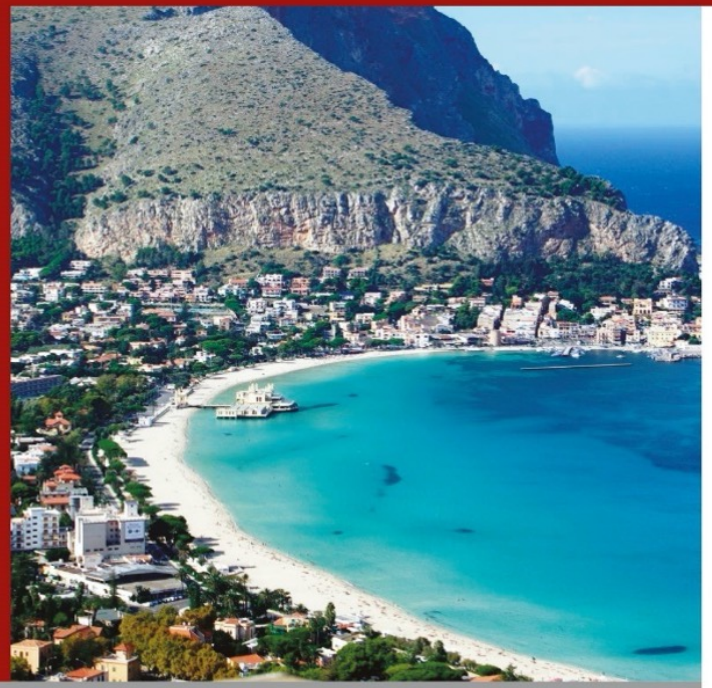
International Palermo Workshop on: Innovative Therapies for Lymphoid Malignancies



Palermo March 18, 2023
Hotel Federico II Central Palace

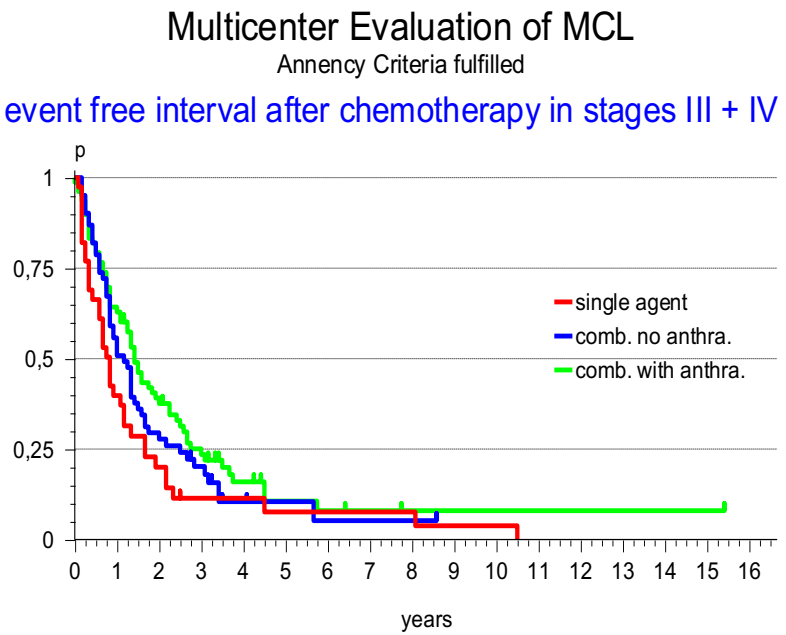
Mantle cell lymphoma

New perspectives in relapsing/refractory Mantle Cell Lymphoma

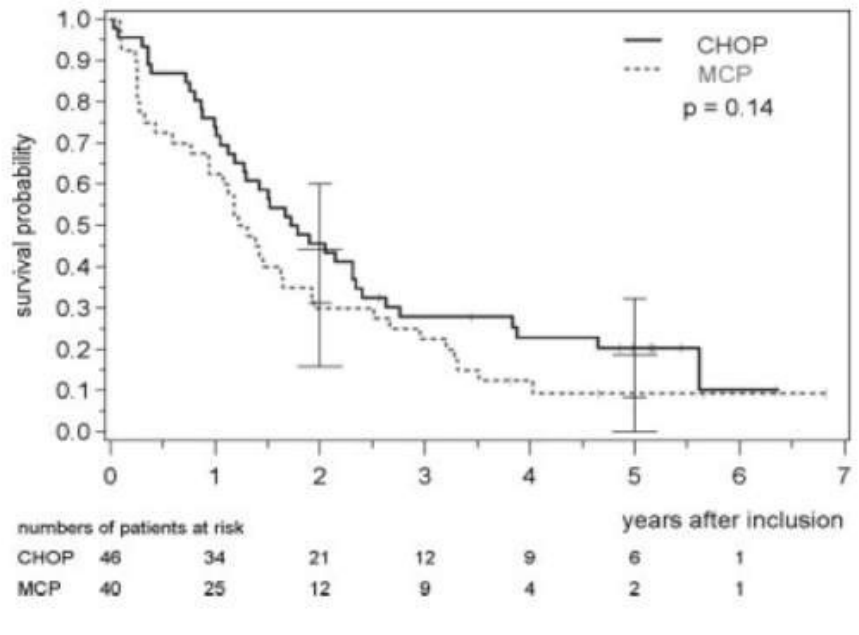
Olivier Hermine MD, PhD
Department of Hematology
INSERM 1163, Imagine Institute
Necker Hospital
Paris, France

European MCL Network
Clinical course (History 2000)

- CR/Cru 25%



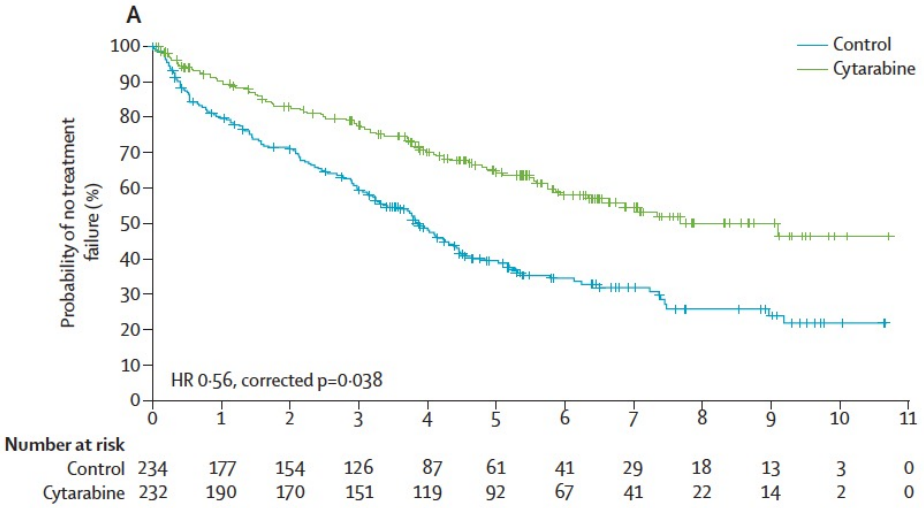
Dreyling, ASCO 1999

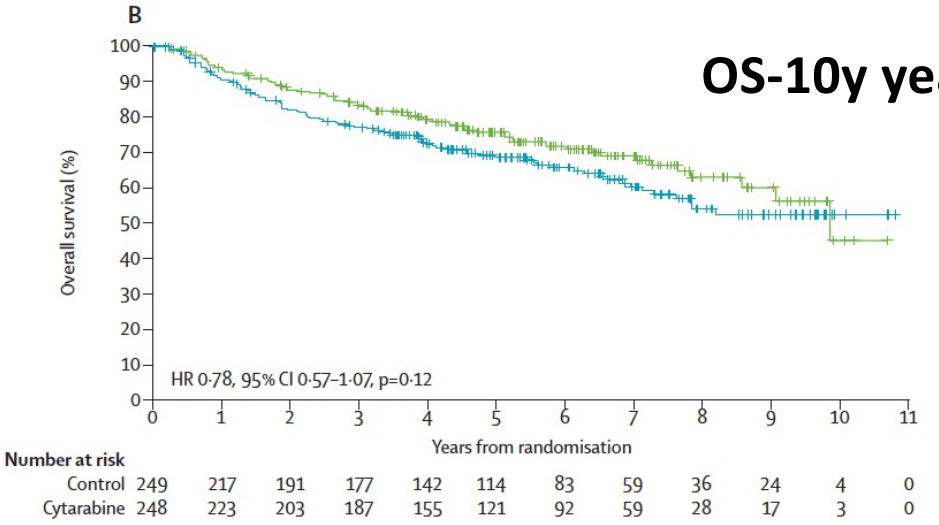


Nickenig, Cancer 2006

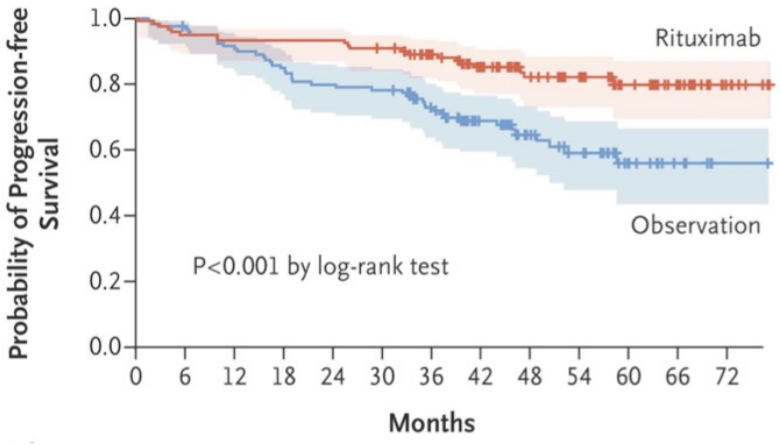
Younger patients

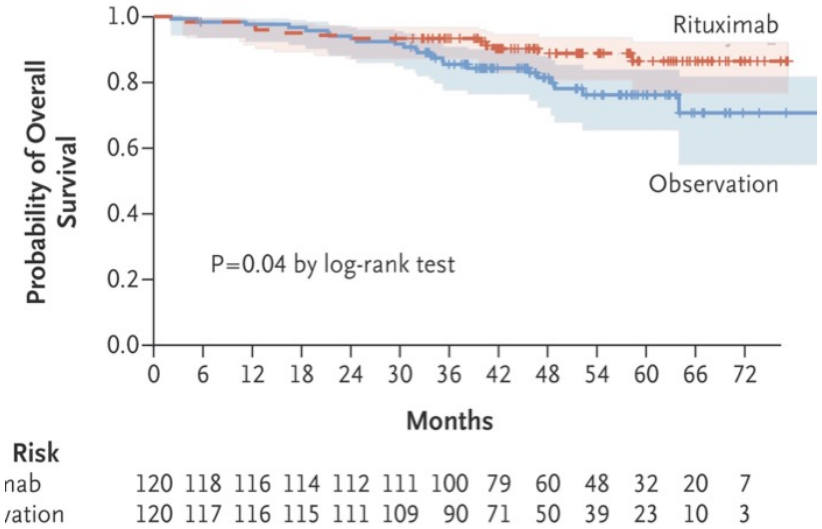
- *Autologous SCT*
- *High-dose cytarabine*
- *Rituximab maintenance*





OS-10y years 60%





OS-4 years 89%
PFS-4 years 83%

Dreyling Blood 2005; Hermine Lancet 2016; Le Gouill NEJM 2017, Hermine JCO 2023

Bendamustine or high-dose cytarabine-based induction with rituximab in transplant-eligible mantle cell lymphoma

Diego Villa*[1], Eva Hoster*[2], Olivier Hermine[3], Wolfram Klapper[4], Michal Szymczyk[5], André Bosly[6], Michael Unterhalt[7], Lisa M. Rimsza[8], Colleen A. Ramsower[8], Ciara L. Freeman[1,9], David W. Scott[1], Alina S. Gerrie[1], Kerry J. Savage[1], Laurie H. Sehn[1], Martin Dreyling[7]

Figure 1

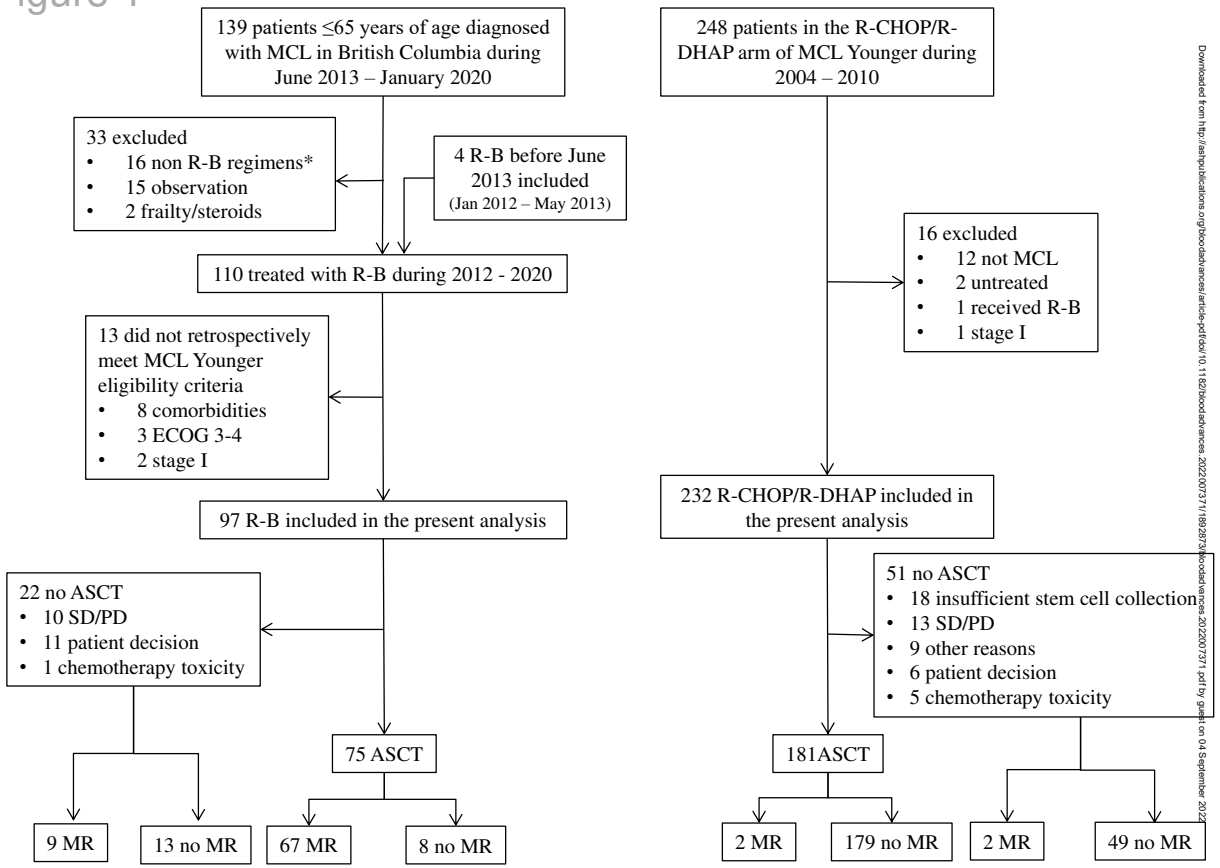


Figure 2B

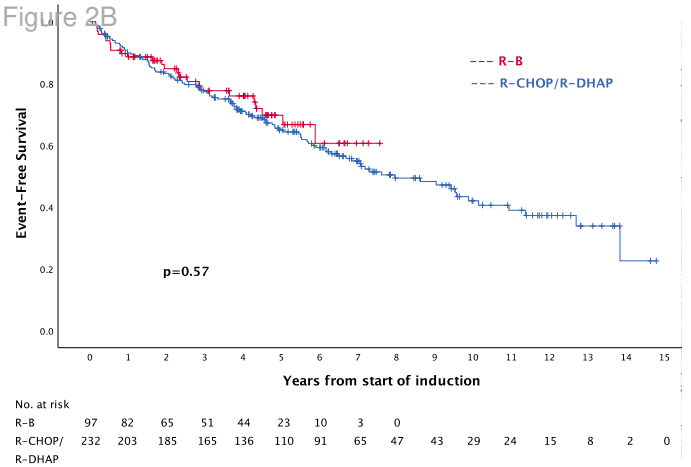
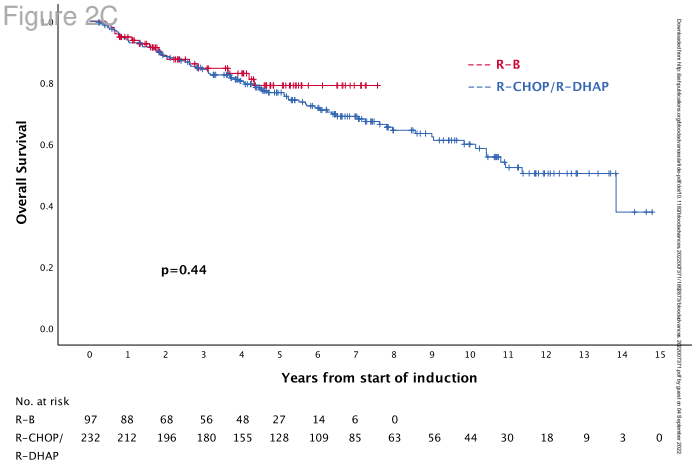
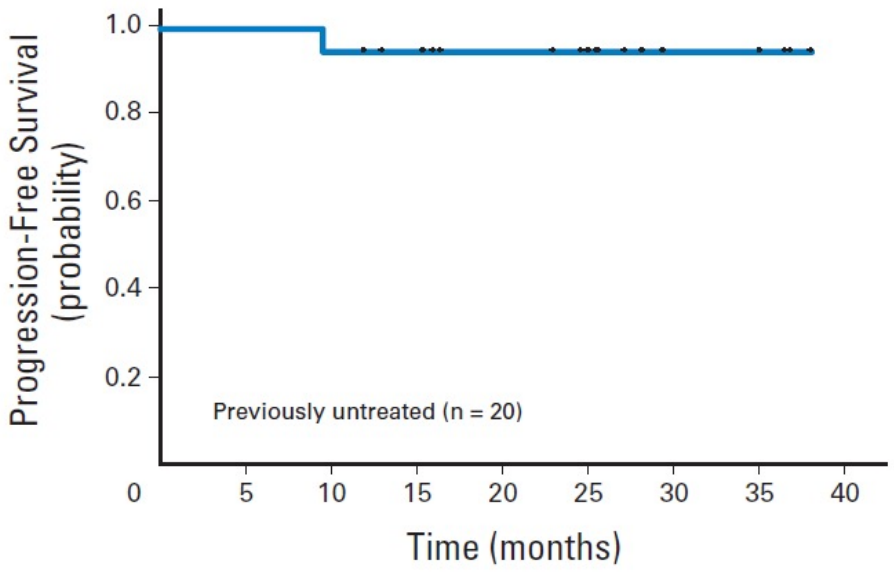


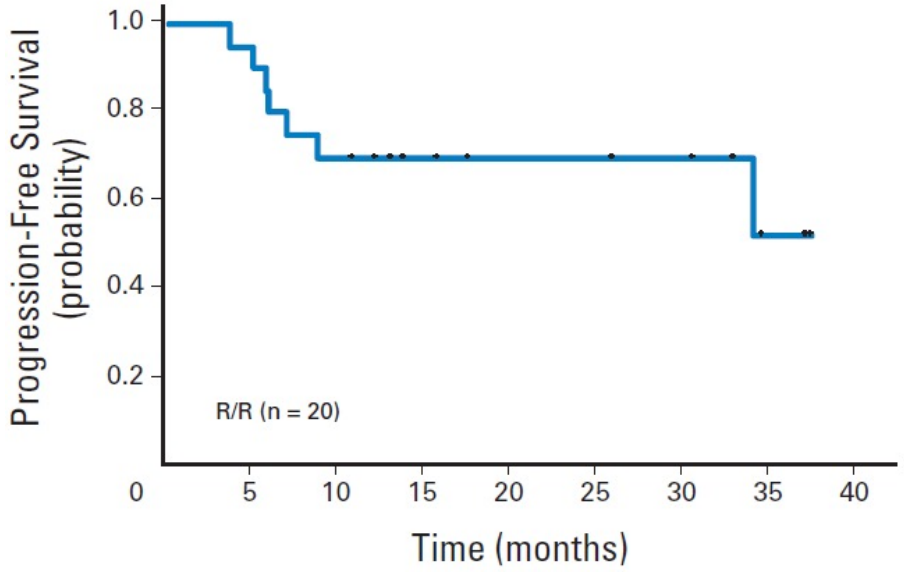
Figure 2C



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

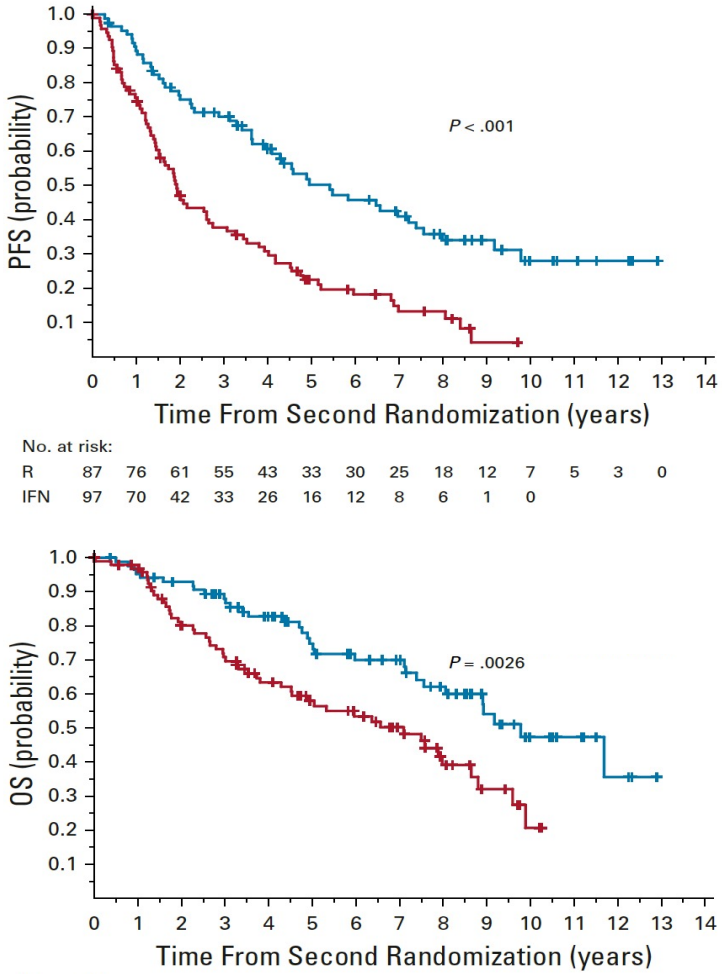




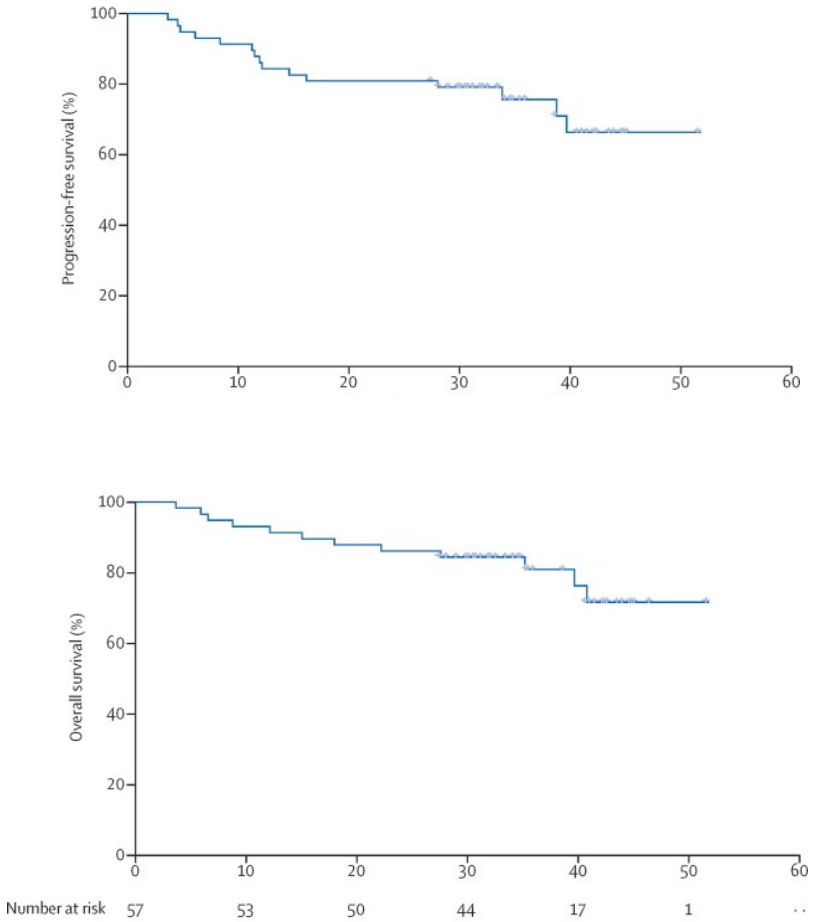
Visco, JCO 2013

Elderly patients

R-CHOP + Ritux *vs*. IFN



R-BAC



- R-CHOP > RFC
- R-BAC500 ?
- R-CHOP/R-HAD ?
- Rituximab maintenance
- R2 maintenance ?

