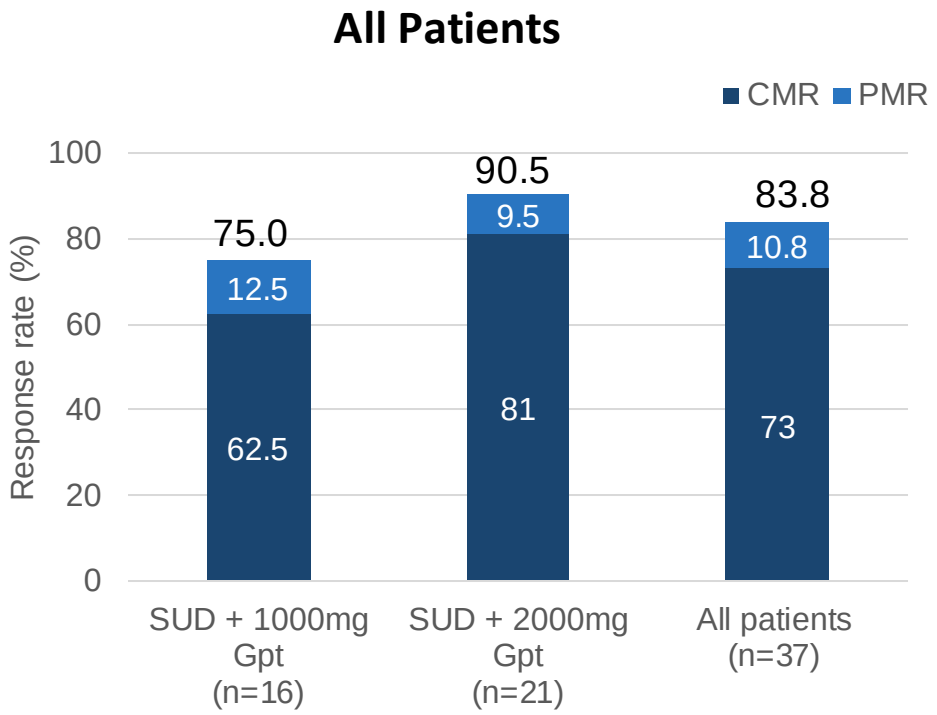
Population characteristics
- Age ≥18 years
- ≥1 prior systemic therapy
- ECOG PS ≤1

