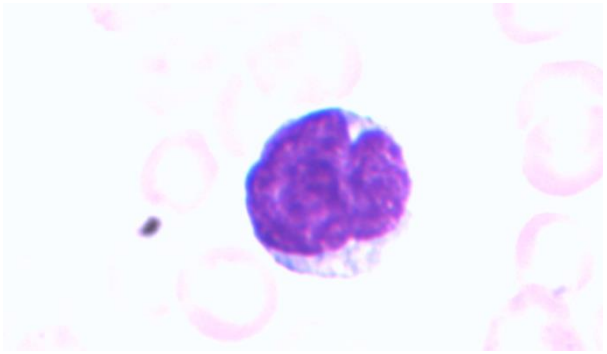


UNIVERSITÄTSmedizin.
uct | Universitäres Centrum für Tumorerkrankungen MAINZ

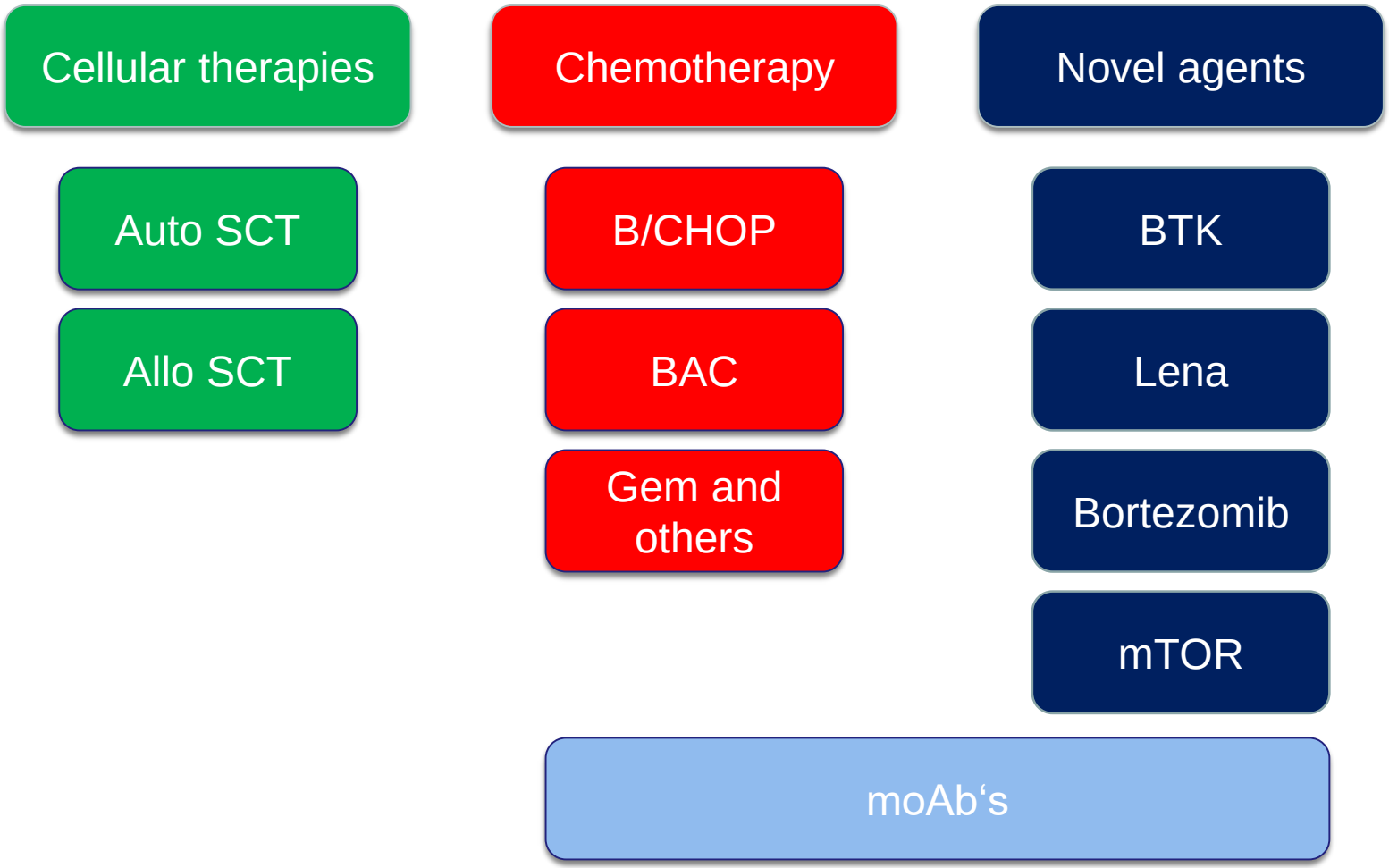
Mantle Cell Lymphoma – Relapse strategies