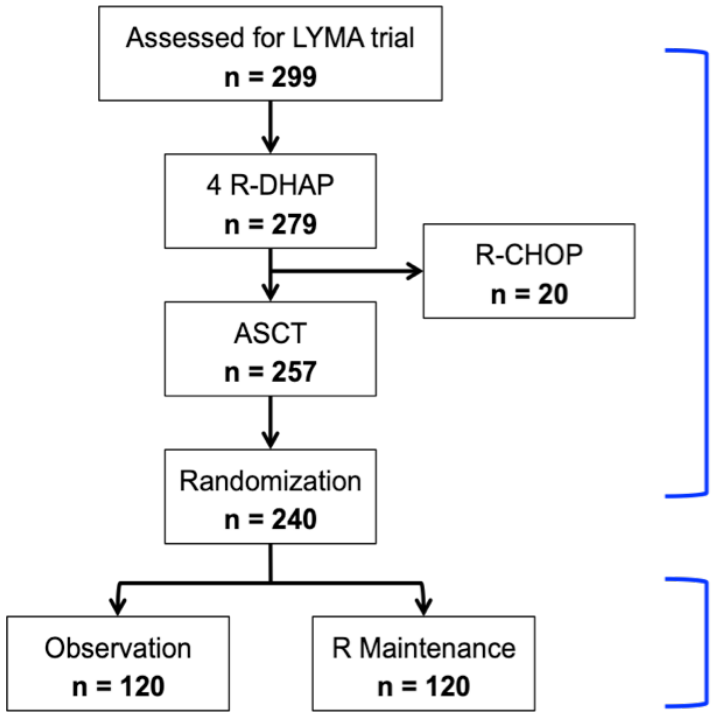
(from end of induction)

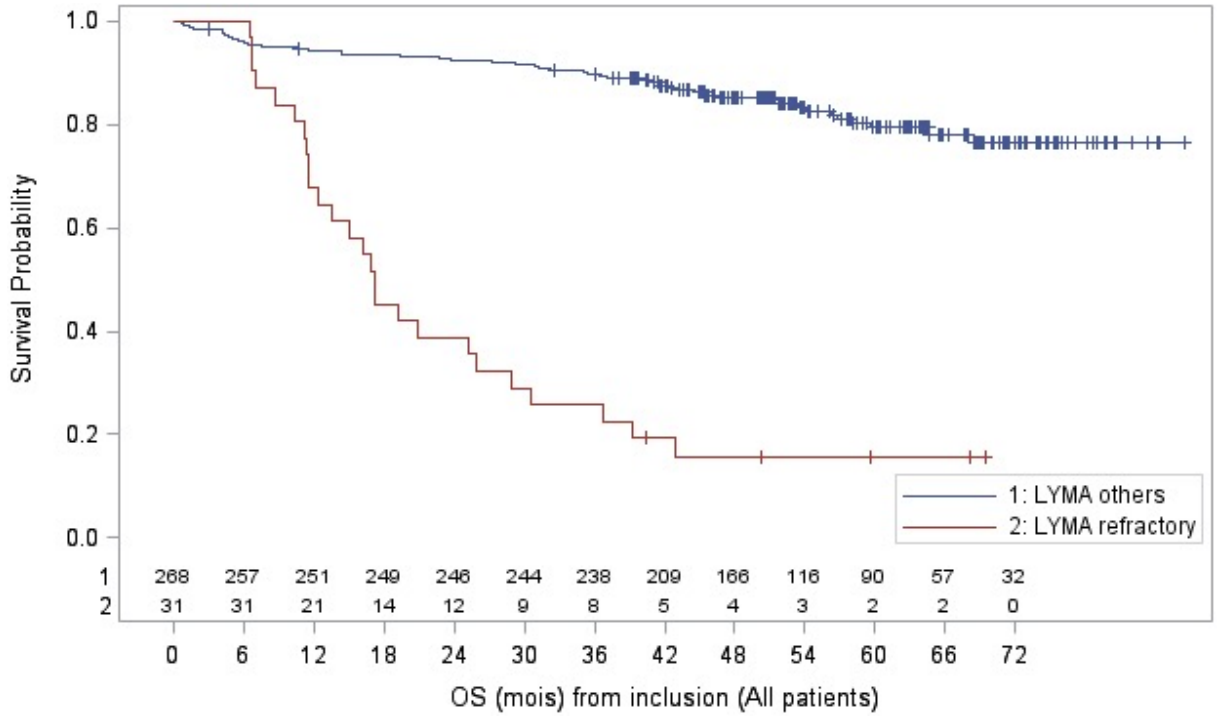
OS-5 years 75%

PFS-5 years 50%

Kluin-Nelemans NEJM 2012 & JCO 2020; Visco Lancet hematol 2017

Identification of very-high risk MCL ?





31 (10.4%) patients →

MIPI high : 16 vs. 45%
Blastoid : 9 vs. 32%
Ki67 > 30 : 31 vs. 71%
MIPI-c : 24 vs. 71%

→ Comparison of VHR and control MCL : known prognostic markers (PET/MRD, *TP53*, *CDKN2A*), genomic analyses

Cheminant et al, unpublished

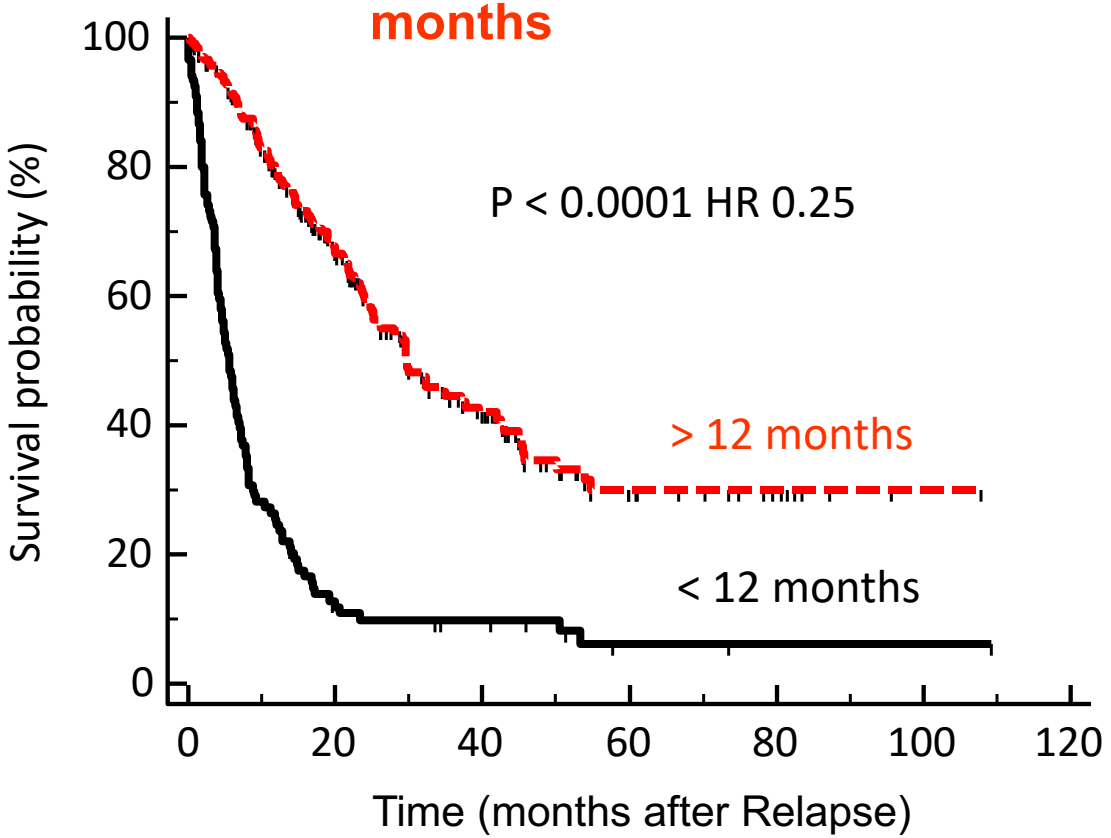
Prognostic factors after autoSCT failure

OS by remission duration after autoSCT

Before BTKi era

< 12 months 120 (33%)

> 12 months 240 (67%)



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

Prognostic factors after autoSCT failure

OS by remission duration after autoSCT

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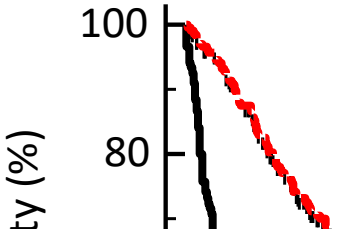
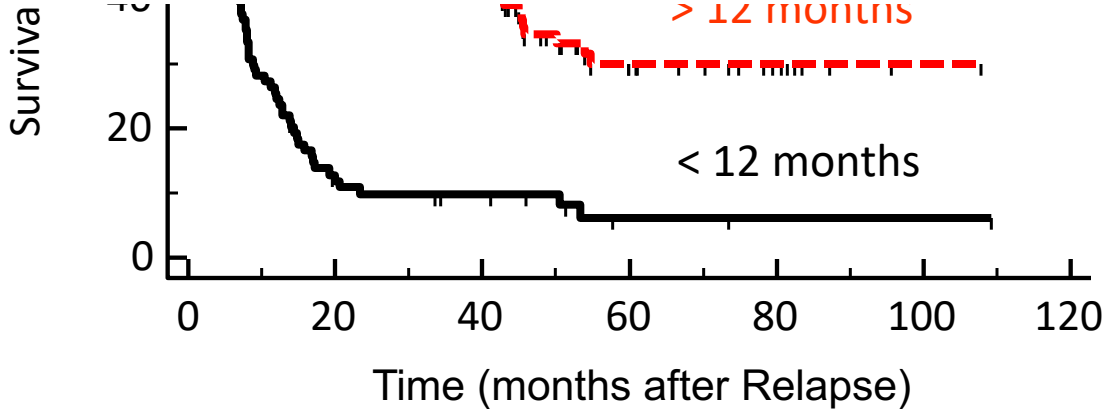
> 12 months **240 (67%)**



P < 0.0001 HR 0.25

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

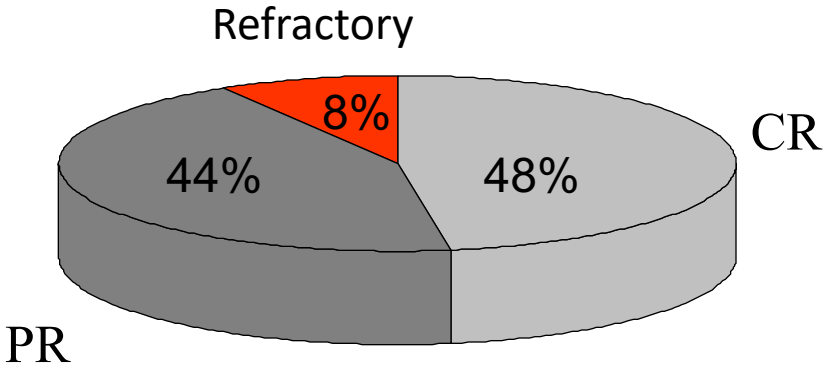


EBMT Registry Analysis, Ann. Onc. 2014, S. Dietrich

Response to salvage chemotherapy

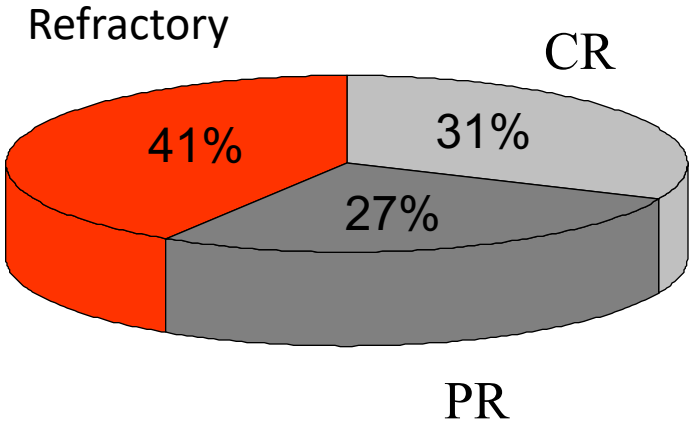
Before BTKi era

Before 1st autoSCT



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

Salvage after autoSCT-relapse



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

Mantle cell lymphoma
R-BAC

Characteristic	All Patients (N = 40)		Previously Untreated Patients (n = 20)		R/R Patients (n = 20)	
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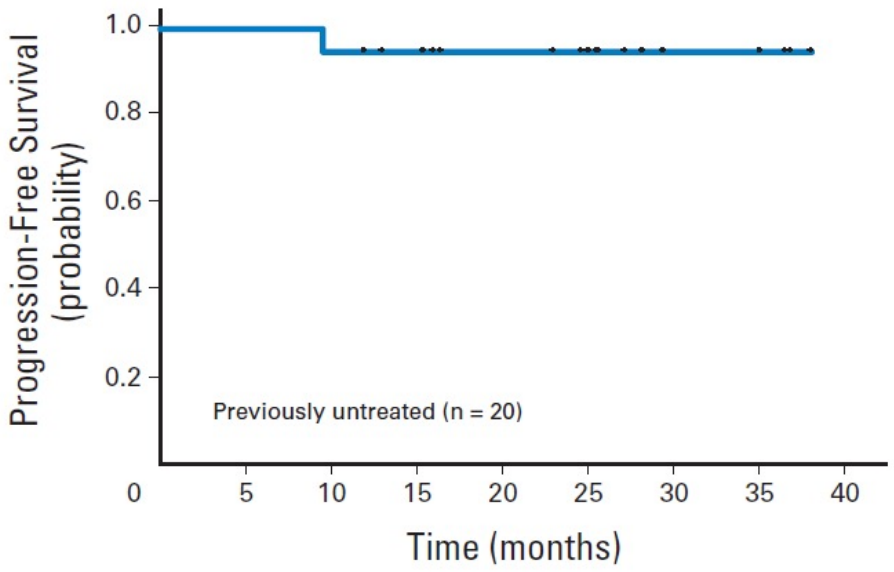
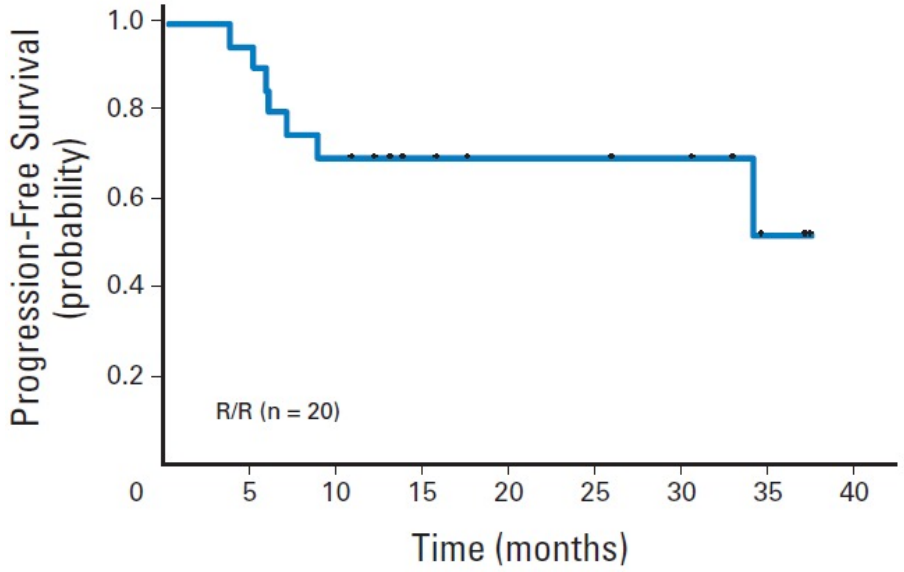




Visco, JCO 2013

ORIGINAL ARTICLE

Safety and efficacy of Temsirolimus in combination with Bendamustine and Rituximab in relapsed mantle cell and follicular lymphoma

G Hess[1], U Keller[2], CW Scholz[3], M Witzens-Harig[4], J Atta[5], C Buske[6], S Kirschey[1], C Ruckes[7], C Medler[7], C van Oordt[1], W Klapper[8], M Theobald[1] and M Dreyling[9]

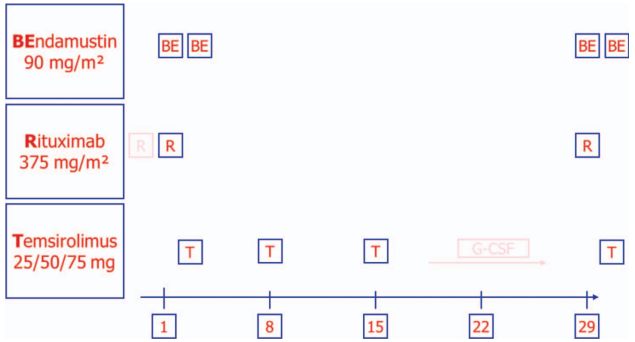
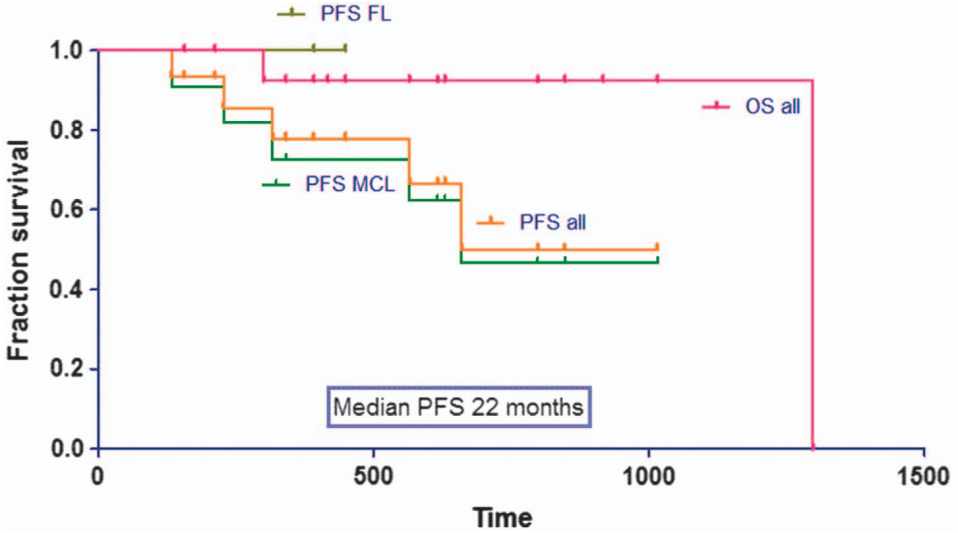


Table 4. Response rates and progression-free and overall survival

Response	*MCL (n = 11)*	*FL (n = 4)*	*Total (n = 15)*
CR	5 (45%)	0 (0%)	5 (33%)
PR[a]	6 (55%)	4 (100%)	10 (67%)
CR+PR[a]	10 (91%)	4 (100%)	14 (93%)
NE[a]	1 (9%)		1 (7%)
Progression-free survival at 19 months			67%
Overall survival at 19 months			92%

Abbreviations: CR, complete response; FL, follicular lymphoma; MCL, mantle cell lymphoma; PR, partial response. [a]Patient received one cycle only, a subsequent CR evaluation 9 months after this cycle revealed PR.



Chemotherapy salvage strategies

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

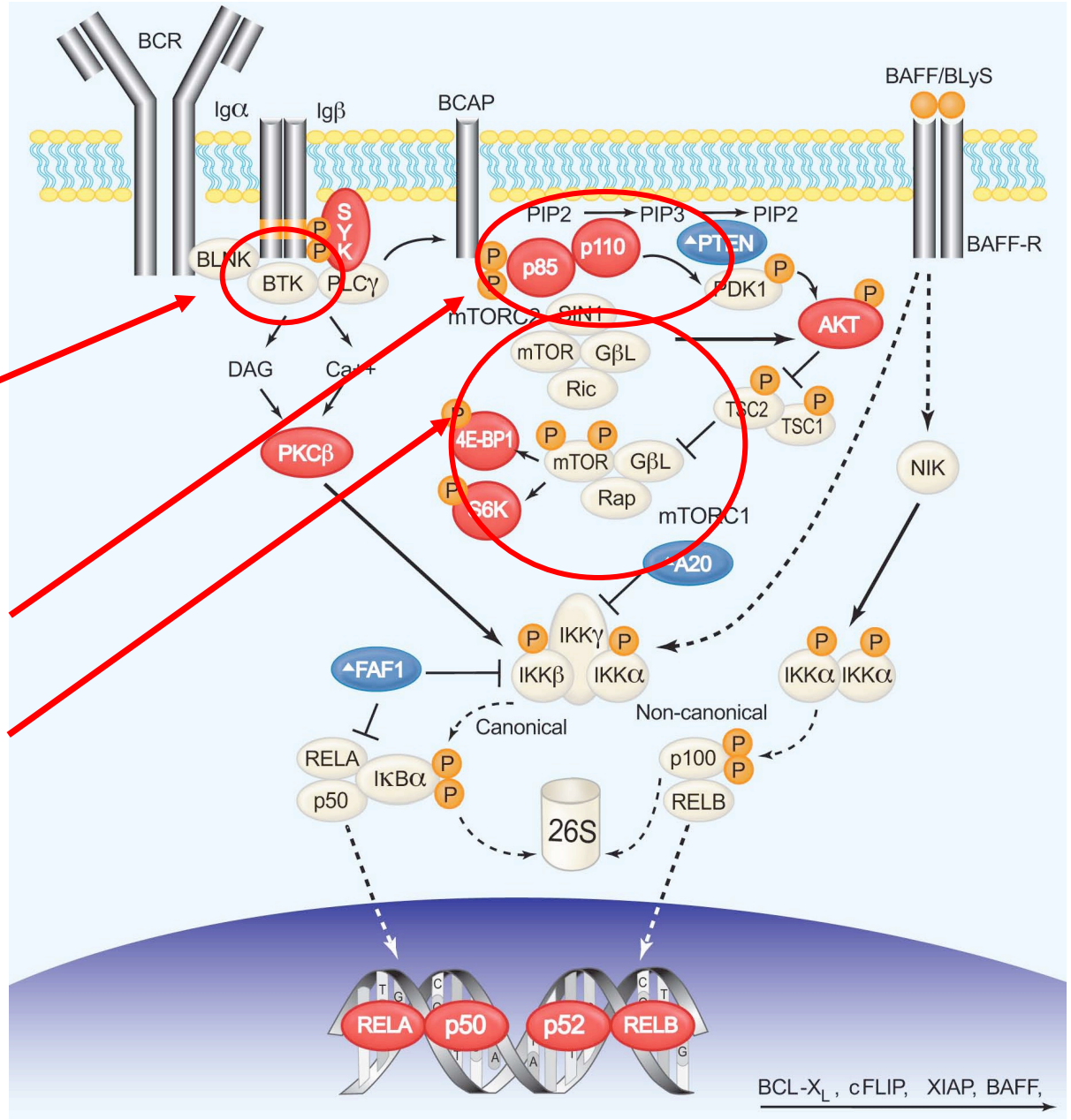
  - patient comorbidities
  - side effect profile of the selected regimen
  - prior therapies
  - clinical situation
  - Consolidation treatment (allo SCT, CAR-T, Bi-spe)