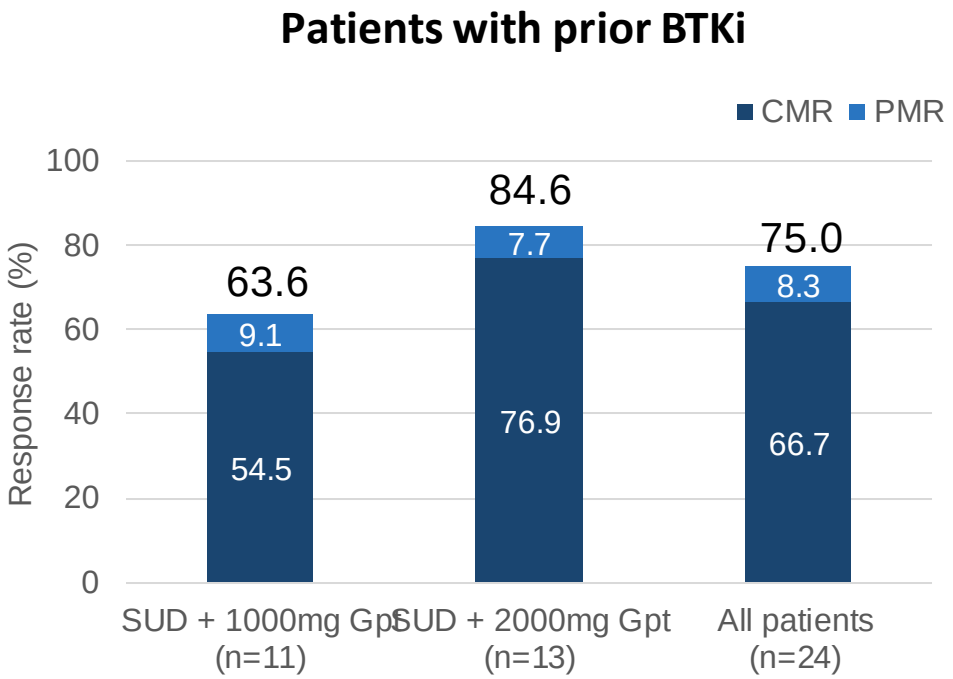
Clinical cutoff date: March 14, 2022



Phillips et al., ASH. 2022

High response rates with glofitamab monotherapy in patients with R/R MCL

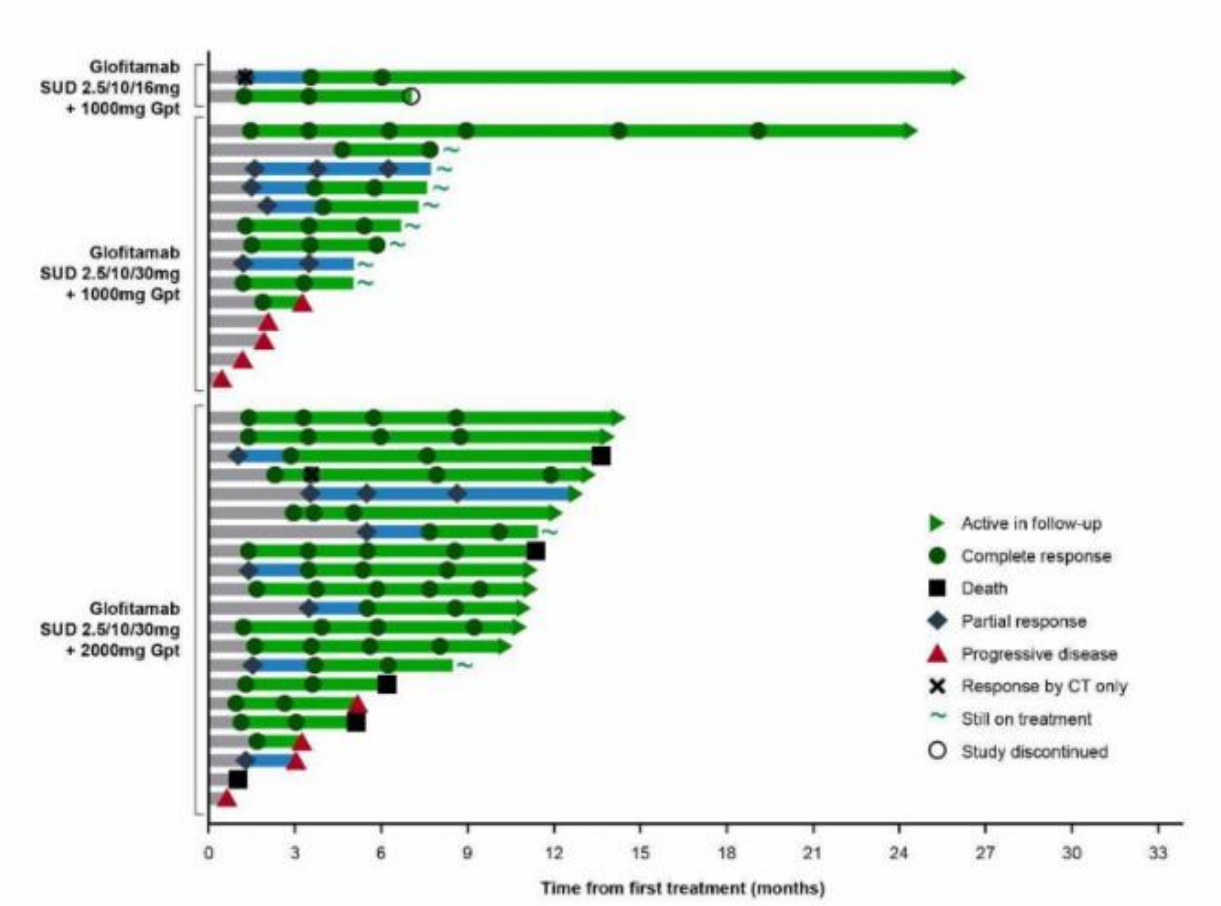




Phillips et al., ASH. 2022

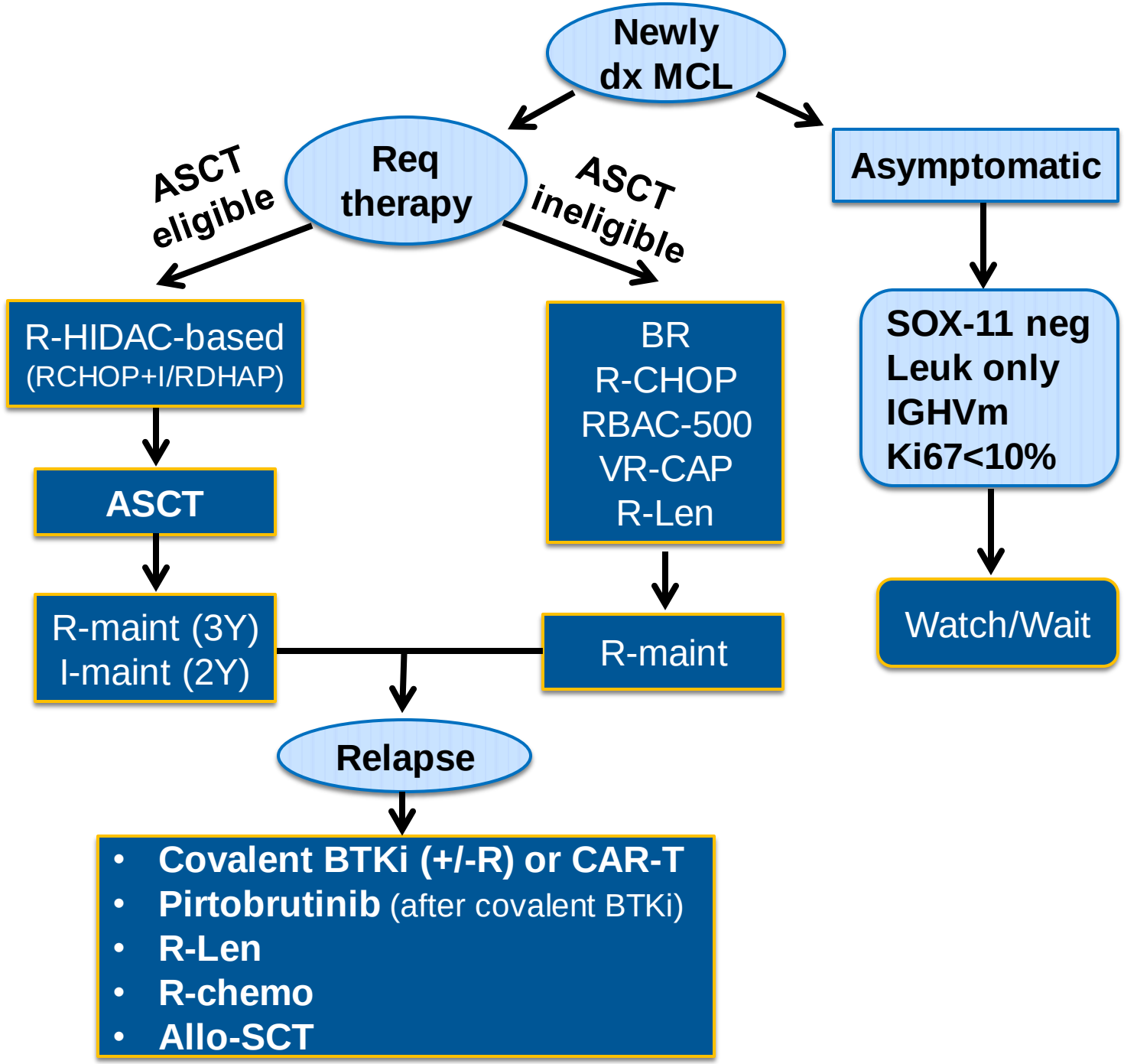
Glofitamab monotherapy produces a high CR rate and durable remissions in heavily pretreated MCL

Figure. Duration of response and time on study by glofitamab dosing cohort



CT, computed tomography; Gpt, obinutuzumab pretreatment; SUD, step-up dose.

Phillips et al., ASH. 2022


Newly dx MCL
Req therapy
ASCT eligible
ASCT ineligible
Asymptomatic
R-HIDAC-based (RCHOP+I/RDHAP)
ASCT
R-maint (3Y) I-maint (2Y)
BR R-CHOP RBAC-500 VR-CAP R-Len
R-maint
SOX-11 neg Leuk only IGHVm Ki67<10%
Watch/Wait
Relapse
• Covalent BTKi (+/-R) or CAR-T
• Pirtobrutinib (after covalent BTKi)
• R-Len
• R-chemo
• Allo-SCT

Thank you