Torino, Italia, Sep. 2018

Georg Heß
III. Med. Klinik und UCT Mainz
Johannes Gutenberg-Universität Mainz

German Lymphoma Alliance

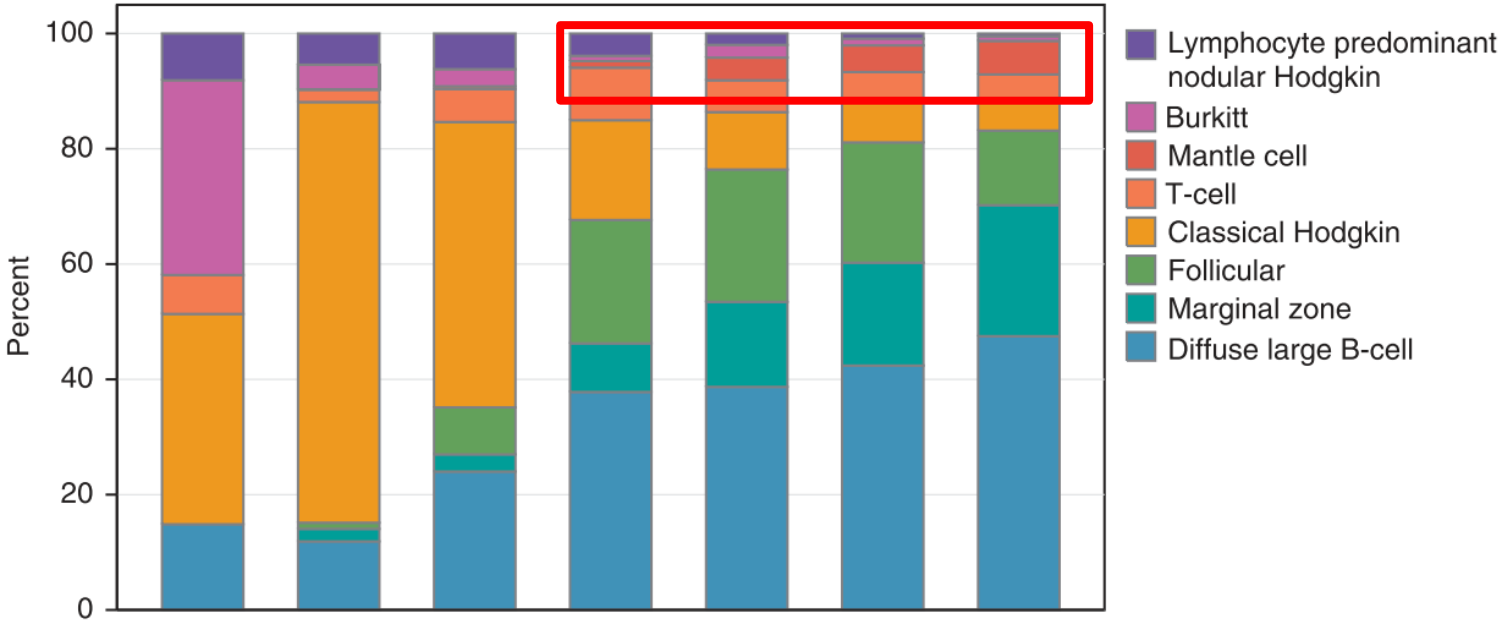
Approved therapeutic options for relapsed MCL