B cell receptor signalling pathways

Bruton ‘s tyrosine kinase

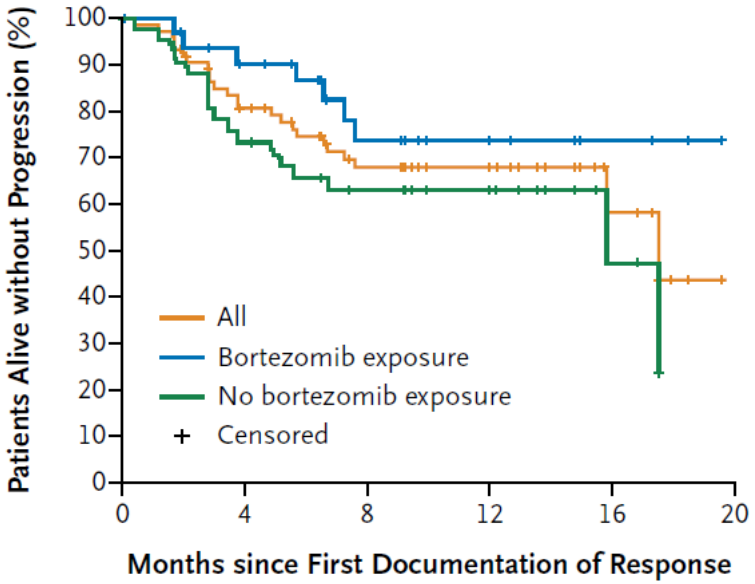
PI3K

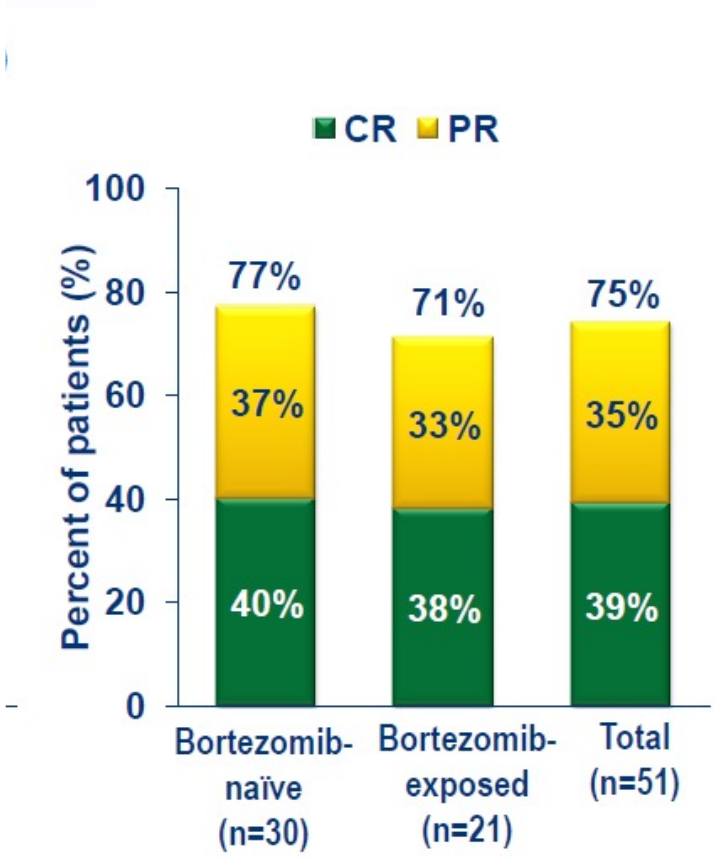
mTOR



Perez-Galan et al, Blood 2010

Ibrutinib for MCL





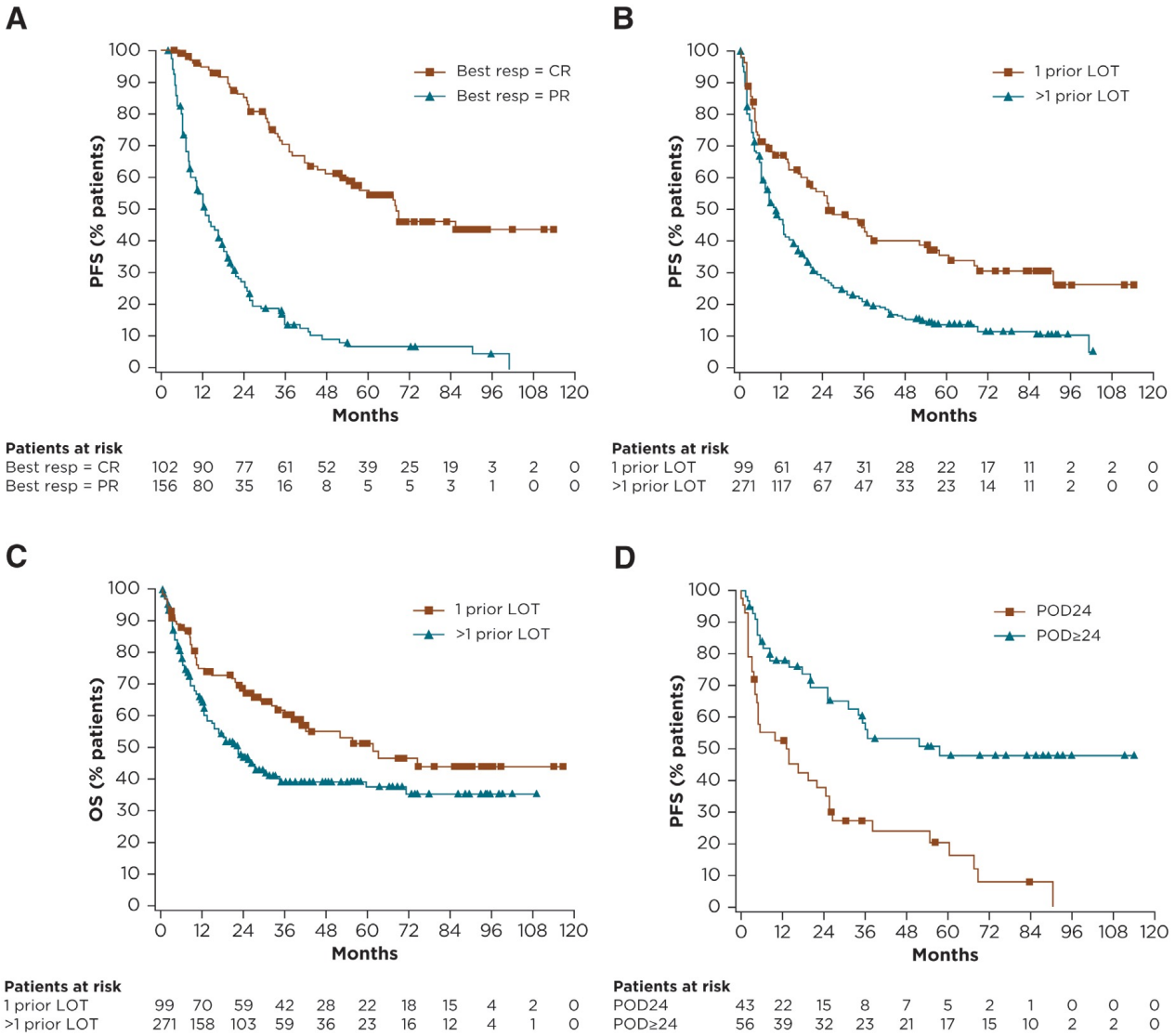
Outcome of patients with MCL treated by BTKi (Ibrutinib)

Long-term Outcomes With Ibrutinib Treatment for Patients With Relapsed/Refractory Mantle Cell Lymphoma: A Pooled Analysis of 3 Clinical Trials With Nearly 10 Years of Follow-up

Martin Dreyling[1], Andre Goy[2], Georg Hess[3], Brad S. Kahl[4], José-Ángel Hernández-Rivas[5], Natasha Schuier[6], Keqin Qi[7], Sanjay Deshpande[8], Angeline Zhu[8], Lori Parisi[8], Michael L. Wang[9]

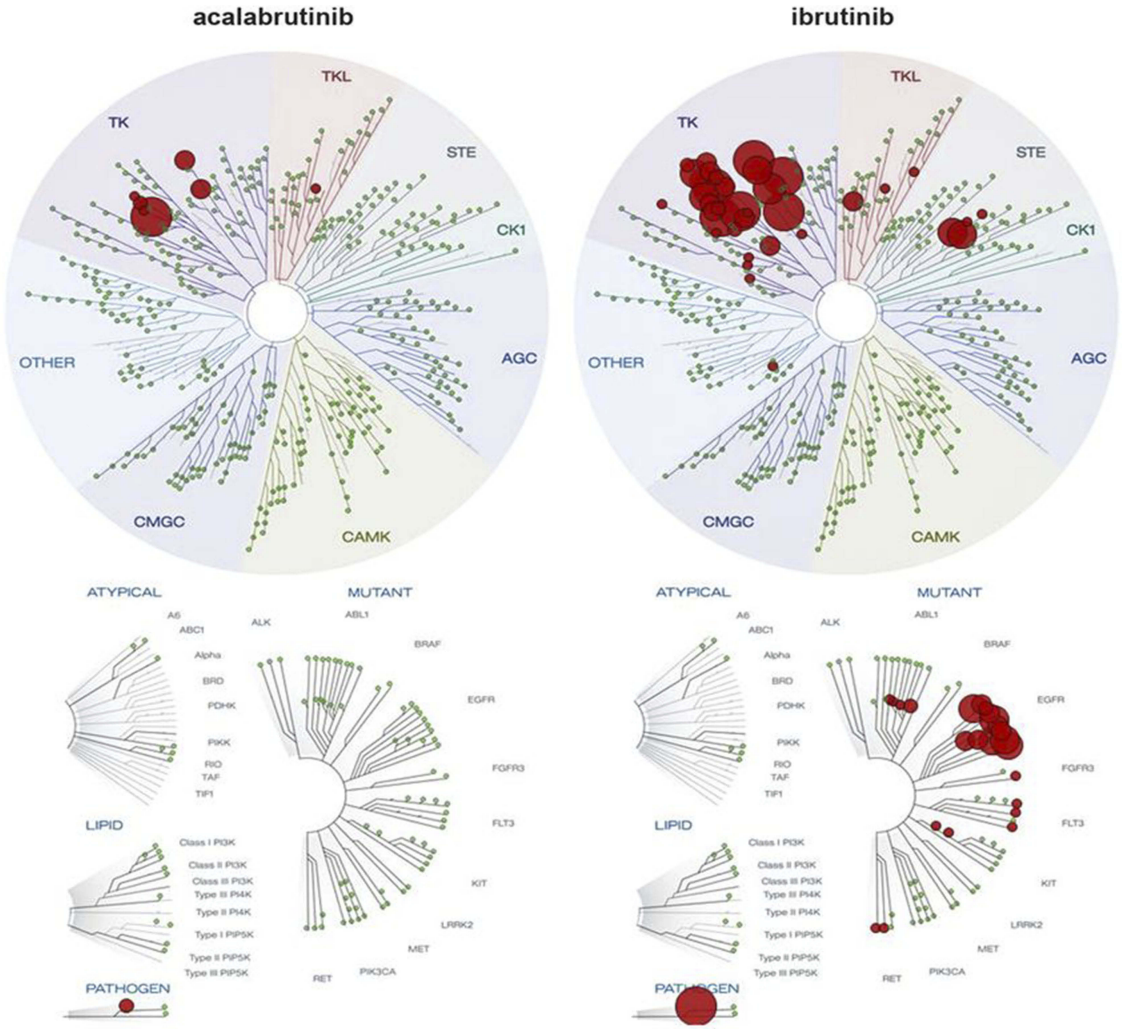
Safety :

Grade 3 (5%),Neutropenia, Thrombocytopenia (12%), Cardiovascular (20%), Atrial Fibrillation (7%), pneumonia (13%)



HemaSphere

Other BTKi



Increase efficacy ?

Increase safety ?

(Cardiovascular)

Other BTKi ?

- Zanubrutinib

Selective BTK inhibitor with a 90% ORR and. 20% CR in a phase I trial in MCL. Another reported an ORR of 81% with a PET-negative CR of 58%.

- LOXO-305

Reversible inhibitor with non-covalent binding to BTK that preserves activity in the presence of the C481S mutations and avoids off-target kinases inhibition.

- Vecabrutinib (SNS-062)

Reversible and non-covalent BTK inhibitor. Does not interact with cysteine 481 residue within the kinase domain unlike other inhibitors and may be relevant in C481S mutants.

- ARQ-531

Reversible inhibitor of BTK with additional activity against Src family kinases and kinases related to ERK signaling. It is tested for ibrutinib resistant cases.

Treatment Landscape in r/r MCL (BTKi)

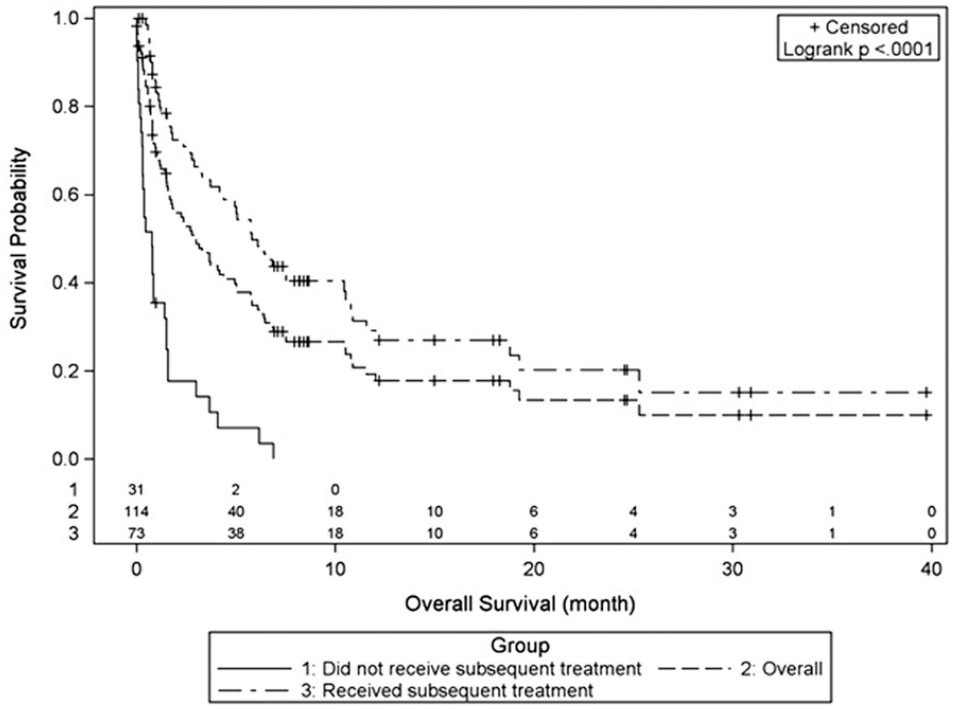
BTKi	Phase	Sample size (median f/up*)	FU in months	ORR% (CR%)	CR	Median PFS (months)	% bleeding events (grade ≥ 3)	% A.fib (grade ≥ 3)
Ibrutinib	II/III	111	20-26.7	67-72	19-23	13-14.6	10 [8] - 59 [5]	4 [4] - 6 [5]
Ibrutinib	Retro	139	20	72	19	14.6	10 [8]	4 [4]
Acalabrutinib	II	124	38.1	81	48	22	5 [4]	0 [0]
Zanubrutinib	Ib	43 - 86	9 - 10.3	84-90	20 -59	18	4.7 - 30.2 [1.2 -7]	0 - 4.7 [NR]
LOXO-305	I/II	8	NR	37.5 [0]		NP	11 [0]	0 [0]
	III	–	–	–	–	–	–	–

Post BTKi failure treatment

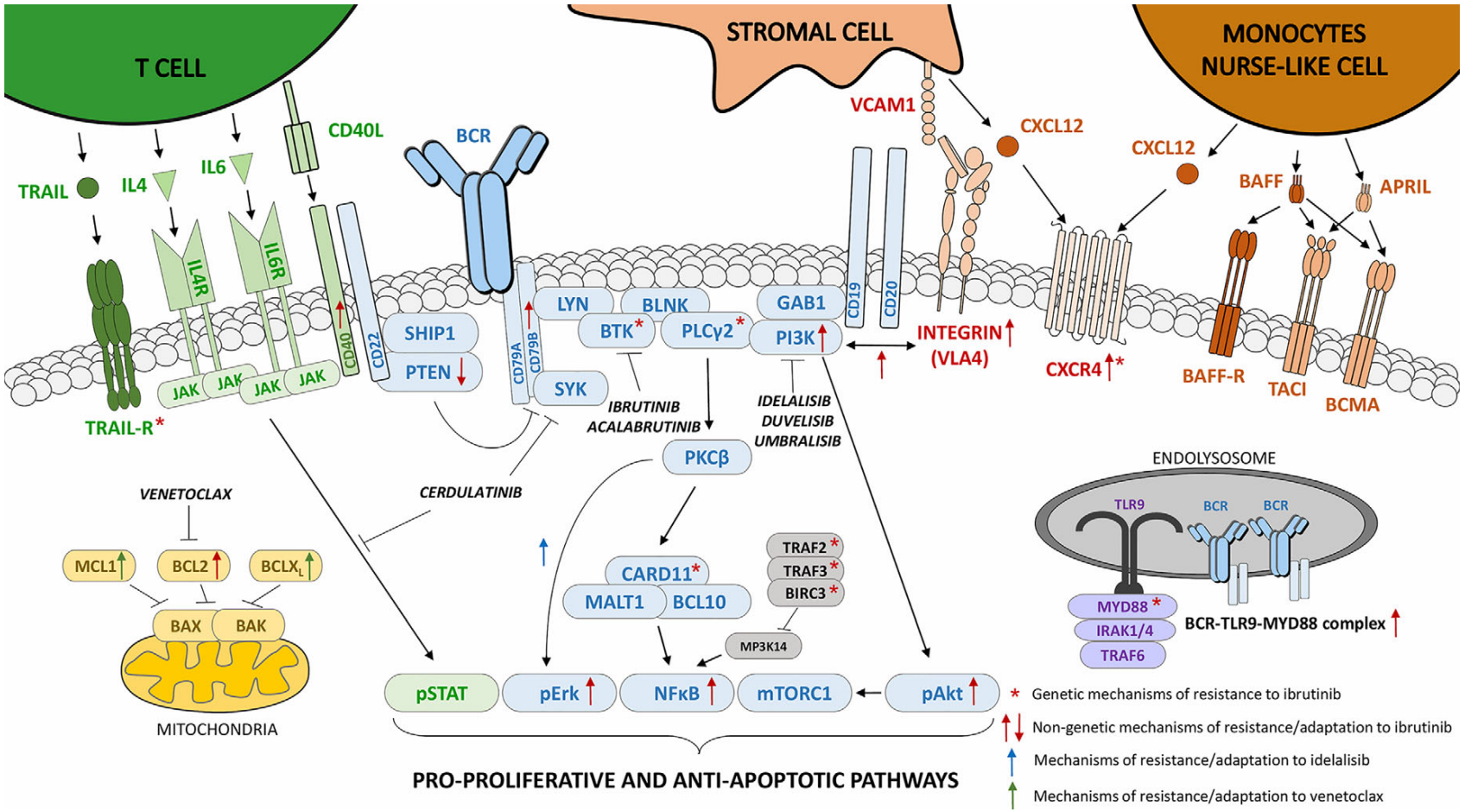
Postibrutinib outcomes in patients with mantle cell lymphoma

Peter Martin,[1] Kami Maddocks,[2] John P. Leonard,[1] Jia Ruan,[1] Andre Goy,[3] Nina Wagner-Johnston,[4] Simon Rule,[5] Ranjana Advani,[6] David Iberri,[6] Tycel Phillips,[7] Stephen Spurgeon,[8] Eliana Kozin,[8] Katherine Noto,[1] Zhengming Chen,[9] Wojciech Jurczak,[10] Rebecca Auer,[11] Ewa Chmielowska,[12] Stephan Stilgenbauer,[13] Johannes Bloehdorn,[13] Craig Portell,[14] Michael E. Williams,[14] Martin Dreyling,[15] Paul M. Barr,[16] Selina Chen-Kiang,[17] Maurizio DiLiberto,[17] Richard R. Furman,[1] and Kristie A. Blum[2]

Characteristics postibrutinib	Number	%
All	104	100%
Received treatment postibrutinib	73	70%
Time from ibrutinib to next therapy	0.3 mo	95% CI, 0.2-0.5
MIPI scores at start of therapy		
High risk	35	48%
Intermediate risk	18	25%
Low risk	9	12%
Unknown	11	15%
Ki67 >30%	11/12	92%
Subsequent treatment		
Rituximab	39	53%
Lenalidomide	19	26%
Cytarabine	13	18%
Bendamustine	12	16%
Bortezomib	7	10%
Anthracycline	5	7%
PI3K inhibitor	4	5%



Mechanisms of BTKi resistance



Mechanisms of BTKi resistance

TABLE 1 | Recurrent mutations in ibrutinib-resistant patients and possible therapeutic strategies to overcome them.

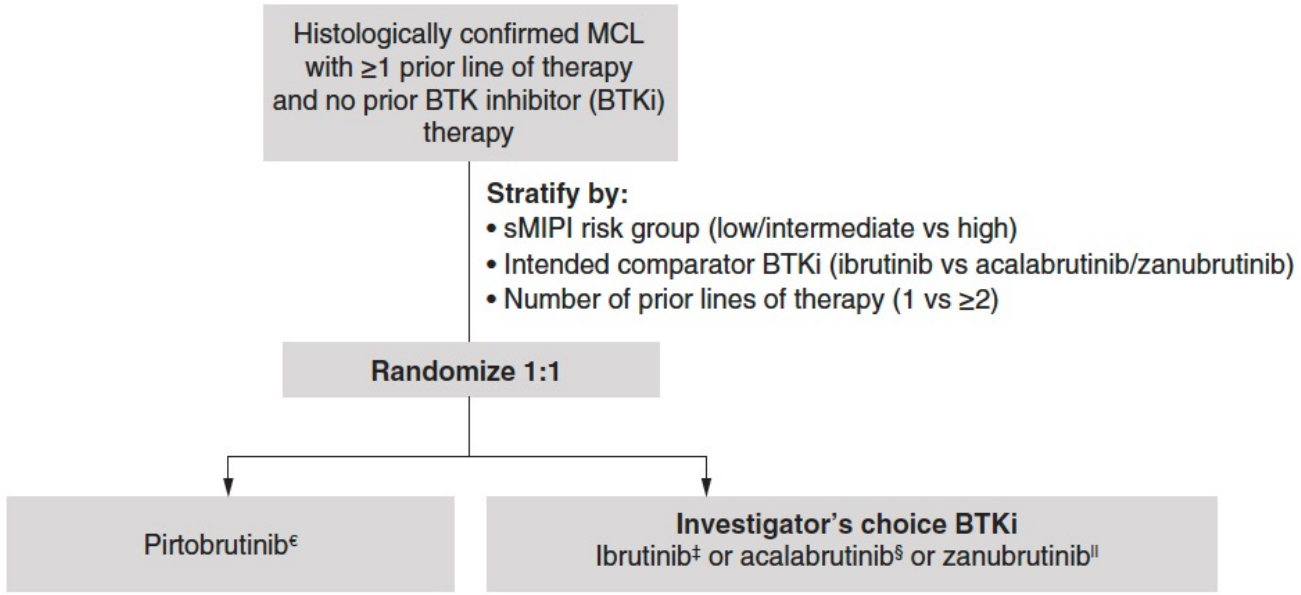
Mutated gene/aberration	Disease	Mechanism	Possible therapeutic strategy	Ref.
BTK	CLL, MCL, WM, MZL	reversible binding of ibrutinib	third-generation BTK inhibitors, PROTAC-BTK, inhibitors of LYN and SYK	(7, 68–77)
PLCG2	CLL, MCL, WM, MZL	BTK-independent activation	inhibitors of RAC2, LYN, and SYK	(7, 68–71, 78, 79)
CARD11	CLL, MCL, WM, DLBCL, FL	↑ NFκB	proteasome or MALT1 inhibitor	(12, 71, 80–83)
BIRC3, TRAF2, TRAF3	MCL	↑ NFκB	MP3K14 inhibitor	(84, 85)
CCND1	MCL	cell cycle progression	unknown	(86)
CDKN2A and *MTAP* co-deletion	MCL	cell cycle progression	PRMT5 inhibitor	(87)
SMARCA2, *SMARCA4*, *ARID2*	MCL	disruption of SWI-SNF complex; ↑ BCL_{XL}	BCL_{XL} inhibitor	(88)
$MYD88^{mt}/CD79B^{wt}$	DLBCL	MYD88-dependent and BCR-independent subtype	SYK or STAT3 inhibitor	(9, 89, 90)
KLHL14	DLBCL	↑ MYD88-TLR9-BCR super-complex	inhibition of BCR-dependent NFκB activation/mTOR inhibitors	(91)
TNFAIP3	DLBCL	↑ NFκB	unknown	(82)
2p+	CLL	↑XPO1	XPO1 inhibition (selinexor)	(92)
Del 8p	CLL	Loss of *TRAIL-R*, insensitivity to TRAIL-induced apoptosis	unknown; possibly venetoclax	(93)
Del 6q	WM	↑ MYD88/NFκB, loss of regulators of apoptosis	unknown	(94, 95)
Del 8p	WM	↑ TLR/MYD88, loss of *DOK2*, *BLK* and *TNFRSF10A/B*	unknown	(94)

Pirtrobrutinib (LOXO305)

Reversible inhibitor with non-covalent binding to BTK that preserves activity in the presence of the C481S mutations and avoids off-target kinases inhibition.

- Phase 1 Pretreated MCL with BTKi (BRUIN)
- Fatigue, Neutropenia, Bruising, diarrhea (grade 1,15%)
- 51% ORR in MCL R/R (BTKi) and 81% in BTKi naive
- FU 2y 61% ongooing response

- Phase 1 Pretreated MCL with BTKi (BRUIN 321 phase III)



Summary

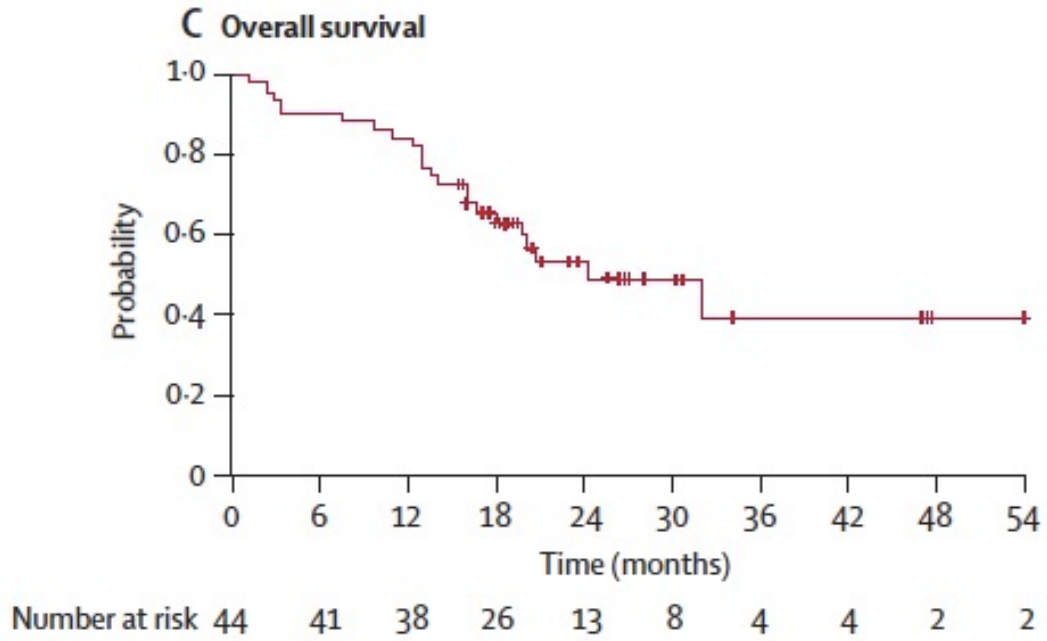
- After BTKi failure overall survival is poor
- ORR is between 20% to 40%
- OS is to 10 months
- And few patients proceed to Allogeneous bone marrow transplantation

- **Which options ? (Few data)**

Rituximab + lenalidomide R/R MCL: Outcome

	Phase 2 (n=44)*
Complete response	16 (36%)
Partial response	9 (20%)
Overall response	25 (57%)
Stable disease	10 (23%)
Progressive disease	9 (20%)
Response duration (months)	18·9 (17·0–NR)
Progression-free survival (months)	11·1 (8·3–24·9)
Overall survival (months)	24·3 (19·8–NR)
Time to first response (months)	2 (2–8)
Time to best response (months)	2 (2–12)
Follow-up time (months)	23·1 (15·6–54·2)

Data are number (%) or median (range). NR=not reached. *Includes six patients from phase 1 who were treated with 20 mg lenalidomide.