How to chose the appropriate treatment - criteria

- The patient
- Disease risk
- Prior treatment
- Relapse characteristics

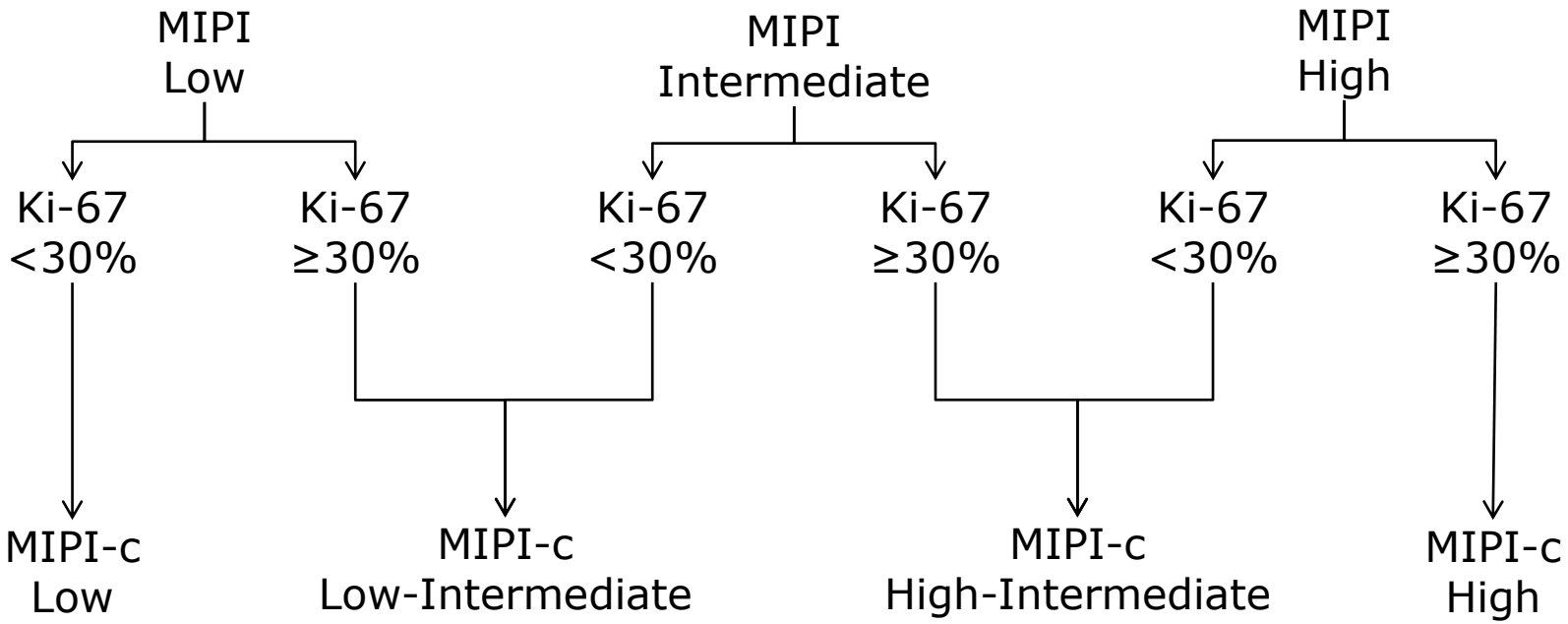
Lymphoma – Epidemiology II



Years	<15	15–24	25–39	40–49	50–59	60–69	≥70
Number	76	186	409	439	818	1366	2502
M/F sex rate ratio	2.2	1.3	1.4	1.5	1.4	1.2	1.5
(95% CI)	(1.3–3.4)	(1.0–1.8)	(1.1–1.7)	(1.3–1.9)	(1.2–1.6)	(1.1–1.4)	(1.4–1.6)

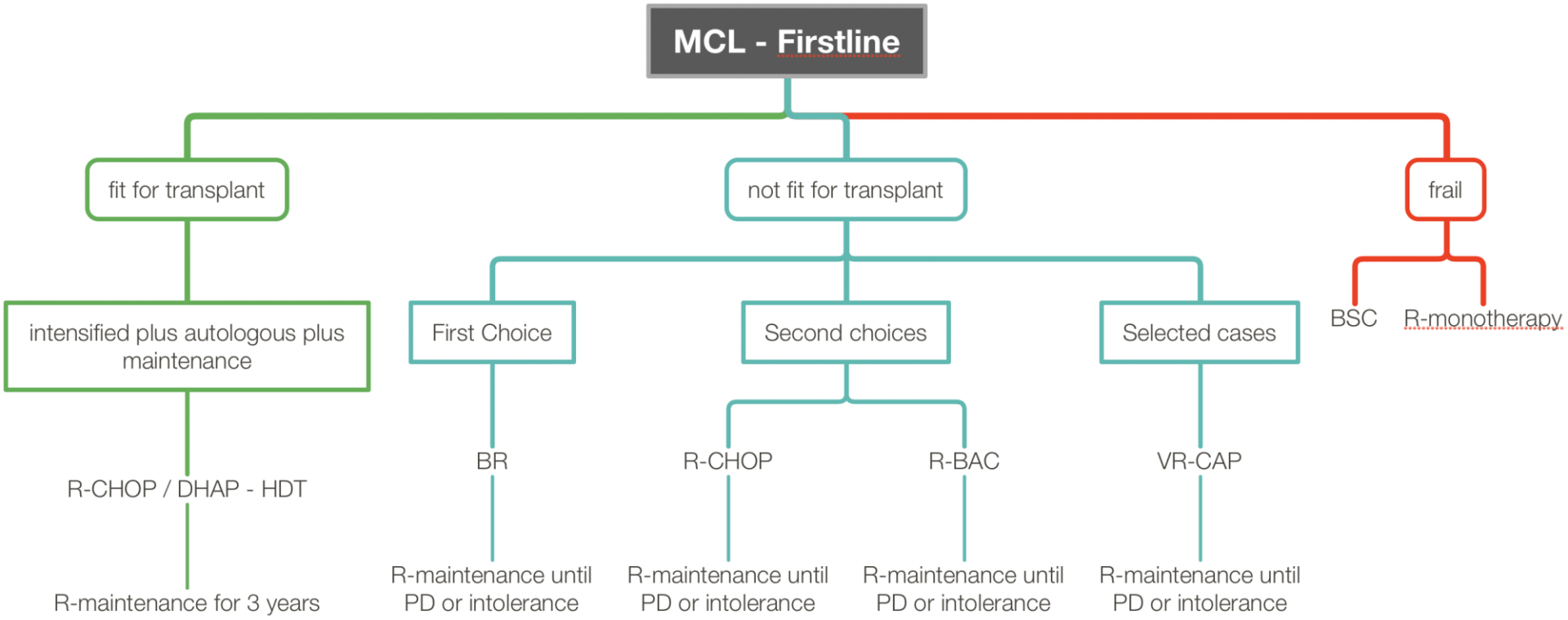
Smith et al, Br J Cancer, 2015c

MIPI / Ki67

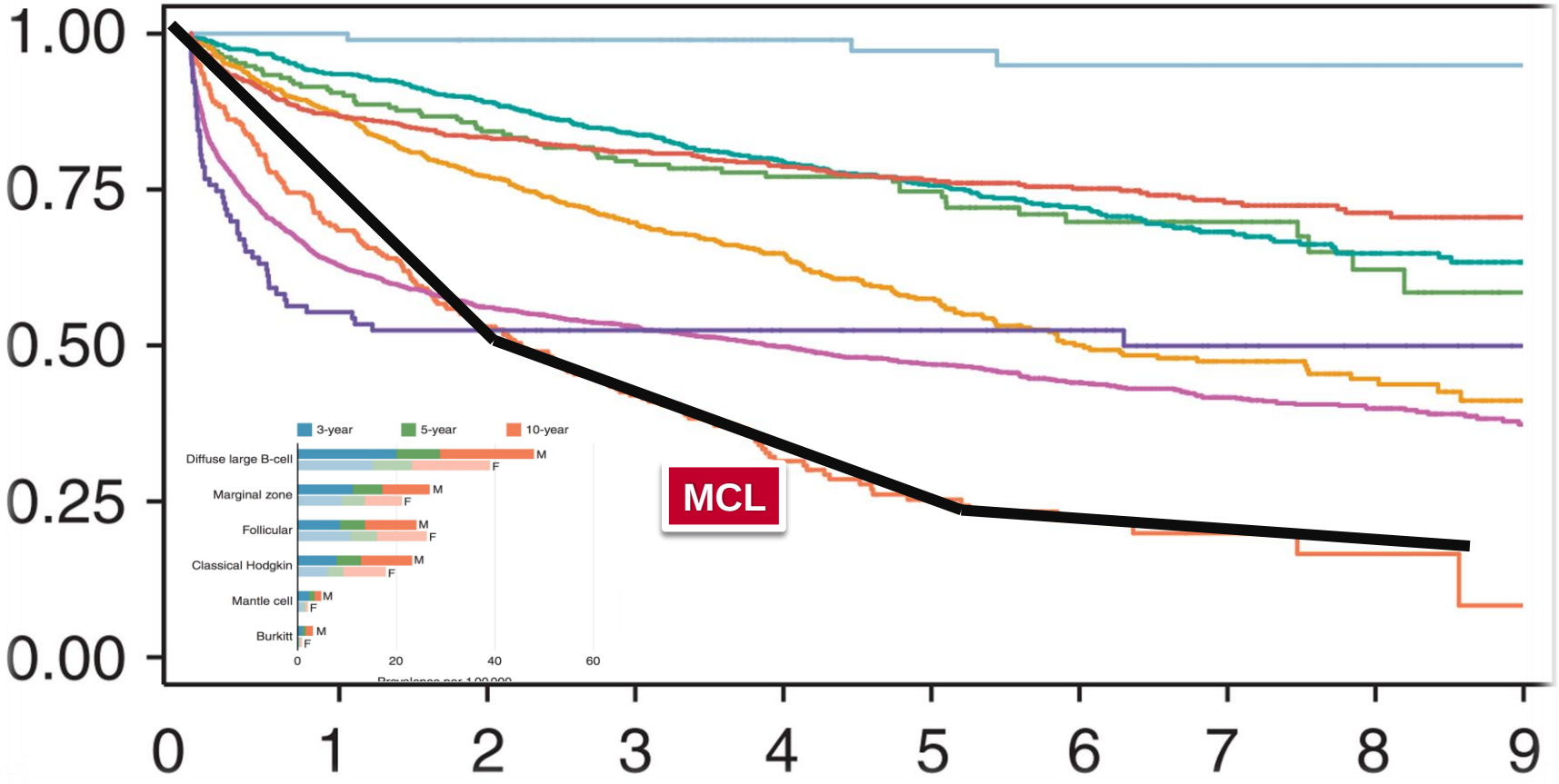


Hoster el al, JCO, 2016

Current firstline treatment



RWE: Mantle cell Lymphoma – Prognosis 2015