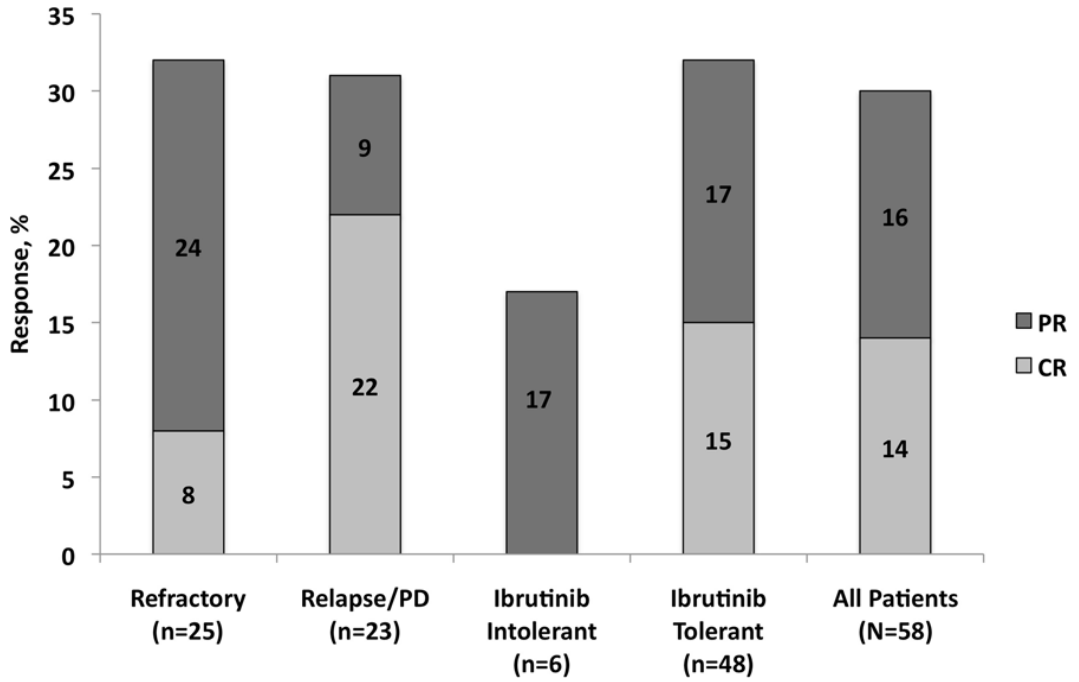
Wang M et al, Lancet Oncol 2012

Lenalidomide after Ibrutinib failure or intolerance

Characteristic	L (*n* = 13)		L + R (*n* = 11)		L + other (*n* = 34)		Overall (*N* = 58)	
	No.	%	No.	%	No.	%	No.	%
Median age, years (range)	67 (54–83)		70 (58–84)		71 (50–89)		71 (50–89)	
≥ 65	6	46	9	82	26	76	41	71
Sex								
Male	11	85	8	73	25	74	44	76
Female	2	15	3	27	9	26	14	24
ECOG PS								
0–1	7	54	5	45	16	47	28	48
2–4	3	23	1	9	4	12	8	14
Missing	3	23	5	45	14	41	22	38
Tumor burden[a]								
High	4	31	1	9	12	35	17	29
Low	1	8	5	45	13	38	19	33
Missing	8	62	5	45	9	26	22	38
Bulky disease[b]								
Yes	2	15	0	0	6	18	8	14
No	2	15	6	55	17	50	25	43
Missing	9	69	5	45	11	32	25	43
Time from diagnosis to first lenalidomide dose, months								
Median	58		47		46		49	
Range	15–144		6–105		4–214		4–214	
Time from end of last prior antilymphoma therapy to first dose of lenalidomide, weeks								
Median	0.7		0.3		0.7		0.7	
Range	0.1–3.5		0.1–21.7		0.1–12.6		0.1–21.7	

Observational study of lenalidomide in patients with mantle cell lymphoma who relapsed/progressed after or were refractory/intolerant to ibrutinib (MCL-004)

Michael Wang[1*], Stephen J. Schuster[2], Tycel Phillips[3], Izidore S. Lossos[4], Andre Goy[5], Simon Rule[6], Mehdi Hamadani[7], Nilanjan Ghosh[8], Craig B. Reeder[9], Evelyn Barnett[10], Marie-Laure Casadebaig Bravo[1] and Peter Martin[12]



Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy

Toby A. Eyre,[1] Harriet S. Walter,[2] Sunil Iyengar,[3] George Follows,[4] Matthew Cross,[3] Christopher P. Fox,[5] Andrew Hodson,[6] Josh Coats,[7] Santosh Narat,[8] Nick Morley,[6] Martin J.S. Dyer[2] and Graham P. Collins[1]

Table 1. Baseline characteristics: prior therapies.

All patients (N = 20)	n (%)
Gender	
Male	17 (85%)
Female	3 (15%)
First-line therapy	
CHOP ± R or CHOP-like	6
Fludarabine-based ± R	4[a]
Maxi-CHOP/HDAC ± R	8
Other	2[b]
ASCT consolidation in first remission	
Yes	6 (30%)
No	14 (70%)
Rituximab maintenance in first remission	
After immunochemotherapy	2 (10%)
After ASCT	0 (0%)
Neither	18 (90%)
Duration of exposure to BTK inhibitor	
Median	4.77 months
Range	0.66 – 34.85 months
Response to prior BTK inhibitor	
Overall response	11/20 (55%)
Complete response	3 (15%)
Partial response	8 (40%)
Stable disease	4 (20%)
Progressive disease	5 (25%)
Reason for BTK inhibitor discontinuation (n = 20)	
Progressive disease	17
Stable disease	1
Toxicity	2

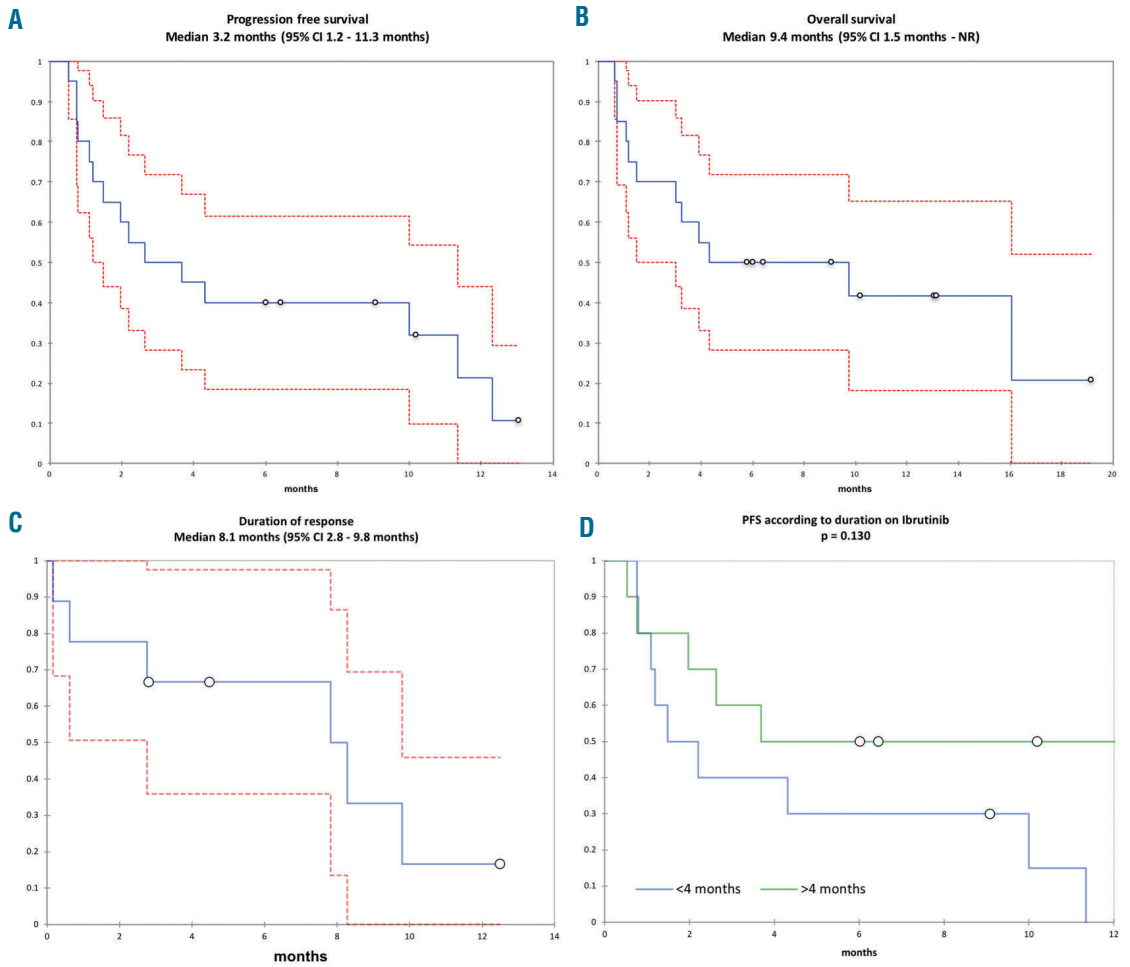
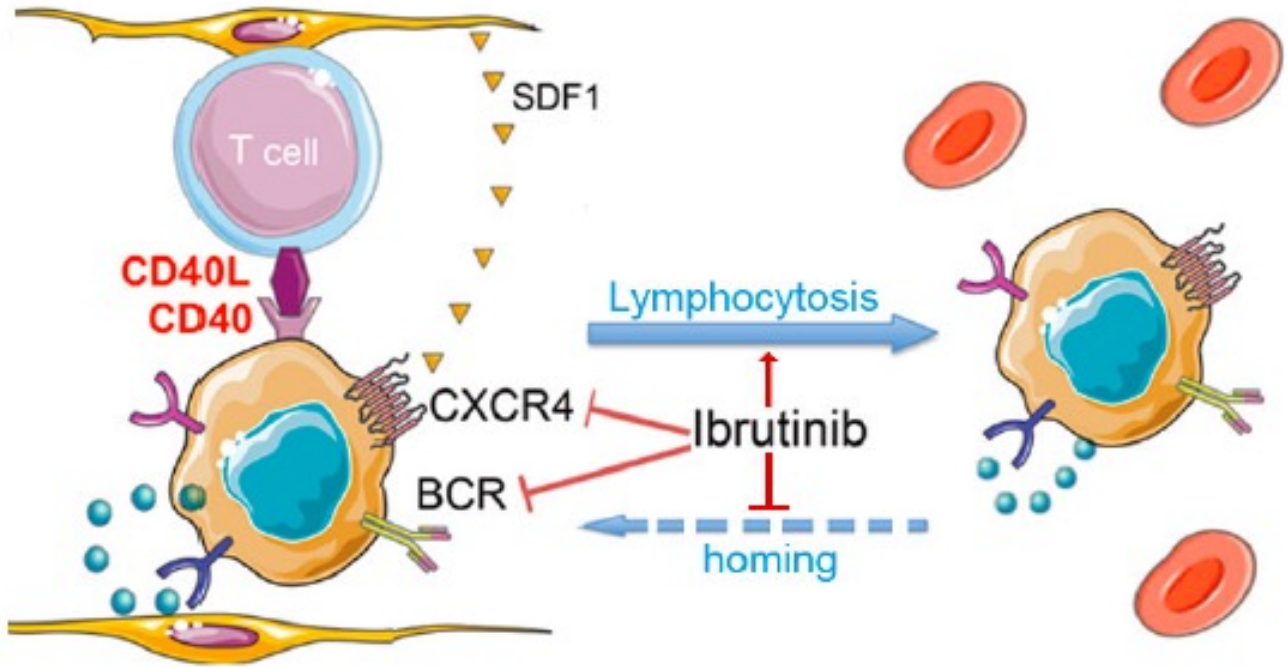


Figure 1. Survival outcome of patients with relapsed, refractory mantle cell lymphoma on venetoclax monotherapy. (A) Progression-free survival of all patients. (B) Overall survival of all patients. (C) Duration of response. (D) Progression-free survival according to duration on ibrutinib therapy.

ABT199 And Ibrutinib



Lymph Nodes

Bcl-xL high

ABT-199 resistant

Peripheral Blood

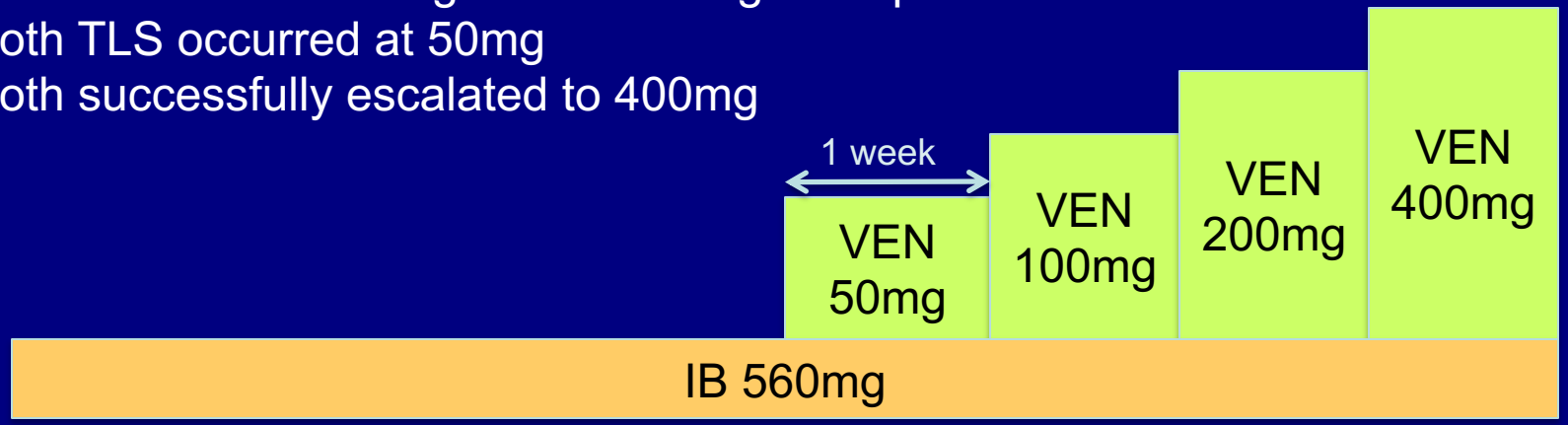
Bcl-xL low

ABT-199 sensitive

Chiron et al, Oncotarget 2015

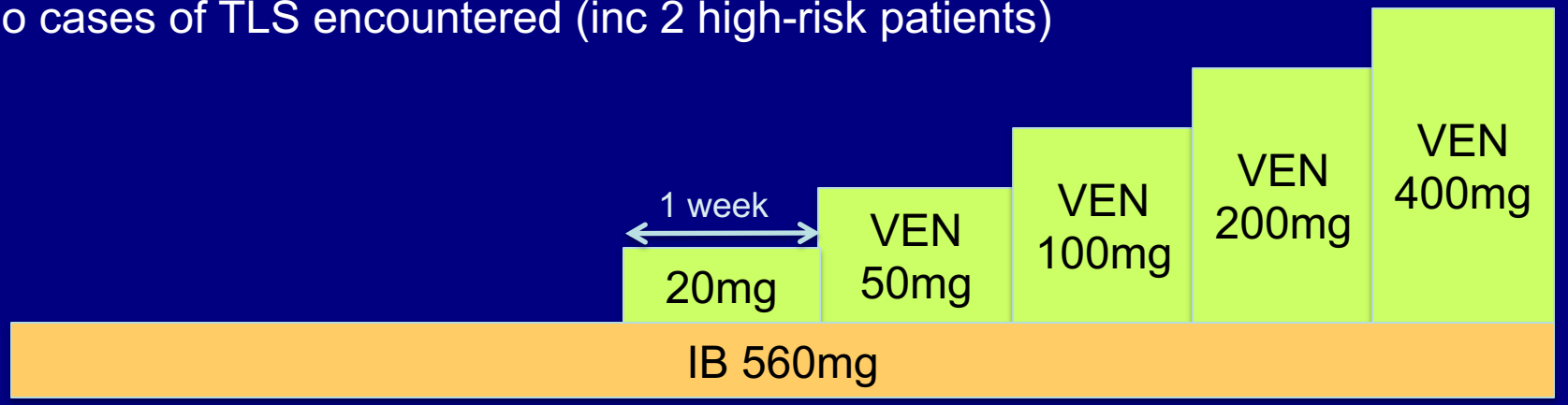
Tumour Lysis Syndrome

N = 15 treated using initial schedule
2 cases of TLS* among 4 baseline high-risk patients
Both TLS occurred at 50mg
Both successfully escalated to 400mg

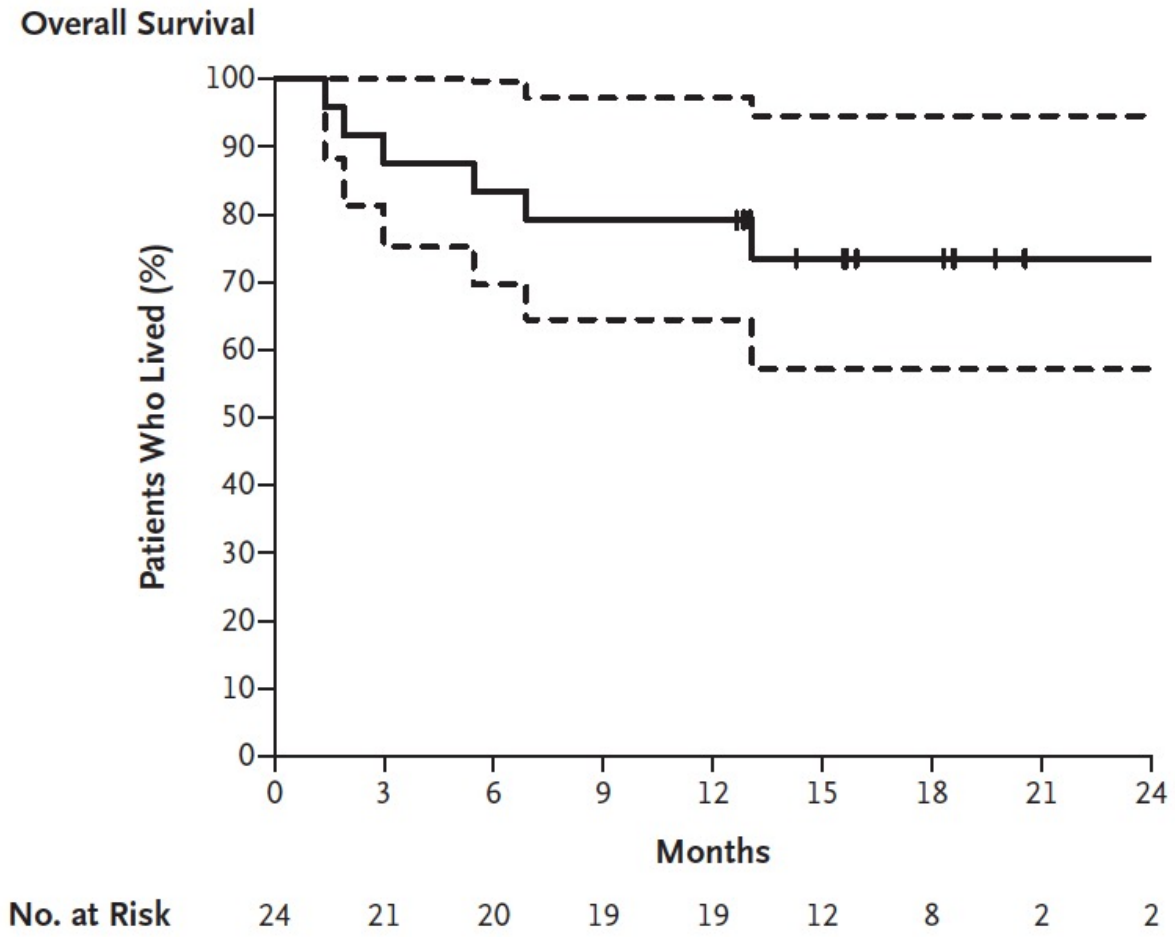


*one case of grade 3 clinical TLS (acute renal impairment); one case of self-limiting fever, hyperphosphataemia and 400% elevation in LDH, regarded as grade 3 biochemical TLS in absence of alternative explanation.

N = 7 treated using revised schedule (20mg start)
No cases of TLS encountered (inc 2 high-risk patients)



AIM: Overall Survival (n=24)



Estimated Progression Free Survival	%	95% CI
12 month	79	64-97
18 month	74	57-95

AIM Study: Impact of *TP53* aberrations and other mutations

	N abnormal	Complete remission
***TP53* mutations and/or deletions**	12	6 (50%)*
***ATM* mutations**	10	10 (100%)
NFKB pathway mutations (*CARD11*, *BIRC3* and/or *TRAF2*)	6	5 (83%)

Venetoclax combinations (*Clinicaltrials.gov*)

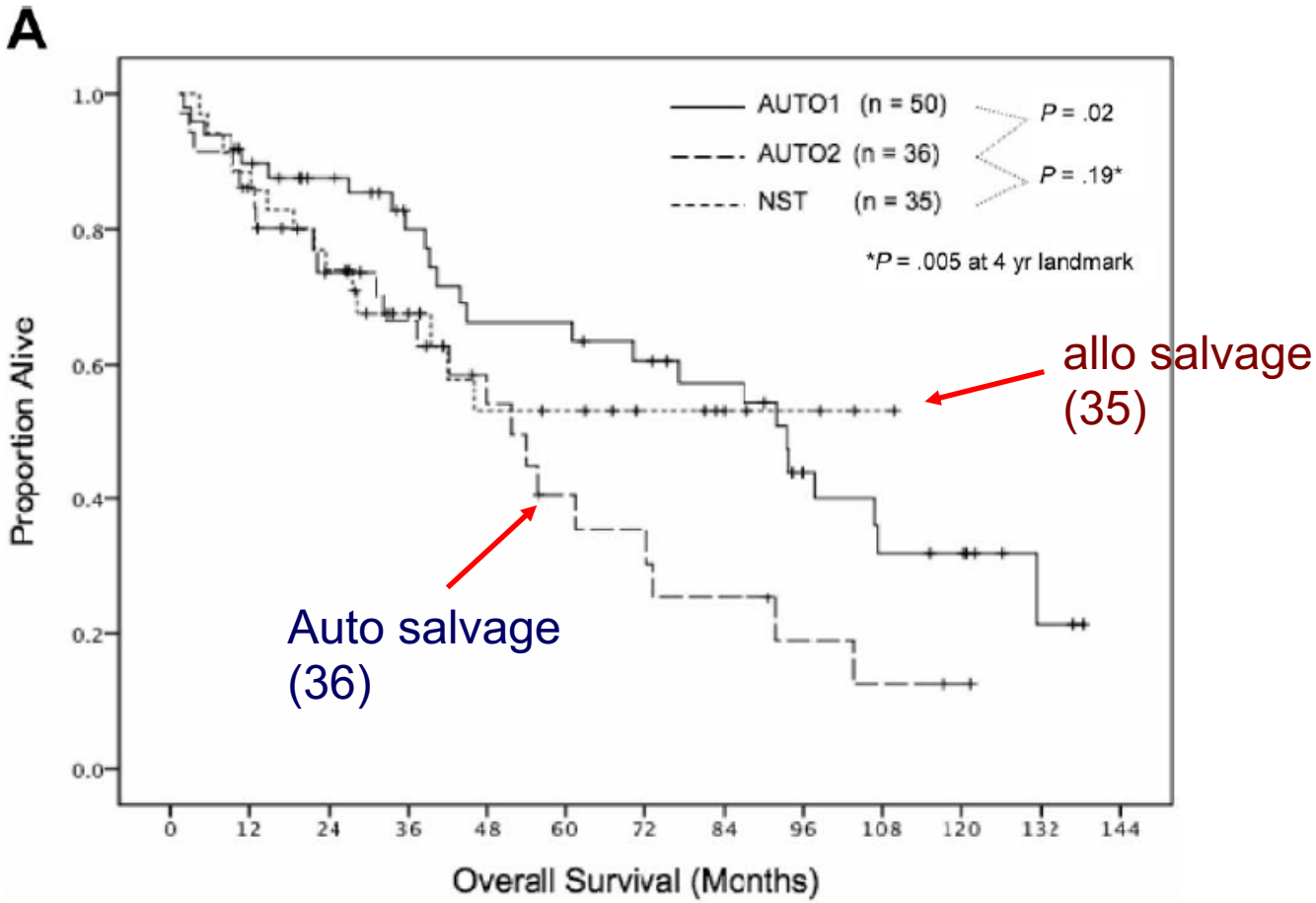
- Venetoclax and acalabrutinib in relapsed or refractory mantle cell lymphoma MCL
- **Venetoclax and lenalidomide and rituximab in patients with Relaspsed refractory MCL**
- Ibrutinib and. Venetoclax. In R/R MCL
- Bendamustine and venetoclax and rituximab in naive. MCL
- Ibru+ritux+venetoclax and combination of chemotherapy
- Obinutuzumab and Ibrutinib in MCL
- **Bendamustine and Obinutuzumab and Venetoclax**
- **R-BAC followed by Venetoclax**
- APR 246 and Ibrutinib and venetoclax in MCL
- **Zanubrutinib and Obinutuzumab and venetoclax**

Relapses and Allo SCT

- In relapse, allo SCT is the only curative procedure after chemotherapy
- 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 and When to perform AlloSCT ?
  - Which conditionning regimen ?
  - Which type of graft ?
  - Which follow up ?