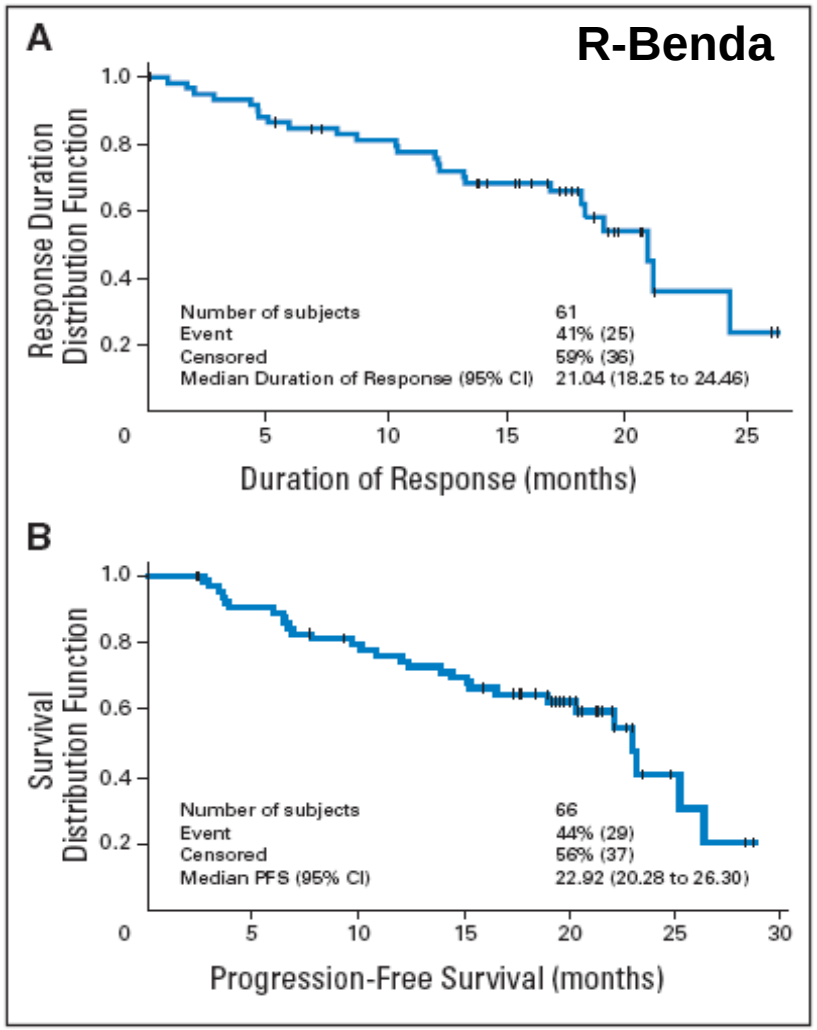


Smith et al, Br J Cancer, 2015

RELAPSE TREATMENTS

Combination chemotherapy in relapsed disease

R-Benda



R-GEMOX

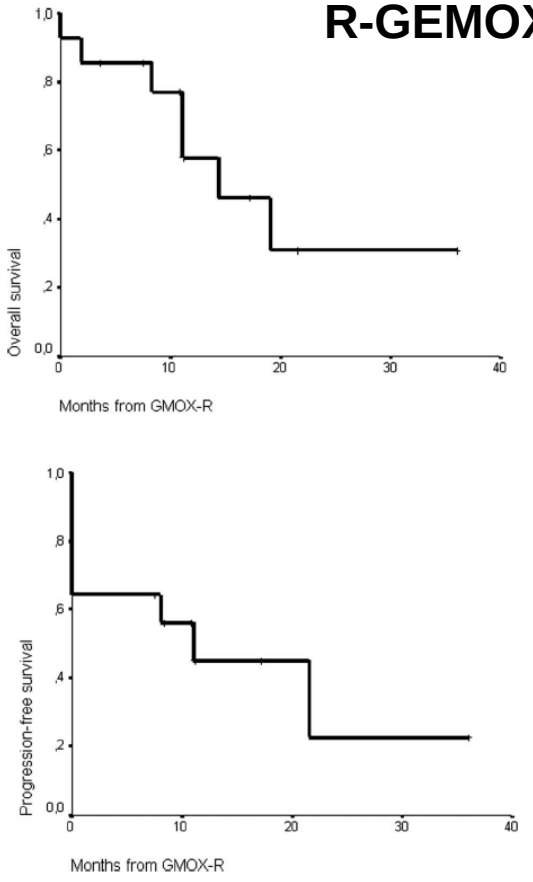
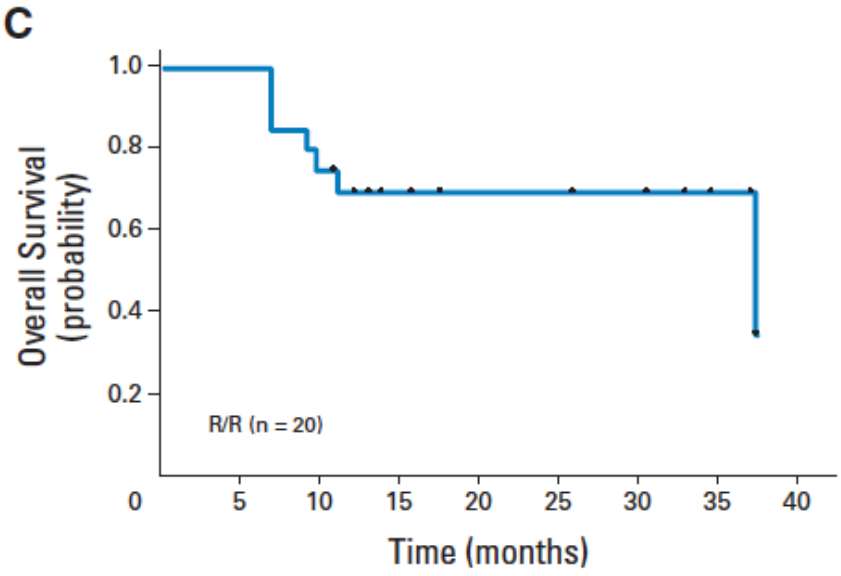
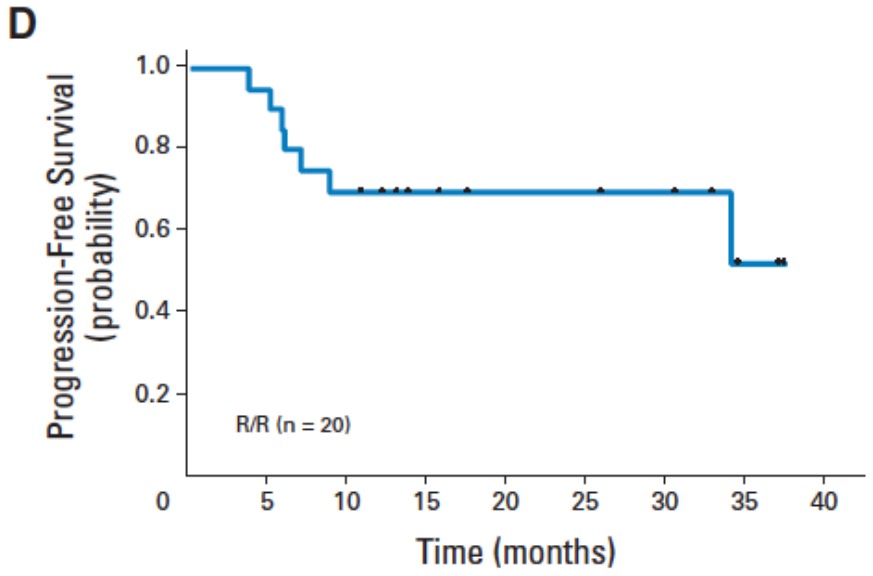


Figure 1. Overall survival and progression-free survival.

Weide, Hess et al, *Leuk Lymph*, 2007;
Robinson KS, et al. *J Clin Oncol.* 2008;
Rodriguez et al., *Leuk and Lymphoma* 2007.