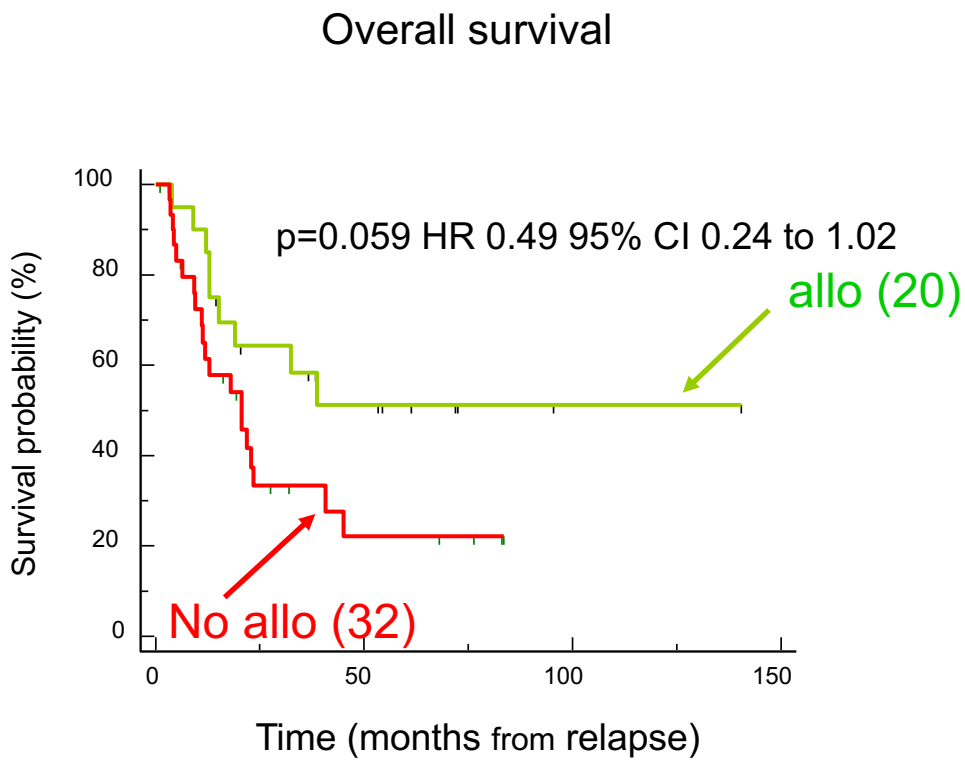
Allo vs Auto at relapse

Mature results of MDACC MCL transplants: OS



Tam et al. Blood 113:4144 (2009)

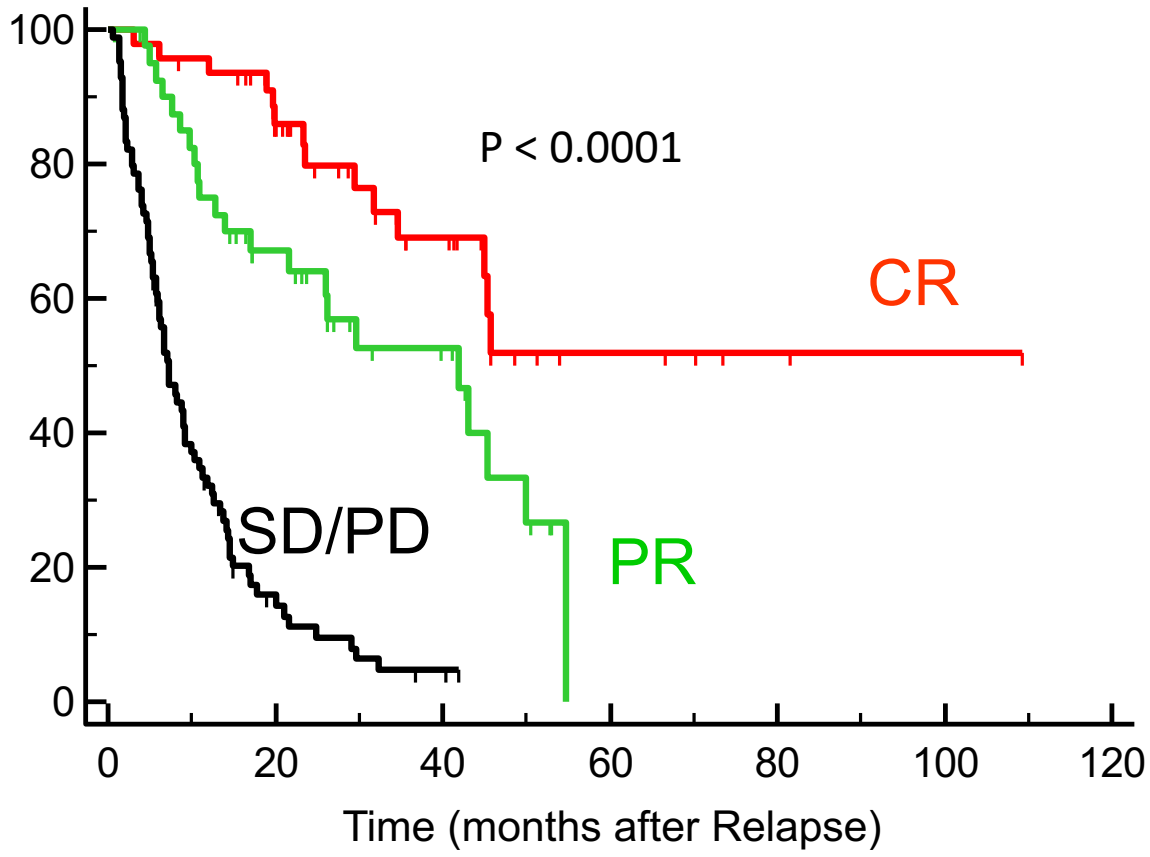
MCL: AlloSCT for autoSCT failure HD/KI/HH 1994-2008 (52 REL after 119 autotransplants)



Cancer

Dietrich et al, Cancer May 1, 2011

OS by response to 1st salvage therapy



Allogenous stem cell transplantation in Tp53 MCL

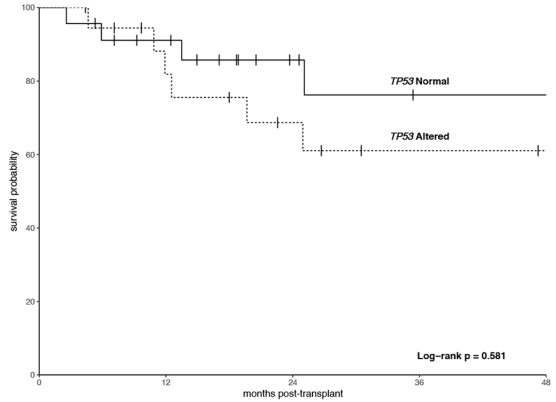
Patient Characteristics.

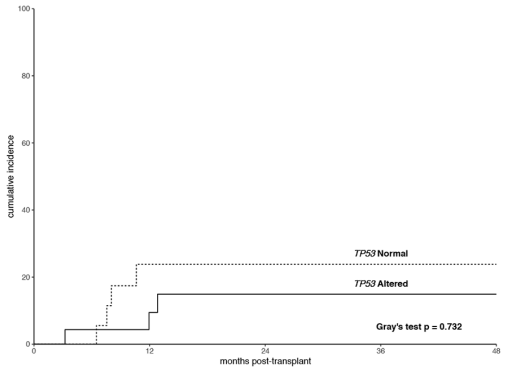
Characteristic	Total (N=42)	TP53 − (N=23)	TP53 + (N=19)	*p* value
Age, years; median (range)	61.2 (33.9–73.7)	61.2 (33.9–71.3)	61.2 (49.1–73.7)	0.570
Female sex, N (%)	3 (7)	2 (9)	1 (5)	>0.999
KPS ≤80, N (%)	12 (29)	5 (22)	7 (37)	0.462
HCT-CI, N (%)				0.481
0	9 (21)	5 (22)	4 (21)	
1–2	16 (38)	7 (30)	9 (47)	
≥3	17 (40)	11 (48)	6 (32)	
Ki67 >30%, N (%)	17 (40)	8 (42)	9 (60)	0.490
MIPI Risk Index, N (%)				0.914
Low risk	16 (38)	8 (35)	8 (42)	
Intermediate risk	20 (48)	11 (48)	9 (47)	
High risk	6 (14)	4 (17)	2 (11)	
Lines of prior therapy; median (range)	3 (1–6)	3 (1–6)	3 (1–6)	0.874
SD/PR at HCT, N (%)	2 (5)	1 (4)	1 (5)	>0.999
Prior ASCT, N (%)	27 (64)	14 (61)	13 (68)	0.853
First-line consolidation, N (%)	8 (19)	5 (22)	3 (16)	0.709
Ibrutinib pre-transplant, N (%)	17 (40)	9 (39)	8 (42)	>0.999
ATG use, N (%)	14 (33)	8 (35)	6 (32)	>0.999
Matched donor, N (%)	31 (74)	19 (83)	12 (63)	0.180
HCT prior to 2011, N (%)	10 (24)	6 (26)	4 (21)	>0.999

Br J Haematol. Author manuscript; available in PMC 2020 March 01.

Allogeneic Haematopoietic Cell Transplantation Impacts on Outcomes of Mantle Cell Lymphoma with *TP53* Alterations

DR. Richard J. Lin, MD, PhD[1], **Caleb Ho, MD**[2], **Patrick D. Hilden, MS**[3], **Juliet N. Barker, MD**[1,5], **Sergio A. Giralt, MD**[1,5], **Paul A. Hamlin, MD**[4,5], **Ann A. Jakubowski, MD, PhD**[1,5], **Hugo R. Castro-Malaspina, MD**[1,5], **Kevin S. Robinson, BS**[1], **Esperanza B. Papadopoulos, MD**[1,5], **Miguel-Angel Perales, MD**[1,5], and **Craig S. Sauter, MD**[1,5]





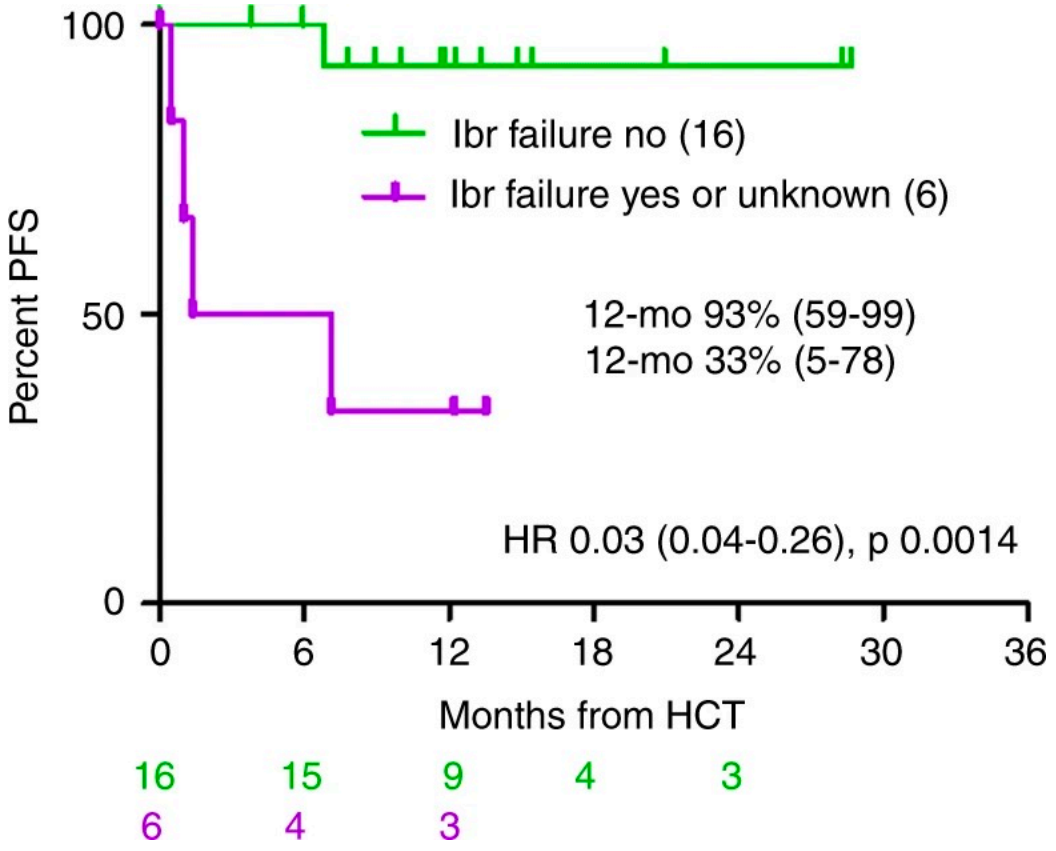
Allogenous stem cell transplantation in MCL

Table 1. Summary of the allo-HCT in MCL studies

Author, year	*N*	Disease status	Conditioning	NRM	GVHD (acute/chronic)	Relapse	Disease-free survival	OS
Prospective								
Khouri et al., 2003	18	R/R	RIC/NMA	2/18	0%/NR	1/18	NR	82% (3 yrs)
Maris et al., 2004	33	R/R	NMA	24%	57%/64%	9%	60% (2 yrs)	65% (2 yrs)
Kruger et al., 2014	39	Frontline= 24 R/R =15	MAC/RIC	24%	57%	15%	67%	73%
Rule et al., 2019	25	Frontline	RIC/NMA	13%	38%/58%	21%	56%	76%
Retrospective								
Robinson et al. EBMT. 2018 [35]	324	Frontline 93 Salvage 231	RIC	24%	52%/41%	40% (5 yrs)	31% (5 yrs)	40% (5 yrs)
Hamadani et al., 2013 CIBMTR [44]	202	202 Mixed	MAC=74 RIC=128	47% 43%	MAC=36/35% RIC=37/43%	33% 32%	MAC=20% RIC=25% (3 yrs)	MAC=25% RIC =30% (3 yrs)
Fenske et al., 2014 [45]	138	Frontline 50 Salvage 88	RIC	17% 25%	NR	15% 38%	F=55% S=29%	25% 31% (5 yrs)
Kharfan-Dabaja et al., 2016*[46]	701	Mixed	MAC=138 RIC=507	MAC= 37% RIC=24%	MAC=36/35% RIC=31/42%	MAC=18% RIC=29%	MAC=34%% RIC 47%	MAC=40% RIC=53%

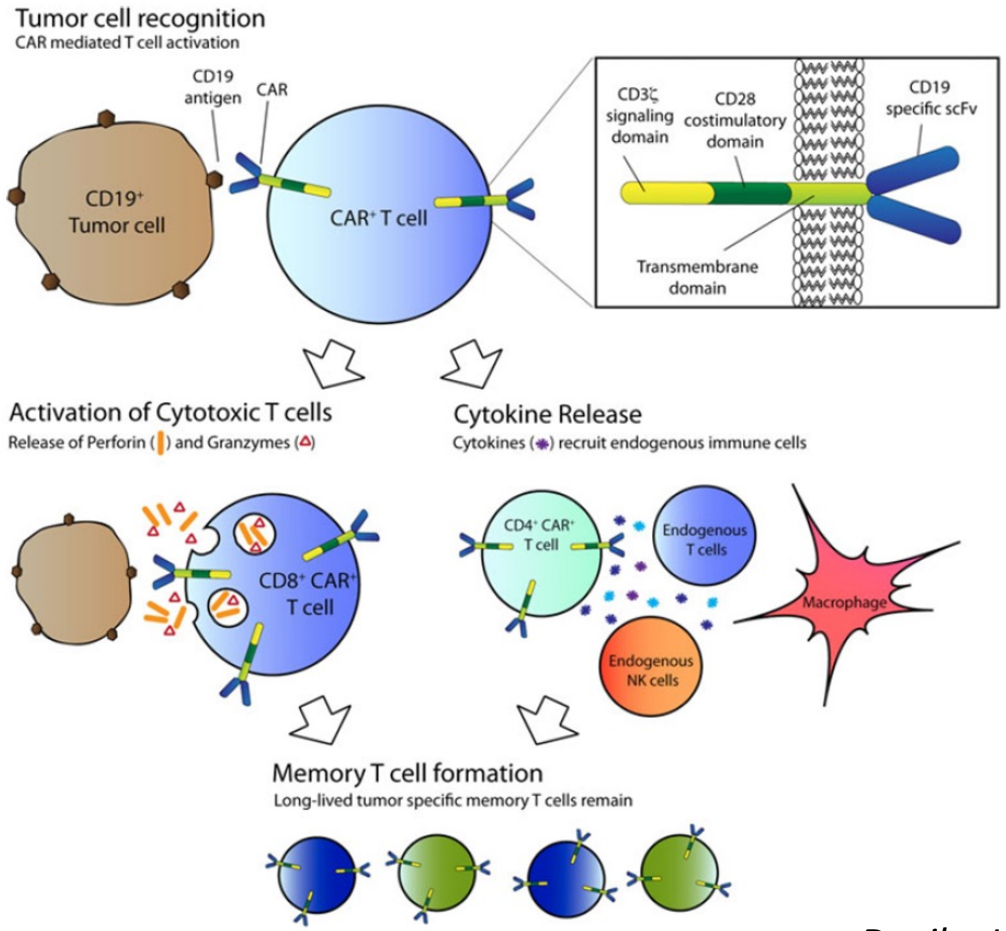
*Systemic review

Ibrutinib for bridging to allogeneic hematopoietic cell transplantation in mantle cell lymphoma



Peter Dreger et al , BMT 2019

CAR-T CD19 : mode of action in MCL ZUMA 2 trial (ASH 2019)



Davila, Int J Hematol 2013

KTE-X19 CAR T-Cell Therapy in BTKi refractory patients

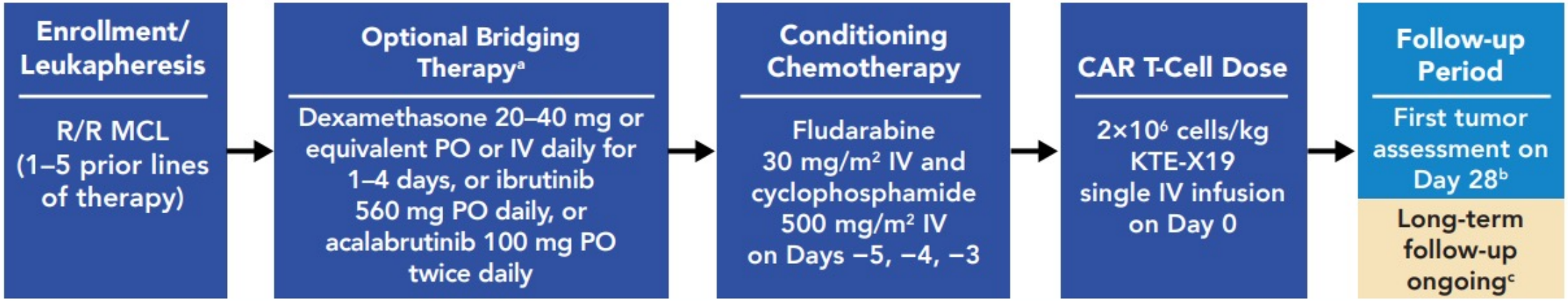
brexucabtagene autoleucel

- KTE-X19 is an autologous anti-CD19 CAR T-cell therapy
  - Produced in a manufacturing process that removes circulating CD19-expressing malignant cells[1]
  - Removal of these cells may limit the potential activation and exhaustion of anti-CD19 CAR T-cells during the *ex vivo* manufacturing process[1]

BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; MCL, mantle cell lymphoma; R/R, relapsed/refractory.

1. Wang M, et al. *N Engl J Med*. 2020; 382:1331-1342. 2. TECARTUS® (brexucabtagene autoleucel) Prescribing information. Kite Pharma, Inc; 2021. 3. TECARTUS® (autologous anti-CD19-transduced CD3+ cells) Summary of Product Characteristics. Kite Pharma EU B.V.; 2021.

ZUMA-2 Phase 2[1]: Three-Year Follow-up



Key ZUMA-2 Eligibility Criteria

- Age ≥18 years with R/R MCL
- 1–5 prior regimens, including anthracycline- or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody, and BTKi therapy

Primary Endpoint

- ORR (CR + PR; IRRC assessed per the Lugano classification[2])

Data cutoff date: July 24, 2021
Median follow-up time: 35.6 months (range, 25.9–56.3)

Key Secondary Endpoints

- DOR, PFS, OS
- AEs

Key Exploratory Endpoints

- MRD
- Prior bendamustine

[a] Administered after leukapheresis and completed ≥5 days before initiating conditioning chemotherapy; PET-CT was required post-bridging. [b] Bone marrow biopsy was to be done at screening and, if positive, not done, or indeterminate, a biopsy was needed to confirm CR. [c] After 3 months, only targeted AEs (neurological, hematological, infections, GVHD, autoimmune disorders, and secondary malignancies) were monitored and reported for 15 years after the initial anti-CD19 CAR T-cell infusion or until disease progression or initiation of subsequent anticancer therapy, whichever occurs first.

1. Wang M, et al. *N Engl J Med*. 2020;382:1331-1342. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; GVHD, graft-versus-host disease; IRRC, independent radiology review committee; IV, intravenous; KTE-X19, brexucabtagene autoleucel; MCL, mantle cell lymphoma; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PET-CT, positron emission tomography–computed tomography; PFS, progression-free survival; PO, orally; PR, partial response; R/R, relapsed/refractory.

Baseline Patient Characteristics

Characteristic	N = 68
Median age (range), years	65 (38 – 79)
≥ 65 years, n (%)	39 (57)
Male, n (%)	57 (84)
Stage IV disease, n (%)	58 (85)
ECOG PS, n (%)	
0	44 (65)
1	24 (35)
Bulky disease (≥ 10 cm), n (%)	7 (10)
Intermediate/high-risk MIPI, n (%)	38 (56)
Ki-67 proliferation index ≥ 50%, n/n (%)*	34/49 (69)
TP53 mutation, n/n (%)	6/36 (17)
Bone marrow involvement, n (%)	37 (54)
Extranodal disease, n (%)†	38 (56)
MCL morphology, n (%)‡	
Classical	40 (59)
Pleomorphic	4 (6)
Blastoid	17 (25)

*Ki-67 data were available for 49 patients at diagnosis. † Excludes bone marrow and splenic involvement. ‡Morphology was unknown for 10 patients.

BTKi, Bruton tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index.

Wang M, et al. *N Engl J Med*. 2020; 382:1331-1342.

Prior Therapies

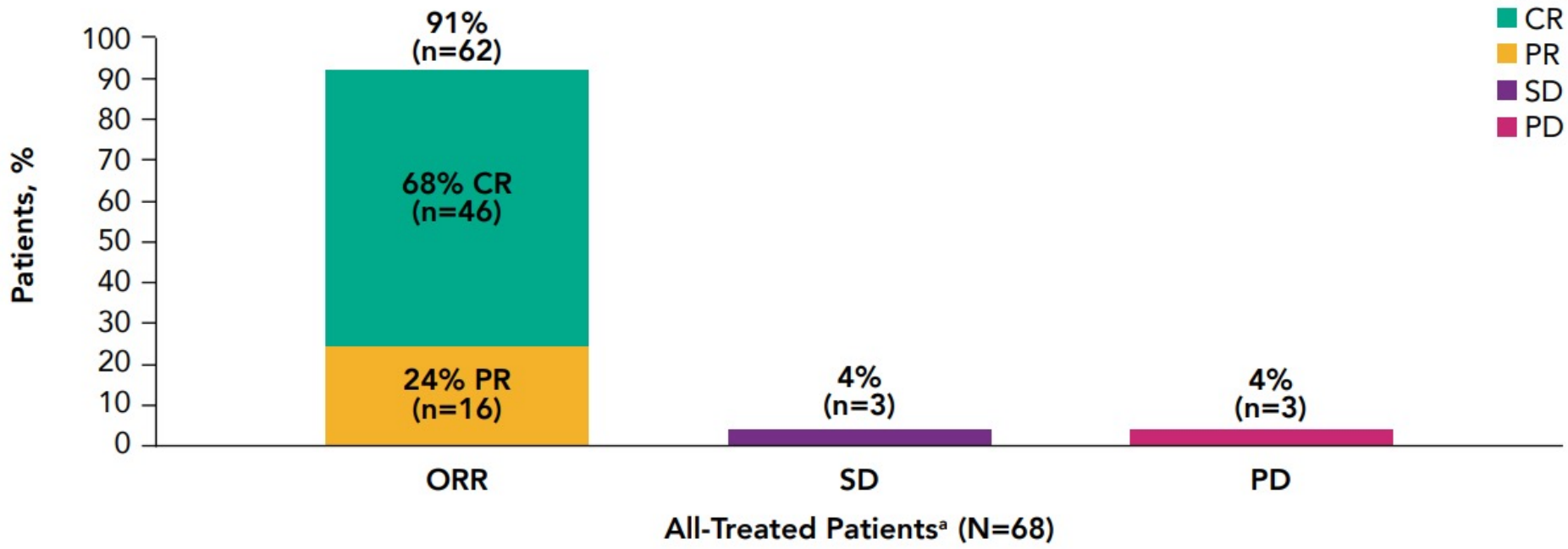
Characteristic	N = 68
Median no. of prior therapies (range)*	3 (1-5)
≥ 3 prior lines of therapy, n (%)	55 (81)
Anthracycline or bendamustine, n (%)	67 (99)
Anthracycline	49 (72)
Bendamustine	37 (54)
BTKi, n (%)	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed/refractory subgroup, n (%)	
Relapsed after autologous SCT	29 (43)
Refractory to last prior therapy	27 (40)
Relapsed after last prior therapy	12 (18)
BTKi relapsed/refractory status, n (%)	68 (100)
Refractory to BTKi	42 (62)
Relapsed on BTKi	18 (26)
Relapsed after BTKi	5 (7)
Intolerant to BTKi†	3 (4)

* Induction plus consolidation/maintenance and/or all treatments occurring between sequential complete responses were counted as 1 regimen.
†Patients had relapsed after or were refractory to subsequent therapies prior to study entry.

BTKi, Bruton tyrosine kinase inhibitor; mAb, monoclonal antibody; SCT, stem cell transplant.

Wang M, et al. *N Engl J Med*. 2020; 382:1331-1342.