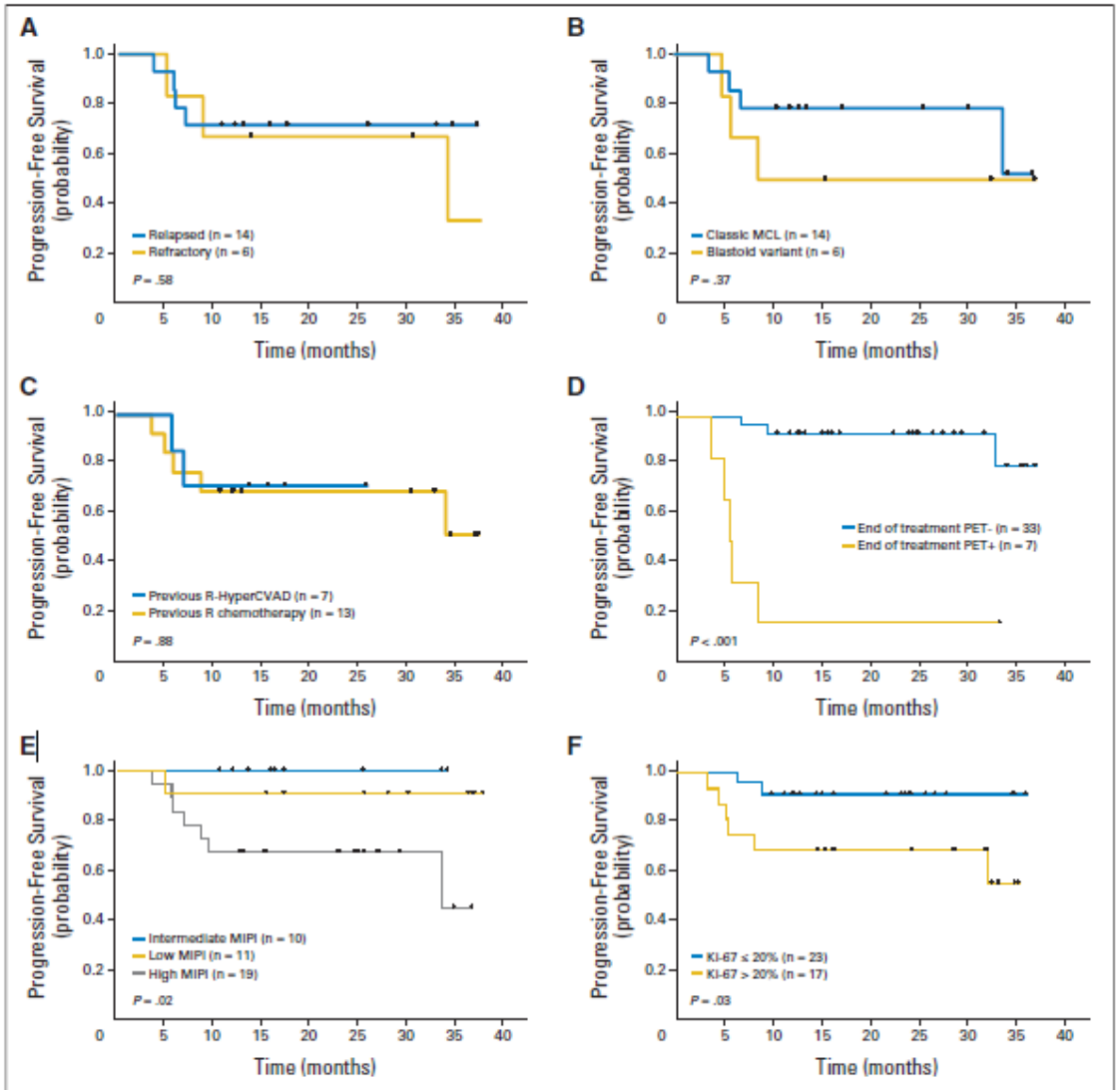
Chemo in Relapse: R-BAC





Visco et al, J Clin Oncol, 2013, 31:1442-1449.

Chemo in Relapse: R-BAC



Visco et al, J Clin Oncol, 2013 31:1442-1449.