ORR by IRRC Assessment in All-Treated Patients (N=68)



- After 35.6 months median follow-up (range, 25.9–56.3), the ORR (CR + partial response [PR]) was 91% (95% CI, 81.8–96.7), with a 68% CR rate (95% CI, 55.2–78.5) in all treated patients
- In the ITT population, ORR was 84% (95% CI, 73.4–91.3), with a 62% CR rate (95% CI, 50.1–73.2)

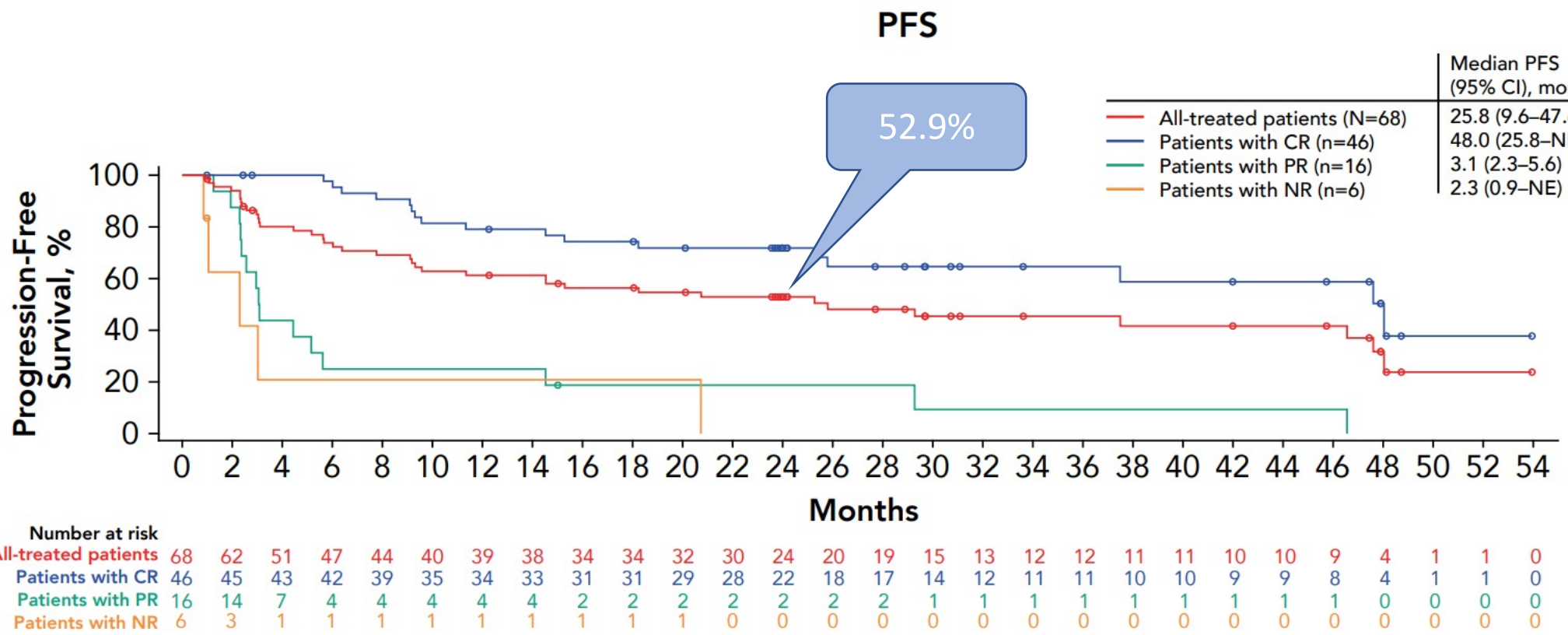
Assessed by an IRRC according to the Lugano Classification.[1]

[a] Since the previous report,[2] IRRC review determined that 1 patient who was previously reported as best response of PR had no disease at baseline; this patient is reported as PD in the current report.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068. 2. Wang M, et al. *Blood*. 2020;136(suppl 1):20-22.

CR, complete response; IRRC, independent radiology review committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

MCL - PFS in All-Treated Patients (N=68)

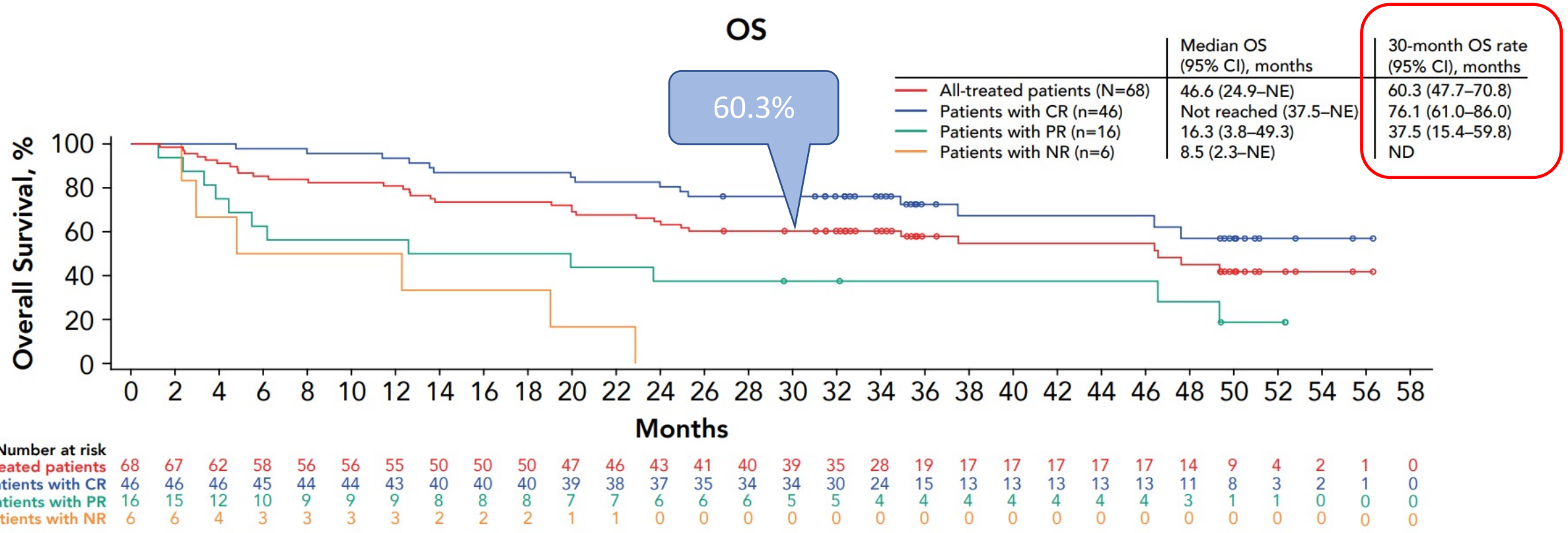


	Median PFS (95% CI), months	24-month PFS rate (95% CI), months
All-treated patients (N=68)	25.8 (9.6–47.6)	52.9 (39.9–64.3)
Patients with CR (n=46)	48.0 (25.8–NE)	71.8 (55.7–82.9)
Patients with PR (n=16)	3.1 (2.3–5.6)	18.8 (4.6–40.2)
Patients with NR (n=6)	2.3 (0.9–NE)	ND

CR, complete response; ND, no data; NE, not estimable; NR, no response; PFS, progression-free survival; PR, partial response.

Wang M et al., ASCO 2022, abstr.. 7518

MCL - OS in All-Treated Patients (N=68)

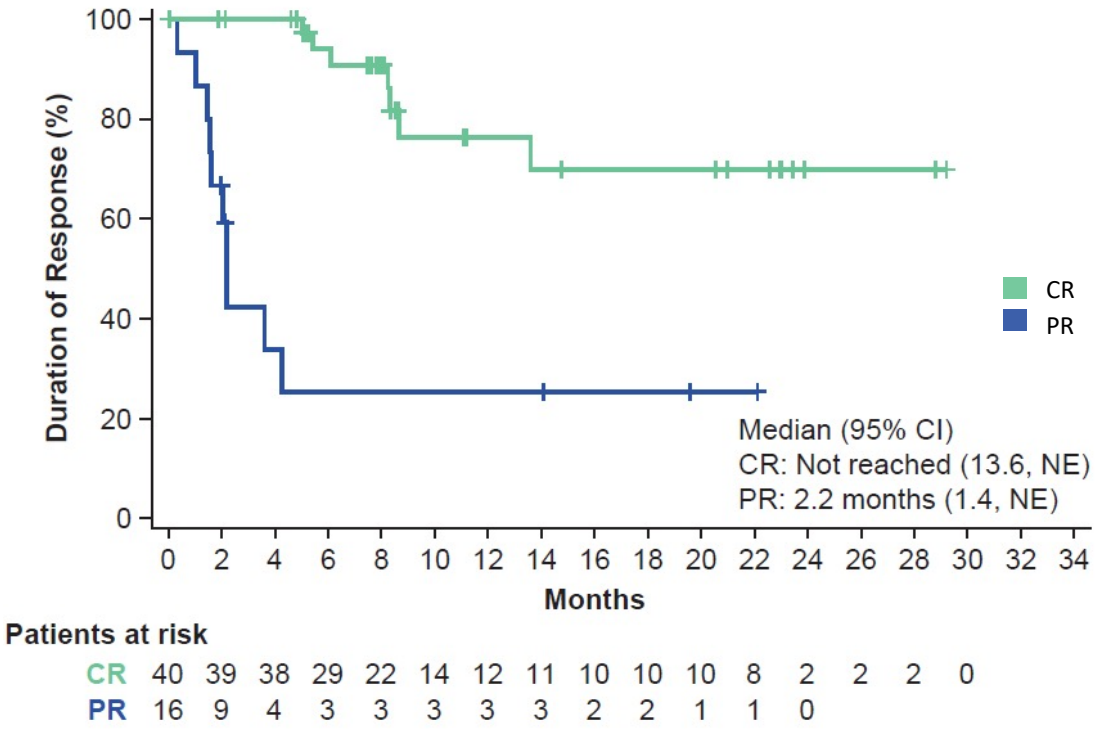


CR, complete response; ND, no data; NE, not estimable; NR, no response; OS, overall survival; PR, partial response.

Wang M et al., ASCO 2022, abstr.. 7518

Duration of Response and Overall Survival by Best Objective Response

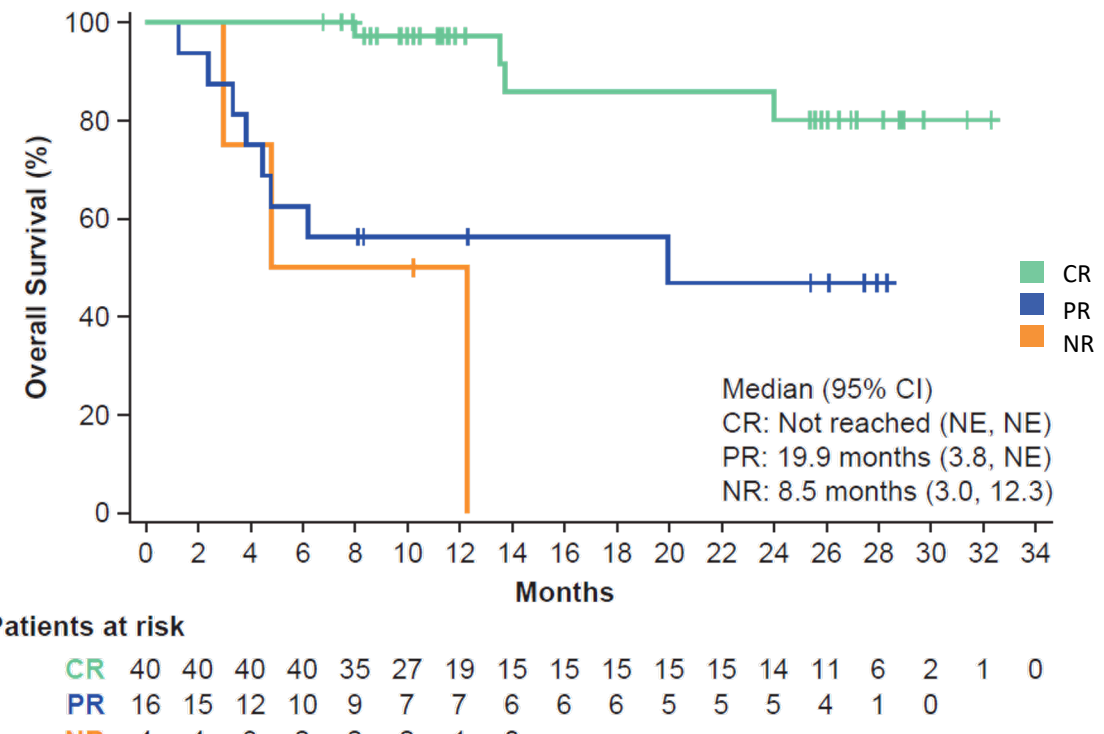
Duration of Response



Patients at risk

CR	40	39	38	29	22	14	12	11	10	10	10	8	2	2	2	0
PR	16	9	4	3	3	3	3	3	2	2	1	1	0			

Overall Survival



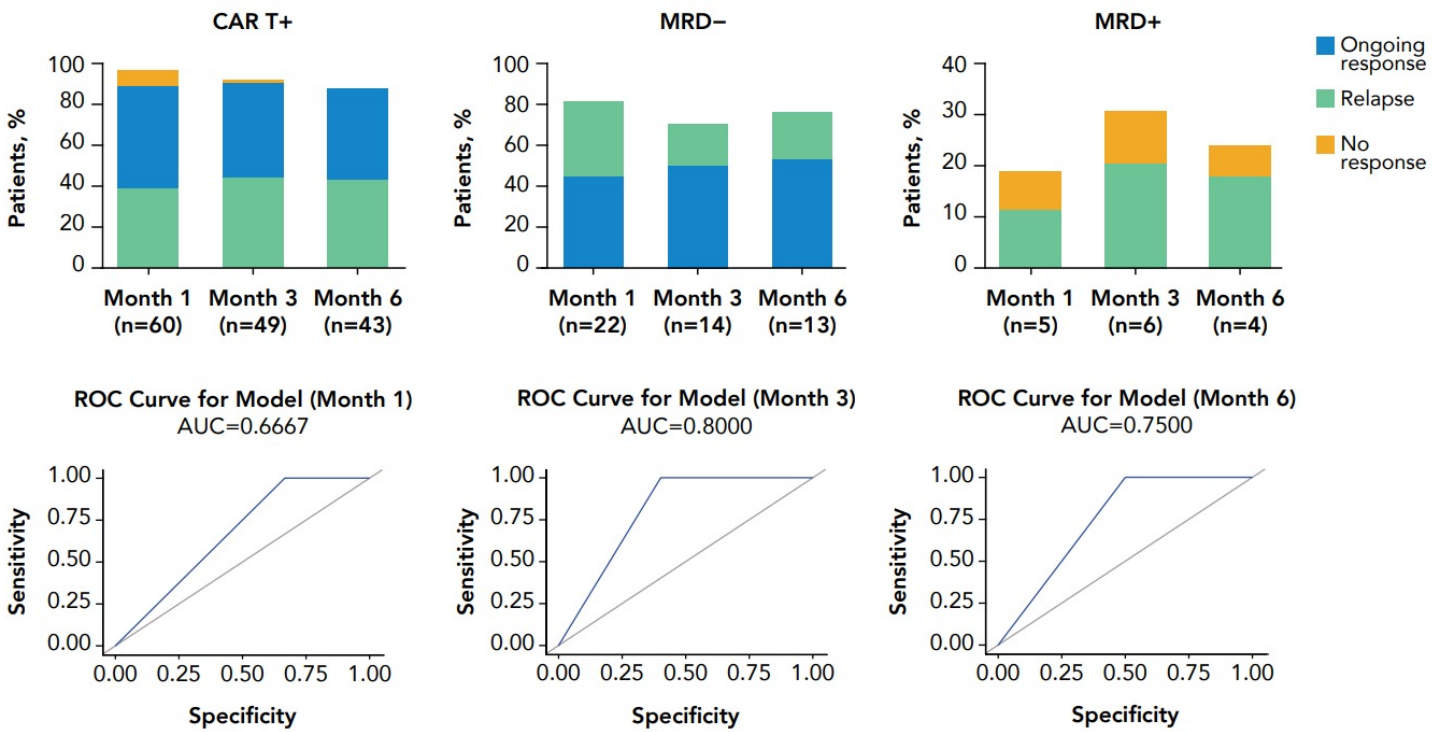
Patients at risk

CR	40	40	40	40	35	27	19	15	15	15	15	15	14	11	6	2	1	0
PR	16	15	12	10	9	7	7	6	6	6	5	5	5	4	1	0		
NR	4	4	3	2	2	2	1	0										

CR, complete response; NE, not estimable; NR, no response; PR, partial response.

Wang M, et al. *N Engl J Med*. 2020; 382:1331-1342.

MRD Detection at 3 and 6 Months Predicts Relapse



- **MRD-negative status** at Months 1, 3, and 6 **was associated with durable response**, with 55%, 71%, and 69% of MRD-negative patients at those timepoints remaining in ongoing CR at data cutoff (median follow-up, 35.6 months)
- Receiver operating characteristic curves of true-positive (sensitivity) versus false-positive (specificity) rates were analyzed for MRD predictability of relapse and nonresponse
  - Analysis of MRD at Months 3 and 6 was found to be predictive of relapse potential (AUC 0.80 and 0.75, respectively)

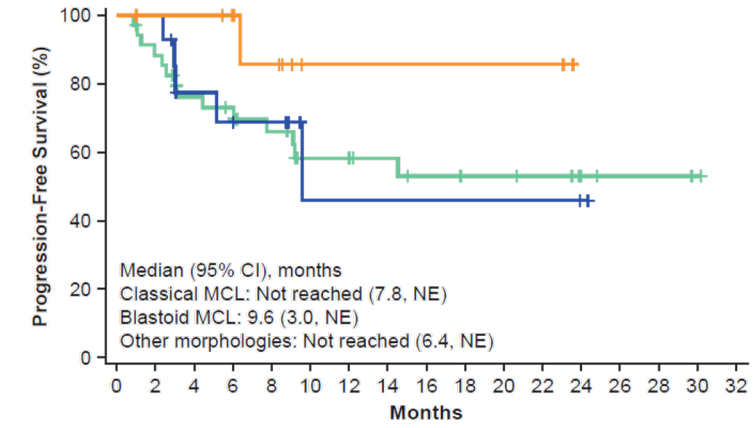
AUC, area under the curve; CAR, chimeric antigen receptor; MRD, minimal residual disease; ROC, receiver operating characteristics.

Wang M et al., ASCO 2022, abstr.. 7518

Progression-Free Survival in High-Risk Subgroups

PFS

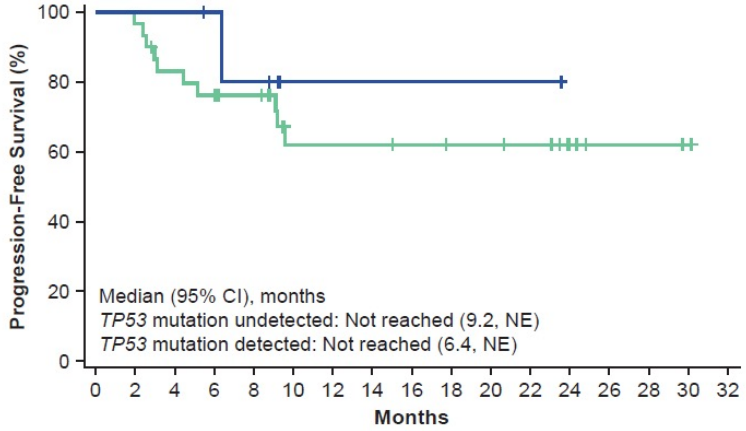
Classical, Pleomorphic, or Blastoid MCL



Patients at risk

Classical	35	30	24	22	18	13	12	11	9	8	8	7	3	2	2	1	0
Blastoid	14	14	9	8	7	2	2	2	2	2	2	2	1	0	0	0	0
Other	11	10	10	8	6	2	2	2	2	2	2	2	0	0	0	0	0

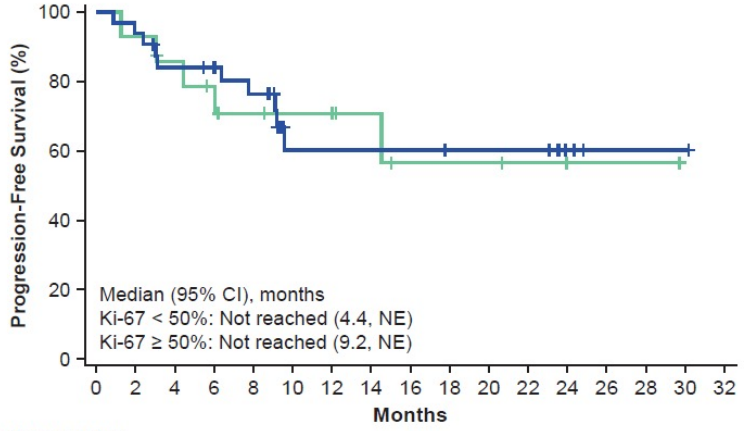
TP53 Mutations Detected vs Undetected



Patients at risk

Mutation undetected	30	29	24	22	20	12	12	12	11	10	10	9	4	2	2	1	0
Mutation detected	6	6	6	5	4	1	1	1	1	1	1	1	0	0	0	0	0

Ki-67 index ≥ 50% vs < 50%



Patients at risk

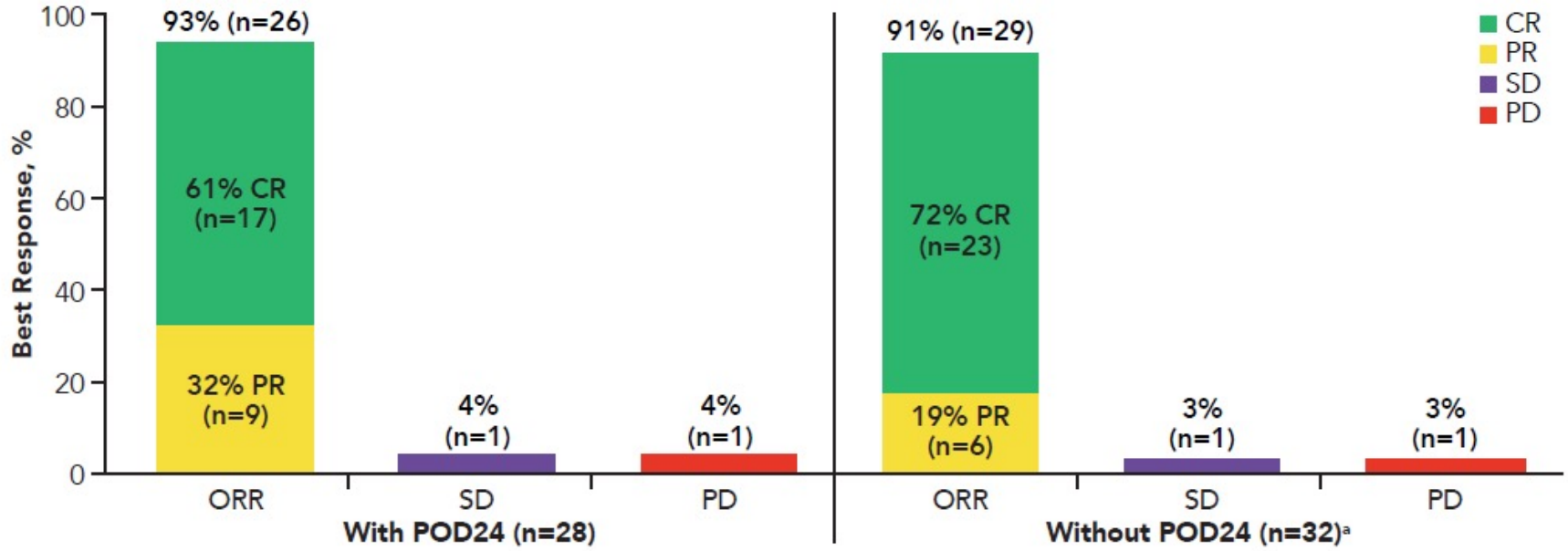
Ki-67 < 50%	14	13	12	10	8	7	6	5	3	3	3	2	1	1	1	0	0
Ki-67 ≥ 50%	32	30	25	23	20	9	9	9	9	8	8	8	3	1	1	1	0

MCL, mantle cell lymphoma; NE, not estimable; PFS, progression-free survival.

Wang M, et al. *N Engl J Med*. 2020; 382:1331-1342.

ORR by IRRC Assessment in Patients With and Without POD24

‡



- The ORR was similar among patients with and without POD24, with a slightly higher CR rate in patients without POD24
- Similar rates of MRD-negativity were also observed among patients with (81%; n=9/11) and without (79%; n=15/19) POD24

Assessed by an IRRC according to the Lugano Classification.[1]

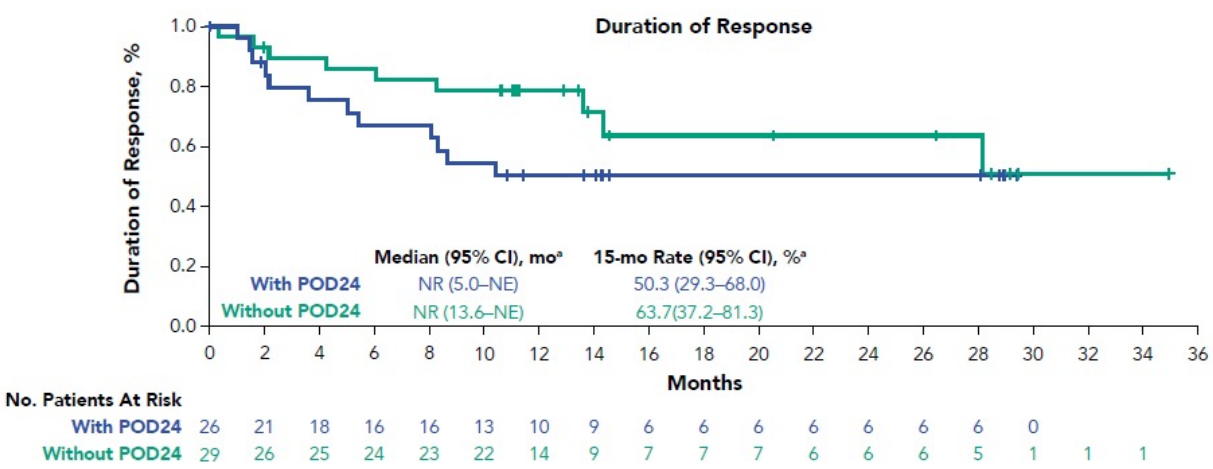
[a] One patient was not evaluable.

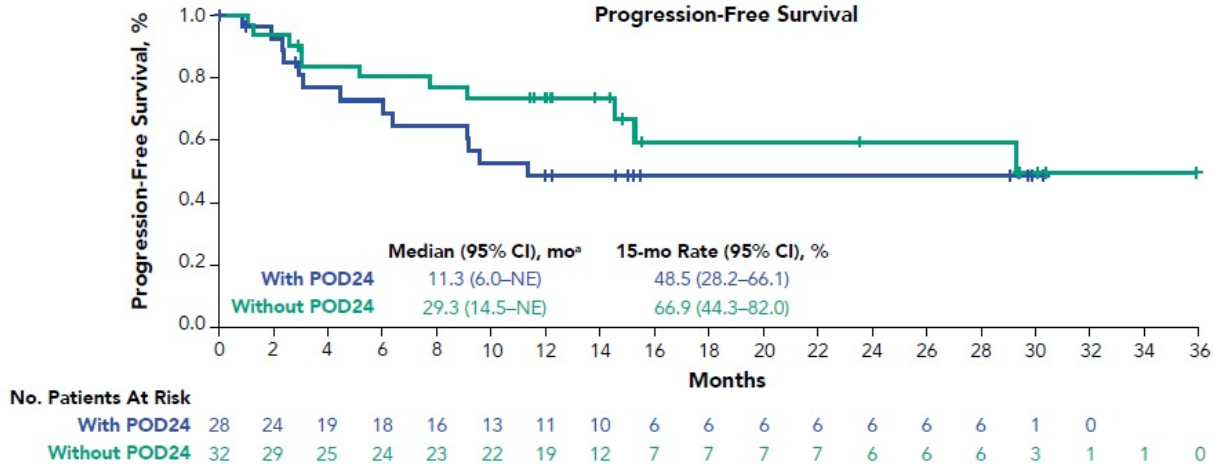
CR, complete response; IRRC, Independent Radiology Review Committee; MRD, minimal residual disease; ORR, objective response rate; PD, progressive disease; with POD24, progression of disease <24 months after initial diagnosis; without POD24, progression of disease ≥24 months after initial diagnosis; PR, partial response; SD, stable disease.

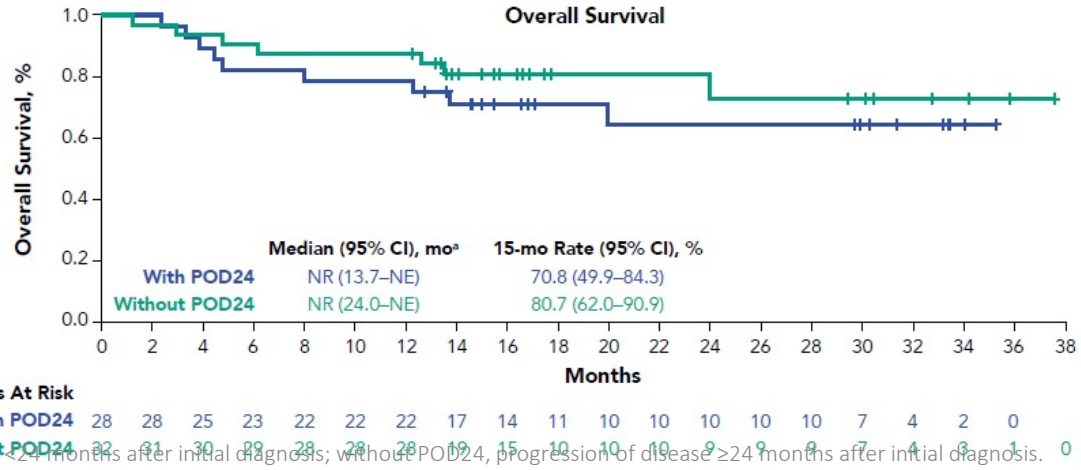
1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-68.

Wang ML, et al. ASCO 2021. Abstract #7547.

Duration of Response, Progression-Free Survival, and Overall Survival by POD24 Status







[a] Of responding patients.

NE, not estimable; NR, not reached; with POD24, progression of disease <24 months after initial diagnosis; without POD24, progression of disease ≥24 months after initial diagnosis.

Wang ML, et al. ASCO 2021. Abstract #7547.

Treatment-Emergent Adverse Events

AE (≥30%), n (%)	N = 68					
	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any AE	**68 (100)**	**0**	**1 (1)**	**11 (16)**	**54 (79)**	**2 (3)**
Pyrexia	64 (94)	14 (21)	41 (60)	9 (13)	0	0
Neutropenia	59 (87)	0	1 (1)	11 (16)	47 (69)	0
Thrombocytopenia	50 (74)	9 (13)	6 (9)	11 (16)	24 (35)	0
Anemia	46 (68)	0	12 (18)	34 (50)	0	0
Hypotension	35 (51)	4 (6)	16 (24)	13 (19)	2 (3)	0
Chills	28 (41)	17 (25)	11 (16)	0	0	0
Hypoxia	26 (38)	2 (3)	10 (15)	8 (12)	6 (9)	0
Cough	25 (37)	14 (21)	11 (16)	0	0	0
Hypophosphatemia	25 (37)	2 (3)	8 (12)	15 (22)	0	0
Fatigue	24 (35)	10 (15)	13 (19)	1 (1)	0	0
Headache	24 (35)	15 (22)	8 (12)	1 (1)	0	0
Tremor	24 (35)	19 (28)	5 (7)	0	0	0
Hypoalbuminemia	23 (34)	5 (7)	17 (25)	1 (1)	0	0
Hyponatremia	22 (32)	15 (22)	0	7 (10)	0	0
Nausea	22 (32)	11 (16)	10 (15)	1 (1)	0	0
Alanine aminotransferase increased	21 (31)	13 (19)	2 (3)	5 (7)	1 (1)	0
Encephalopathy	21 (31)	5 (7)	3 (4)	7 (10)	6 (9)	0
Hypokalemia	21 (31)	12 (18)	4 (6)	3 (4)	2 (3)	0
Tachycardia	21 (31)	14 (21)	7 (10)	0	0	0

Grade 5 AEs: organizing pneumonia (n = 1)* and staphylococcal bacteremia (n = 1)†

*Related to conditioning chemotherapy.
†Related to conditioning chemotherapy and KTE-X19.

Wang M, et al. *N Engl J Med*. 2020; 382:1331-1342.

Cytokine Release Syndrome

	N = 68		
	Any Grade	Grade 3	Grade 4
CRS, n (%)*	62 (91)	8 (12)	2 (3)
Most common symptoms, n (%)†			
Pyrexia	62 (91)	7 (10)	0
Hypotension	35 (51)	14 (21)	1 (1)
Hypoxemia	23 (34)	8 (12)	4 (6)
Chills	21 (31)	0	0
Tachycardia	16 (24)	0	0
Headache	15 (22)	0	0
	N = 68		
AE management (%)			
Tocilizumab	59		
Glucocorticoids	22		
Vasopressors	16		
Median time to onset, days (range)			
Any grade	2 (1 – 13)		
≥ Grade 3	4 (1 – 9)		
Median time to event resolutions, days	11		

*CRS was graded per Lee DW, et al. *Blood*. 2014;124:188-195. Individual symptoms of CRS were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03.

†Events of any grade that occurred in at least 20% of the patients.

No Grade 5 CRS occurred

AE, adverse event; CRS, cytokine release syndrome.

Wang M, et al. *N Engl J Med*. 2020; 382:1331-1342.

For Reactive Use

Neurologic Events

	N = 68		
	Any Grade	Grade 3	Grade 4
Neurologic events, n (%)*	43 (63)	15 (22)	6 (9)
Most common symptoms, n (%)†			
Tremor	24 (35)	0	0
Encephalopathy	21 (31)	7 (10)	6 (9)
Confusional state	14 (21)	8 (12)	0
	N = 68		
AE management (%)			
Tocilizumab	26		
Glucocorticoids	38		
Median time to onset, days (range)			
Any grade	7 (1 – 32)		
≥ Grade 3	8 (5 – 24)		
Median duration of events, days	12		
Patients with resolved events, n (%)	37/43 (86)‡		

*Neurologic events were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03.
†Events of any grade that occurred in at least 20% of the patients.
‡Four patients had ongoing neurologic events at data cutoff: Grade 1 tremor (n = 3), Grade 2 concentration impairment (n = 1), and Grade 1 dysesthesia (n = 1).

- **No Grade 5 neurologic events occurred**

- **One patient had Grade 4 cerebral edema**
  - The patient fully recovered with aggressive multimodality therapy including ventriculostomy

AE, adverse event.

Wang M, et al. *N Engl J Med*. 2020; 382:1331-1342.

Adverse Events at 1-Year Follow-Up

AE, n (%)[a]	All Treated Patients (N = 68)			
	Present ≥ 3 Months Post-Infusion		Present ≥ 6 Months Post-Infusion	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any AE	55 (81)	33 (48)	49 (72)	25 (37)
Anemia	22 (32)	9 (13)	13 (19)	4 (6)
Neutropenia	20 (29)	16 (24)	14 (21)	11 (16)
Thrombocytopenia	20 (29)	14 (21)	14 (21)	9 (13)
White blood cell count decrease	16 (24)	9 (13)	12 (18)	6 (9)
Fatigue	10 (15)	0	10 (15)	0
Pneumonia	9 (13)	5 (7)	6 (9)	4 (6)
Cough	8 (12)	0	7 (10)	0
Hypogammaglobulinemia	8 (12)	0	7 (10)	0
Upper respiratory tract infection	7 (10)	2 (3)	5 (7)	1 (1)

AE, n (%)	All Treated Patients (N = 68)	
	Occurred Between Last DCO and Current DCO[b]	
	Any Grade	Grade ≥ 3
Any AE	13 (19)	9 (13)
Neutropenia	6 (9)	6 (9)
Infection	5 (7)	1 (1)
Anemia	3 (4)	1 (1)
Neurologic event	2 (3)[c]	1 (1)
Thrombocytopenia	2 (3)	2 (3)
CRS	0	0
Hypogammaglobulin-emia	0	0
Tumor lysis syndrome	0	0

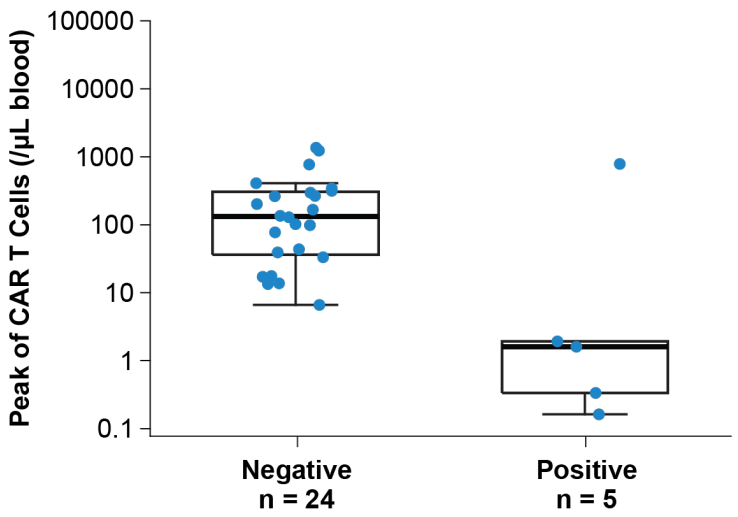
- No new safety signals were observed with additional follow-up
- No new CRS or new Grade 5 events occurred since the previous report

[a] Includes AEs of any grade occurring in ≥ 10% of patients.
[b] Includes all AEs that occurred after the primary analysis data cutoff date (July 24, 2019) and by the data cutoff date of the current analysis (December 31, 2019).
[c] Grade 1 impaired balance (n = 1, Day 106); Grade 3 encephalopathy (n = 1, Day 397).
AE, adverse event; CRS, cytokine release syndrome; DCO, data cutoff.

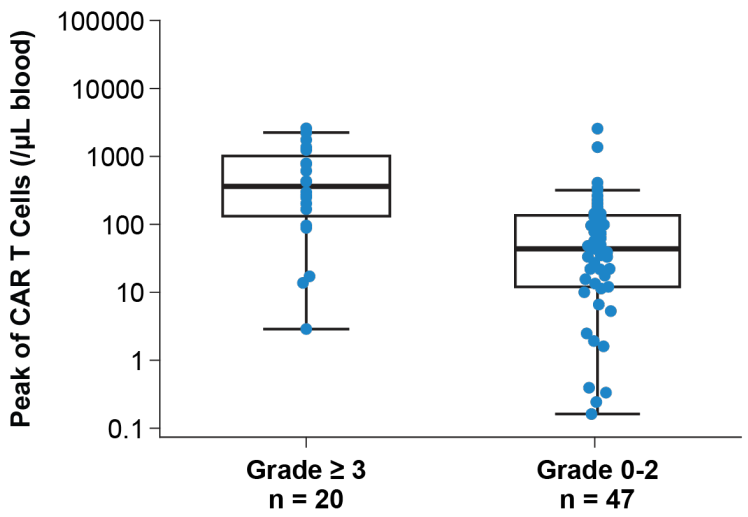
Wang ML, et al. ASH 2020. Abstract #1120.

Association of CAR T Cell Expansion With Minimal Residual Disease and Toxicity

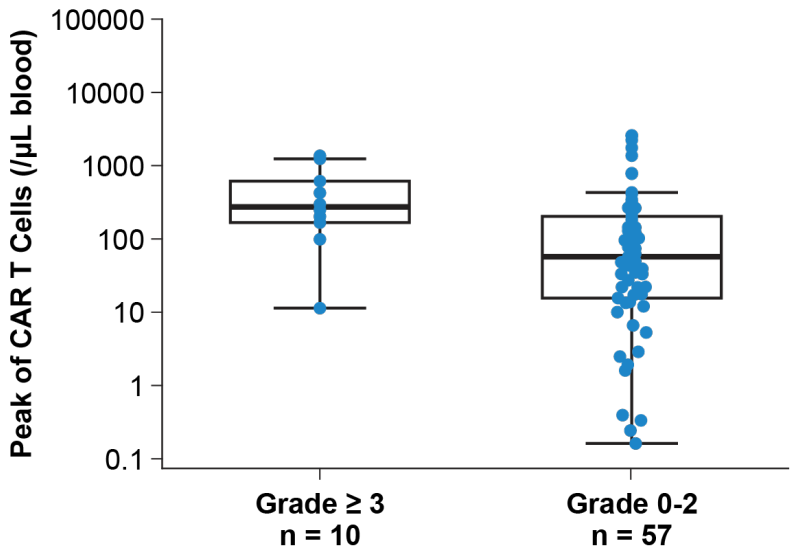
MRD at Week 4
***P* = 0.03**



Neurologic Events
***P* < 0.01**



Cytokine Release Syndrome
***P* = 0.02**



- Robust expansion of anti-CD19 CAR T cells in blood was associated with high-sensitivity molecular MRD assessed by NGS at 10^{-5}
- Patients with the most robust expansion were at a higher risk for experiencing Grade ≥ 3 vs ≤ 2 CRS and NEs

CRS, cytokine release syndrome; MRD, minimal residual disease; NE, neurologic event; NGS, next-generation sequencing.

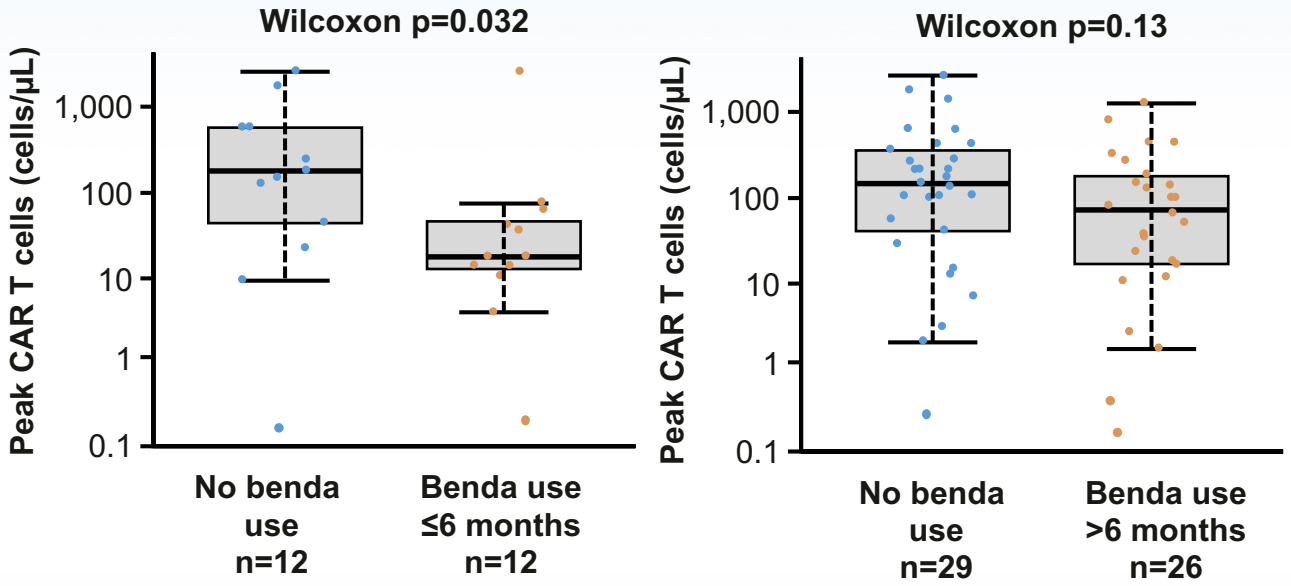
Wang M, et al. *N Engl J Med*. 2020; 382:1331-1342.

What are the effects of prior bendamustine use on CAR T-cell therapy?

Exploratory post hoc analysis of the impact of the timing of bendamustine on CAR T-cell therapy (n=37)[1,2]

54% of patients in ZUMA-2 received prior bendamustine[1,2]
Median time from last bendamustine exposure to brexucabtagene autoleucel infusion was 20.9 months[1,2]

Peak CAR T-cell levels

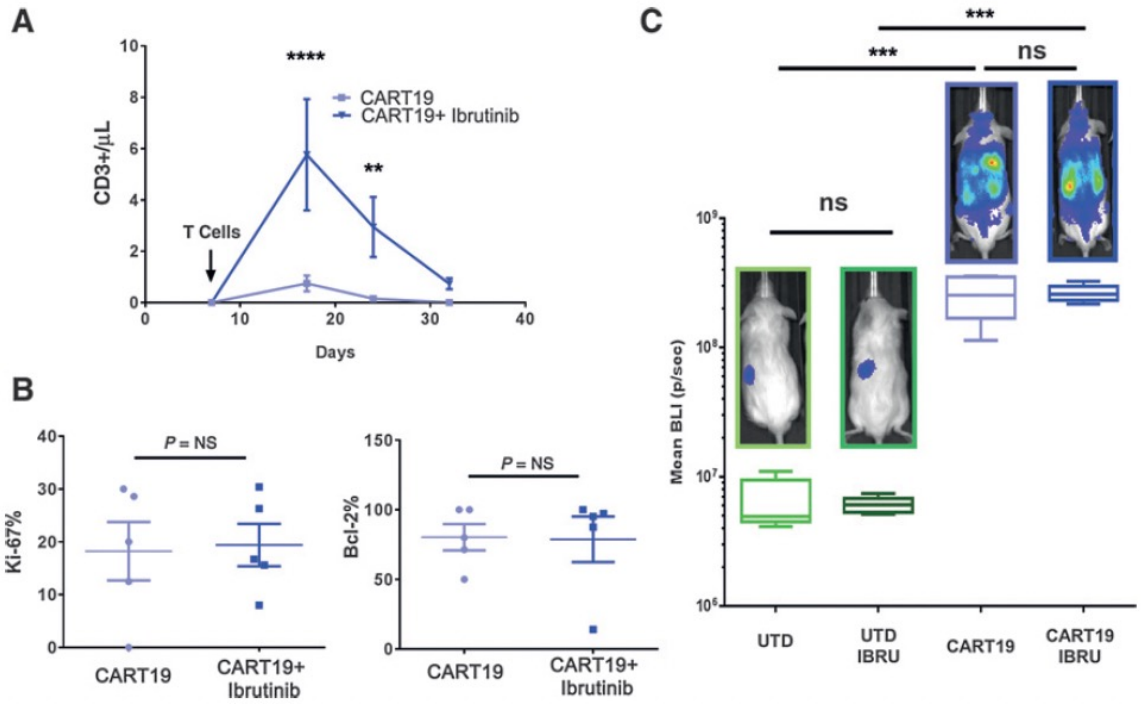


Patients treated with brexucabtagene autoleucel could benefit from longer time spans between prior bendamustine and CAR T therapy; however, further analysis is required

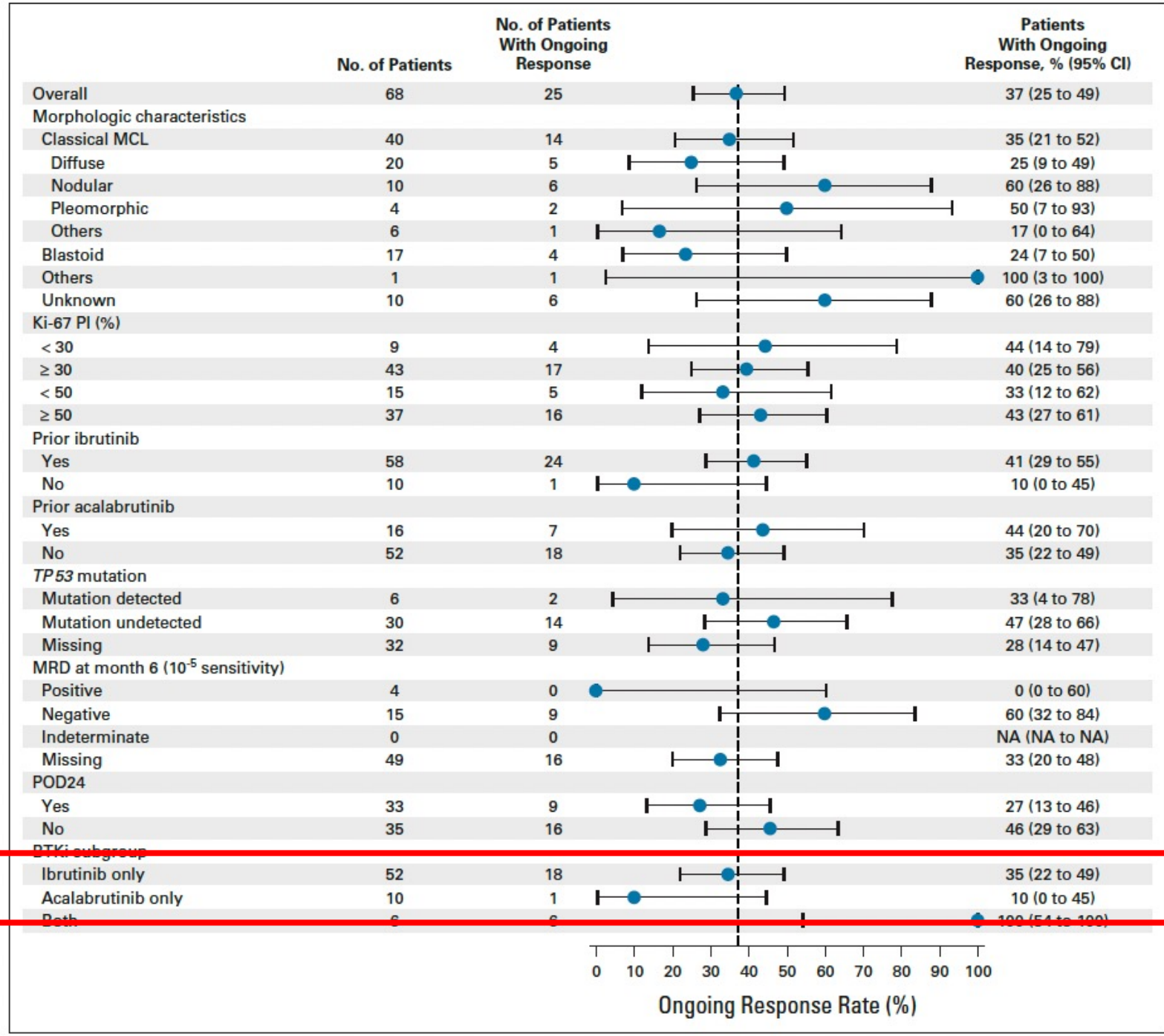
1. Wang M, *et al. J Clin Oncol* 2022; ePub ahead of print. 2. Wang ML, *et al.* ASCO 2022 (Abstract 7518; poster).

The Addition of the BTK Inhibitor Ibrutinib to Anti-CD19 Chimeric Antigen Receptor T Cells (CART19) Improves Responses against Mantle Cell Lymphoma

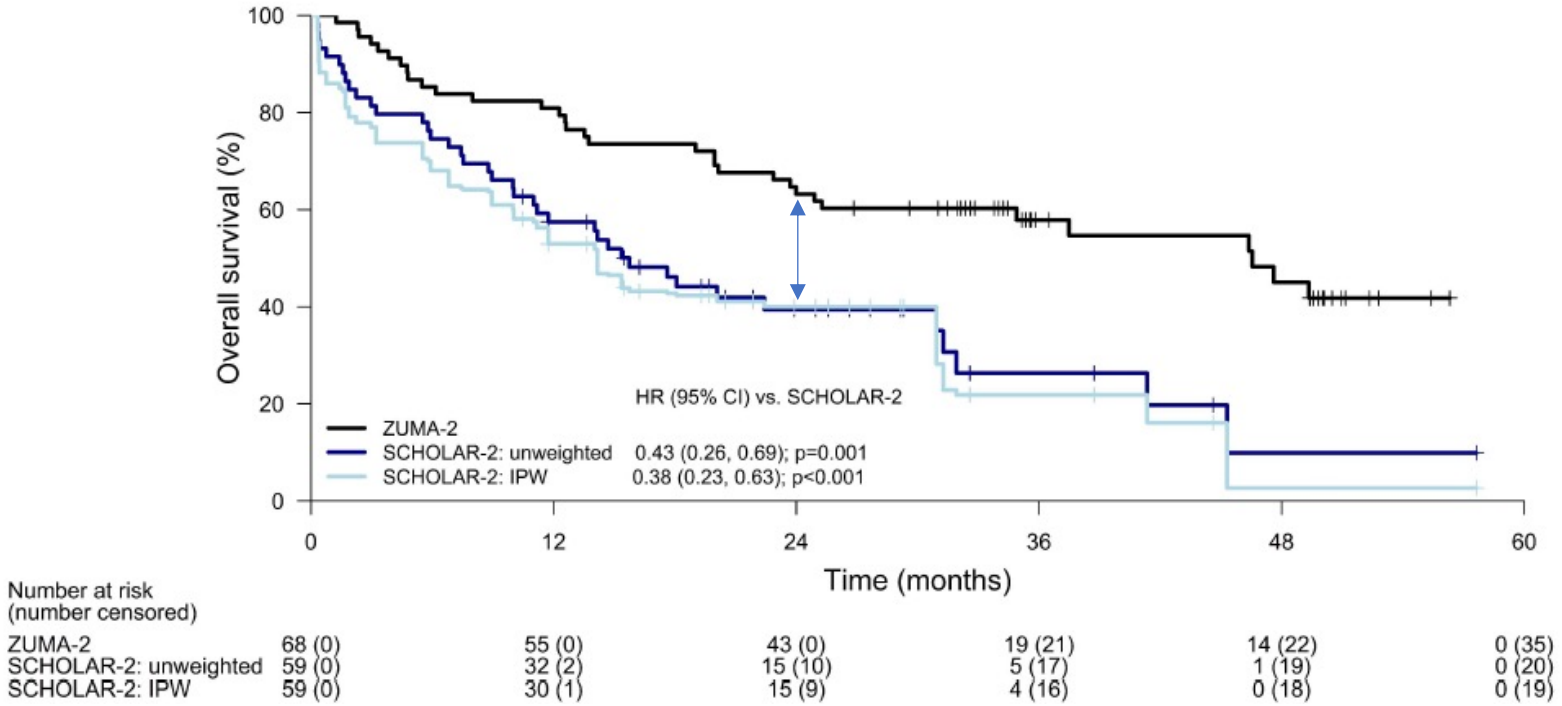
Marco Ruella[1], Saad S. Kenderian[1,2], Olga Shestova[1], Joseph A. Fraietta[1], Sohail Qayyum[3], Qian Zhang[3], Marcela V. Maus[1,4,5], Xiaobin Liu[3], Selene Nunez-Cruz[1], Michael Klichinsky[1], Omkar U. Kawalekar[1], Michael Milone[1,3,5], Simon F. Lacey[1,3], Anthony Mato[4,5], Stephen J. Schuster[4,5], Michael Kalos[1,3], Carl H. June[1,3,5], Saar Gill[1,4,5], and Mariusz A. Wasik[3,5]



BTKi exposure
Enhance T cell phenotype and function
Down regulation of PD1 on T cells and CD200 (on B cells)
Increase CAR-T cells of CD-8+ central memory CD62L+CD127+
ITK inhibition (Ibrutinib) Th2 toward Th1


No. of Patients
No. of Patients With Ongoing Response
Patients With Ongoing Response, % (95% CI)
Overall 68 25 37 (25 to 49)
Morphologic characteristics
Classical MCL 40 14 35 (21 to 52)
Diffuse 20 5 25 (9 to 49)
Nodular 10 6 60 (26 to 88)
Pleomorphic 4 2 50 (7 to 93)
Others 6 1 17 (0 to 64)
Blastoid 17 4 24 (7 to 50)
Others 1 1 100 (3 to 100)
Unknown 10 6 60 (26 to 88)
Ki-67 PI (%)
< 30 9 4 44 (14 to 79)
≥ 30 43 17 40 (25 to 56)
< 50 15 5 33 (12 to 62)
≥ 50 37 16 43 (27 to 61)
Prior ibrutinib
Yes 58 24 41 (29 to 55)
No 10 1 10 (0 to 45)
Prior acalabrutinib
Yes 16 7 44 (20 to 70)
No 52 18 35 (22 to 49)
TP53 mutation
Mutation detected 6 2 33 (4 to 78)
Mutation undetected 30 14 47 (28 to 66)
Missing 32 9 28 (14 to 47)
MRD at month 6 (10^{-5} sensitivity)
Positive 4 0 0 (0 to 60)
Negative 15 9 60 (32 to 84)
Indeterminate 0 0 NA (NA to NA)
Missing 49 16 33 (20 to 48)
POD24
Yes 33 9 27 (13 to 46)
No 35 16 46 (29 to 63)
BTKi subgroup
Ibrutinib only 52 18 35 (22 to 49)
Acalabrutinib only 10 1 10 (0 to 45)
Both 6 6 100 (54 to 100)
0 10 20 30 40 50 60 70 80 90 100
Ongoing Response Rate (%)

A Comparison of Overall Survival with Brexucabtagene Autoleucel (Brexu-cel) CAR T-Cell Therapy (ZUMA-2) and Standard of Care (SCHOLAR-2) in Patients with Relapsed/Refractory Mantle Cell Lymphoma (R/R MCL) Previously Treated with a Covalent Bruton Tyrosine Kinase Inhibitor (BTKi)



Time-points (months)	Overall survival rate, % (95% confidence interval)		
	ZUMA-2	SCHOLAR-2: unweighted	SCHOLAR-2: IPW
6	85.3 (74.4, 91.8)	74.6 (61.4, 83.8)	68.1 (50.9, 80.3)
12	80.9 (69.4, 88.4)	57.5 (43.9, 68.9)	52.9 (36.5, 66.9)
18	73.5 (61.3, 82.4)	46.1 (32.8, 58.4)	42.8 (27.3, 57.3)
24	63.2 (50.6, 73.4)	39.5 (26.4, 52.2)	40.0 (24.8, 54.7)
30	60.3 (47.7, 70.8)	39.5 (26.4, 52.2)	40.0 (24.8, 54.7)
36	57.9 (44.9, 68.9)	26.3 (12.9, 41.8)	21.8 (7.7, 40.5)
42	54.7 (40.9, 66.5)	19.7 (7.0, 37.2)	16.1 (4.1, 35.2)
48	45.0 (30.2, 58.7)	9.9 (1.0, 31.3)	2.6 (0.1, 14.1)

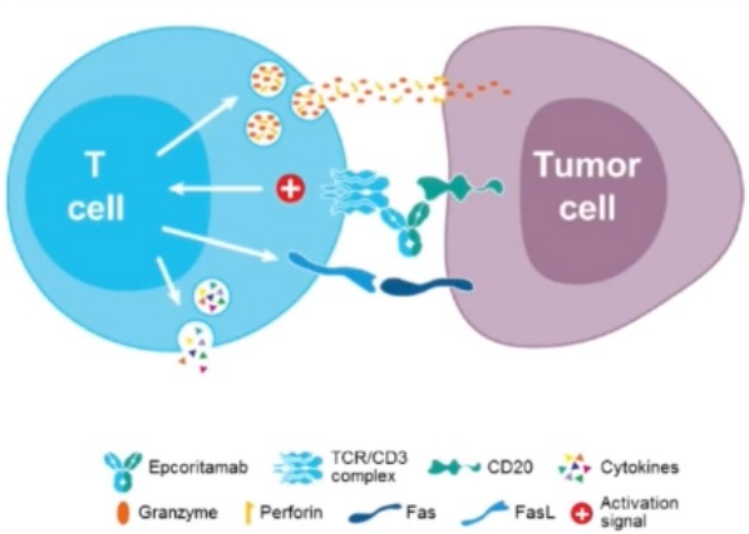
- With IPW, the adjusted OS KM curve for SOC shifted slightly downward, with a median OS of 14.2 (95% CI: 6.8, 30.9) months
- Similar to the unadjusted results, the IPW-adjusted OS HR of 0.38 (95% CI: 0.23, 0.63; *P*<0.001) suggested that brexu-cel reduced the risk of death relative to SOC

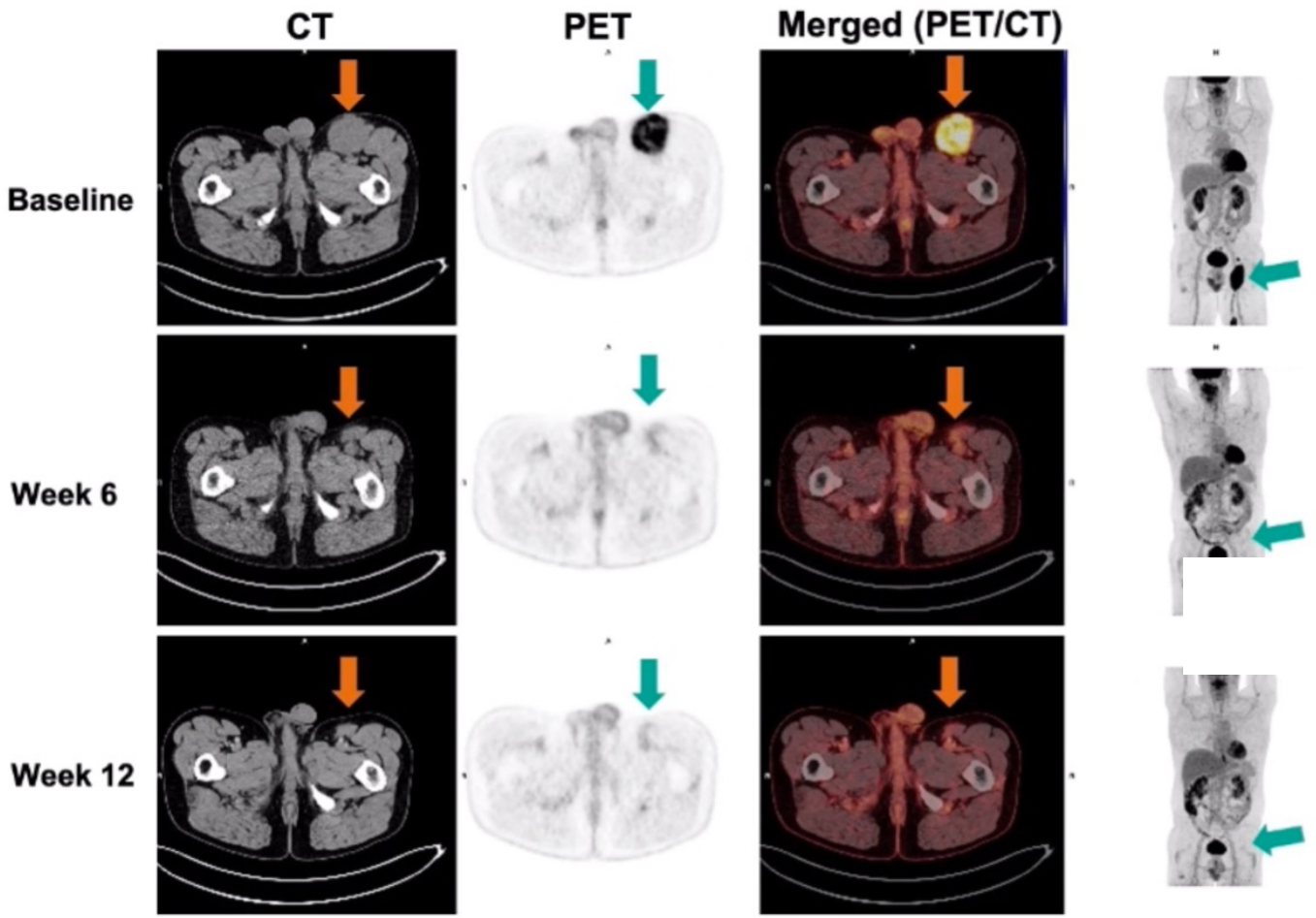
Hess G et al. ASH 2022, abstr. 4627

R/R MCL Clinical Outcome

	N	Response (ORR/CR)	PFS	OS	Tox (G ≥3)	Comments	
ZUMA-7 (Brexucel)	**68**	**91%/68%**	**52.9% (24m)**	**60.3% (24m)**	**NE 32%**		**Wang ASH/ASCO 2022**
RWE (Brexucel)	**33**	**85%/59%**	**50.8% (12m)**	**61.4% (12m)**	**NE 36%**	**5 G5 events**	**Iacoboni Blood Adv. 2022 Jun 28;6(12):3606-3610**
RWE (O´Reilly et al.) (Brexucel)	**50 (infused)**	**89.6%/**	**56.1% (12m)**	**72.3% (121m)**			**O´Reilly et al. ASH 2022**
TRANSCEND (Lisocel)	**32**	**84%/59% DL2: 88%/65%**			**NE 10%**	**Cytopenias**	Palomba ML,et al. ASH 2020
Tarmac (Tisacel)	**20 (infused)**	**90%/85%**			**1 AF,, 1NE**		**Minson A et al., ASH 2022**

BiTE CD3-CD20 mosunetuzumab / glofitamab / odronextamab / epcoritamab





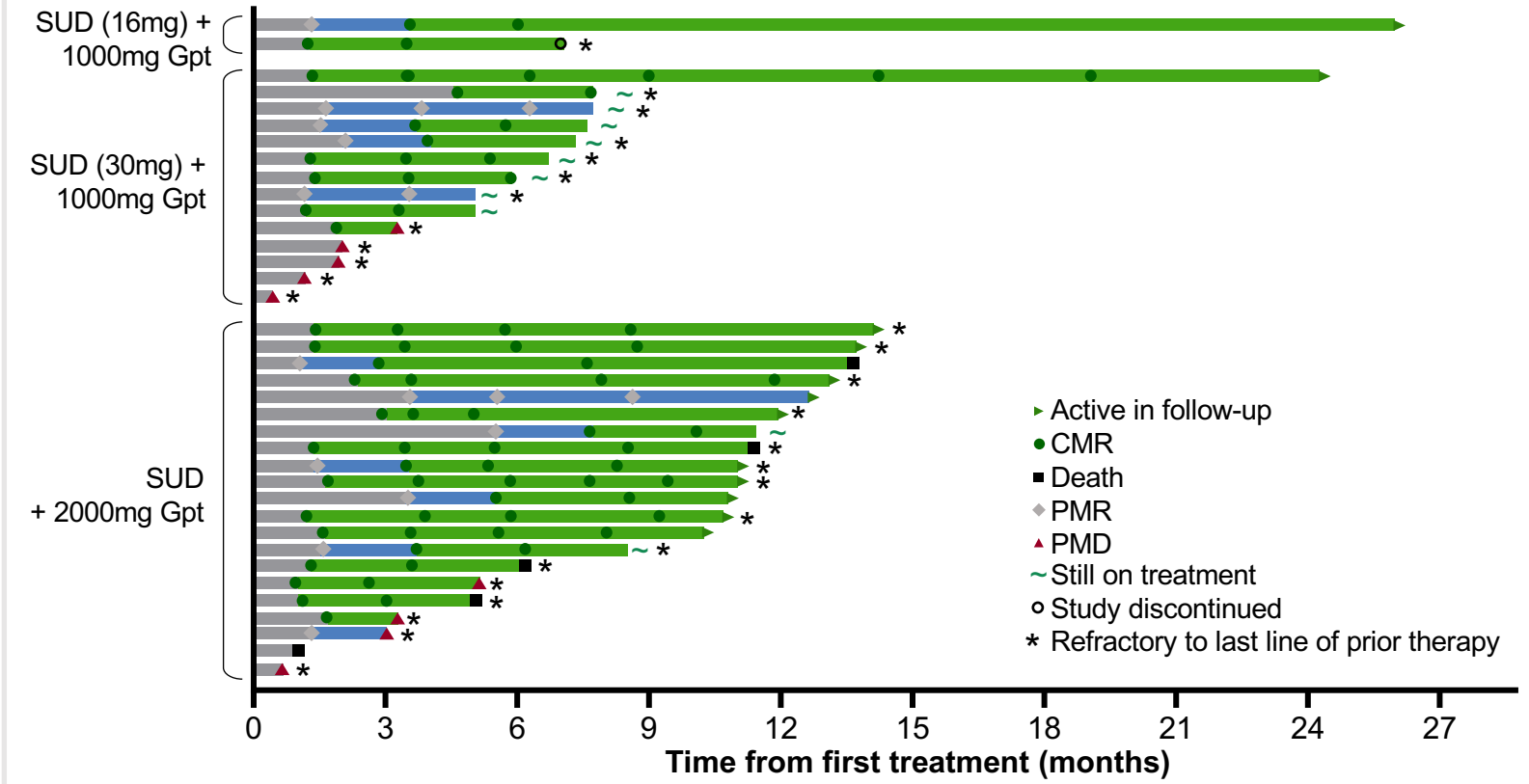
MCL, 56y
3 prior ttt lines
(including ibrutinib)

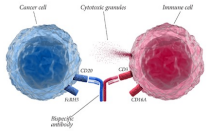
abstr. 400-404 ASH 2020

Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated Relapsed or Refractory Mantle Cell Lymphoma

Time on treatment and response

Durability of response in efficacy-evaluable patients





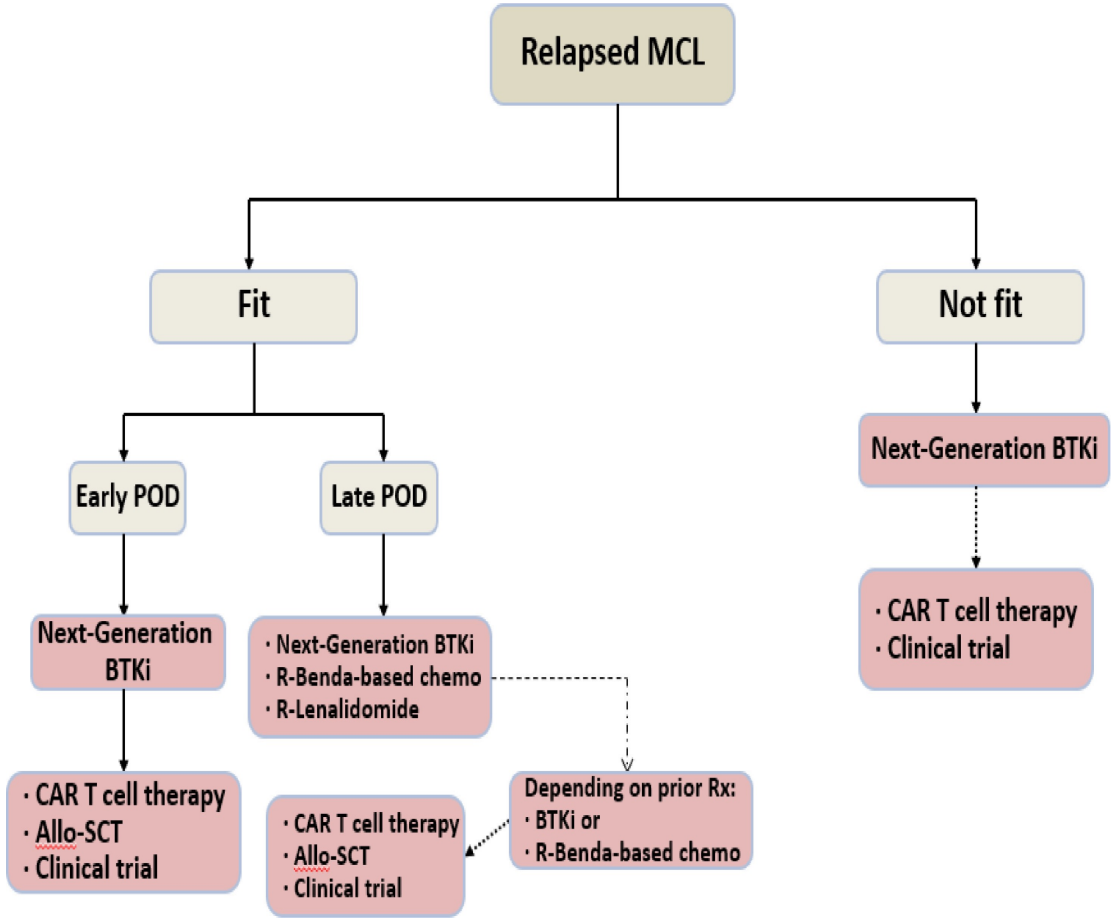
- **Median follow-up (months):**
  - 8.0 months
- **Median time to first response:**
  - **51 days** (range, 29–234)
- **Response at first assessment:**
  - **CRR: 48.6%, ORR: 73.0%**
- **No PD was reported beyond EOT in patients with response at EOT**

Most responses were achieved early and were durable

EOT, end of treatment; CRR, complete response rate; ORR, overall response rate.

Philipps T et al., ASH 2022, abstr. 74

Mantle Cell Lymphoma: Open Questions

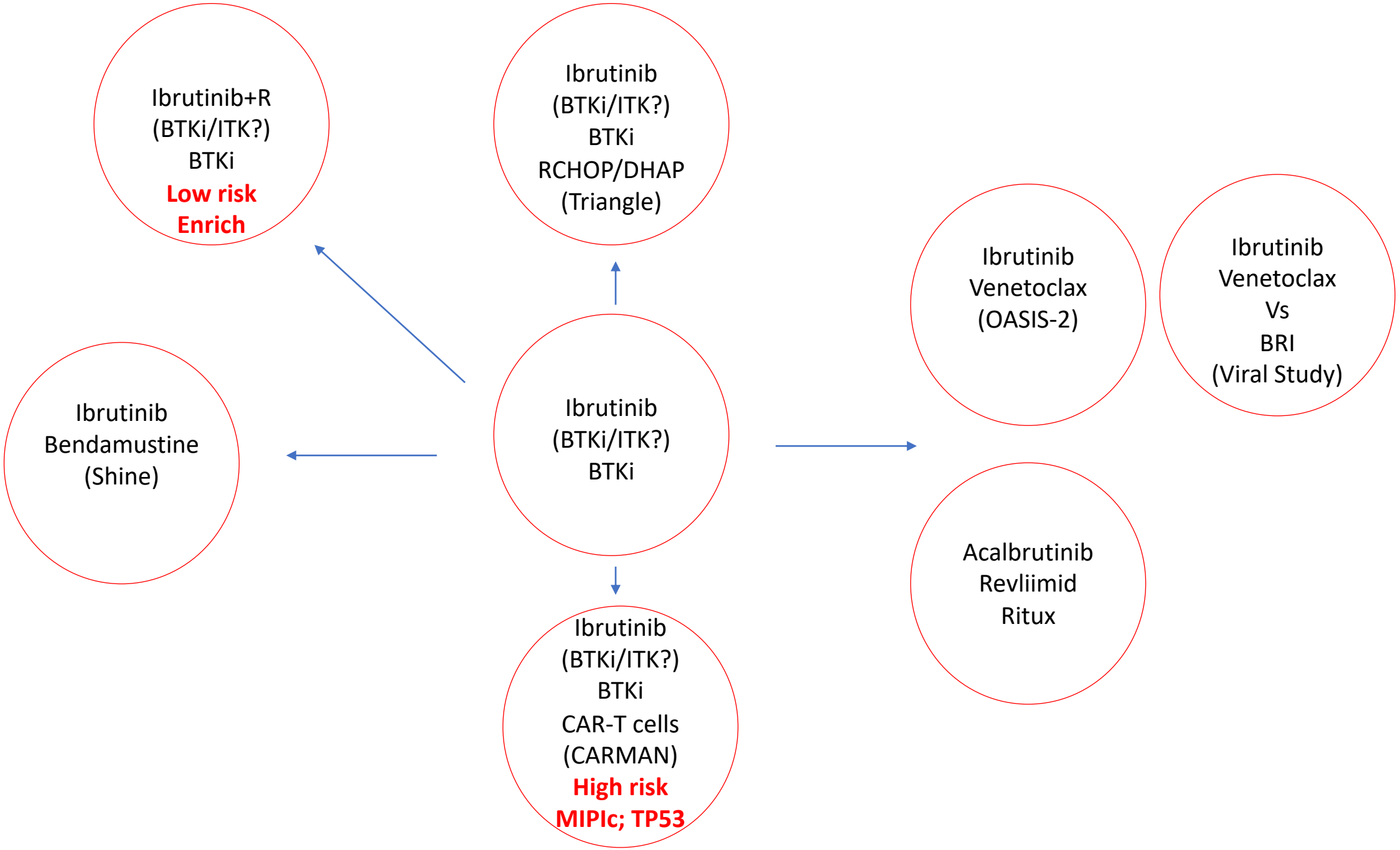


Treatment that preserves T cell function
Role of Bendamustine, High dose ARA-C
Use immune enhancer like BTKi+++
AlloSCT in fit patients vs CAR-T vs Bispe ?

Al-Mansour M. Treatment Landscape of Relapsed/Refractory Mantle Cell Lymphoma: An Updated Review. Clin Lymphoma Myeloma Leuk. 2022 Nov;22(11):e1019-e1031. doi: 10.1016/j.clml.2022.07.017. Epub 2022 Aug 3. PMID: 36068158.

Ongoing/Recent Clinical Trials in Relapsed or Refractory MCL

Combination	ClinicalTrials.gov	Phase	Patient status	Endpoints
Ibrutinib + venetoclax vs. ibrutinib (Sympathico)	NCT03112174	3	First line or R/R	CR, PFS
Ibrutinib + ixazomib	NCT03323151	1/2	R/R	MTD, CR
Tisagenlecleucel + ibrutinib	NCT04234061	2	R/R	CR
Loncastuximab tesirine + ibrutinib	NCT03684694	1/2	R/R	Safety, CR
CA-4948m ± ibrutinib	NCT03328078	1/2	R/R	CR, ORR. DOR, Safety
Acalabrutinib + rituximab+ bendamustine or venetoclax	NCT02717624	1b/2	First line or R/R	Safety, CR
Acalabrutinib + venetoclax	NCT03946878	2	R/R	CR, PFS
Venetoclax + lenalidomide + rituximab (Valeria)	NCT03505944	1/2	R/R	ORR, PFS
Lenalidomide + blinatumumab	NCT02568553	1	R/R	MTD/CR


Ibrutinib+R
(BTKi/ITK?)
BTKi
Low risk
Enrich
Ibrutinib
(BTKi/ITK?)
BTKi
RCHOP/DHAP
(Triangle)
Ibrutinib
Venetoclax
(OASIS-2)
Ibrutinib
Venetoclax
Vs
BRI
(Viral Study)
Ibrutinib
Bendamustine
(Shine)
Ibrutinib
(BTKi/ITK?)
BTKi
Acalbrutinib
Revliimid
Ritux
Ibrutinib
(BTKi/ITK?)
BTKi
CAR-T cells
(CARMAN)
High risk
MIPIc; TP53