Data on allogeneic transplantation

Literatur	n	Alter	Spender	Konditionierung	Status	TRM	PFS	OS
Khouri JCO 2003	18	56.5	78% related 22% unrelated	Flu/Cis/Cytarabine Flu/Cy/Rituximab	Relapsed	11.1%	3-yr: 82%	3-yr:85.5%
Robinson Blood 2002	22	52	–	Varied	Relapsed	2-yr: 82%	2-yr: 0%	2-yr: 12.8%
Le Gouill Ann Oncol 2012	70	56	53% related 47% unrelated	Varied	Relapsed	2-yr: 32%	2-yr EFS: 50%	2-yr: 53%
Maris Blood 2004	33	53.5	48% related 52% unrelated	Flu/TBI	Relapsed	2-yr:24%	2-yr: 60%	2-yr: 64%
Cruz Ther Adv Hematol 2011	21	56	Related	Flu/Mel	Relapsed/ 1st remission	3-yr: 19.5%	5-yr: 80%	5-yr: 80%
Krüger Ann Hematol 2014	33	59	24% related 76% unrelated	Flu/Treosulfan/± Rituximab Bu/Cy	Relapsed/ 1st remission	24%	5-yr: 67%	5-yr: 73%
Gopal Blood 2011	8		Not stated	90Y-Ibritumomab tiuxetan/flu/TBI	Relapsed		6-mo: 50%	1-yr: 38%
Bethge Blood 2010	8		Not stated	^{90}Y-Ibritumomab tiuxetan/flu/TBI	Relapsed	62.5%	2-yr EFS: 37%	2-yr OS: 37%
Fenske JCO 2014	88	58	41% related 59% unrelated	Varied	Relapsed	1-yr: 17%	5-yr: 24%	5-yr: 31%
	50	54	52% related 48% unrelated	Varied	1st Remission	1-yr: 25%	5-yr: 55%	5-yr: 62%
Hamadani BBMT 2013	128	54	68% related 32% unrelated	Varied	Chemorefract	3-yr: 43%	3-yr: 25%	3-yr: 30%
Cook BBMT 2010	70	52.2	60% related 40% unrelated	Varied	Rel/Ref	5-yr: 21%	5-yr: 14%	5-yr: 37%
Magnusson Clin Lymphoma Myeloma Leuk 2014	28	51	61% related 39% umbilical cord blood	Flu/TBI + Cy or Bu	Rel/Ref/ 1st Remission	2-yr: 15%	5-yr: 34%	5-yr: 53%

Cohan et al, EJH, doi:10.1111/ejh.12442

Allo SCT in refractory disease

Biol Blood Marrow Transplant 19 (2013) 625–631

Allogeneic Hematopoietic Cell Transplantation for Chemotherapy-Unresponsive Mantle Cell Lymphoma: A Cohort Analysis from the Center for International Blood and Marrow Transplant Research

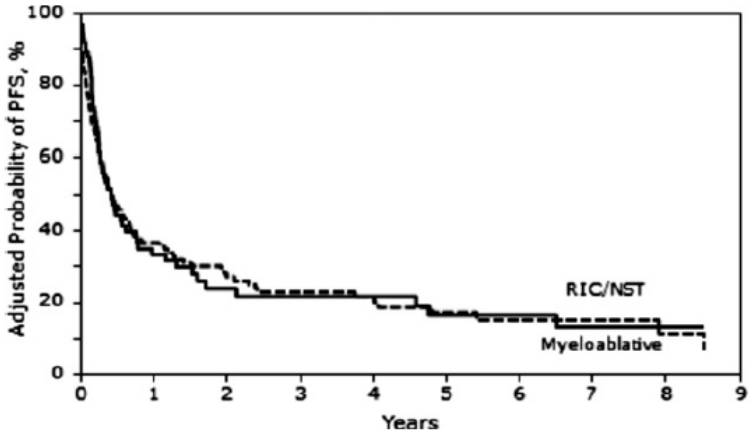


Figure 1. Kaplan-Meier estimates of adjusted PFS after allo-HCT for mantle cell lymphoma.

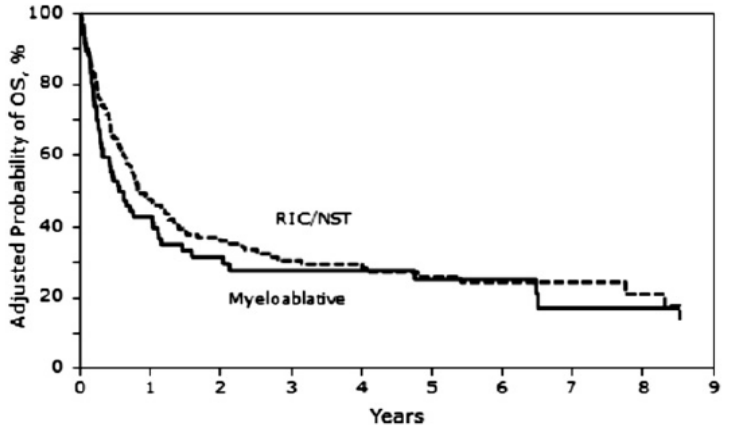
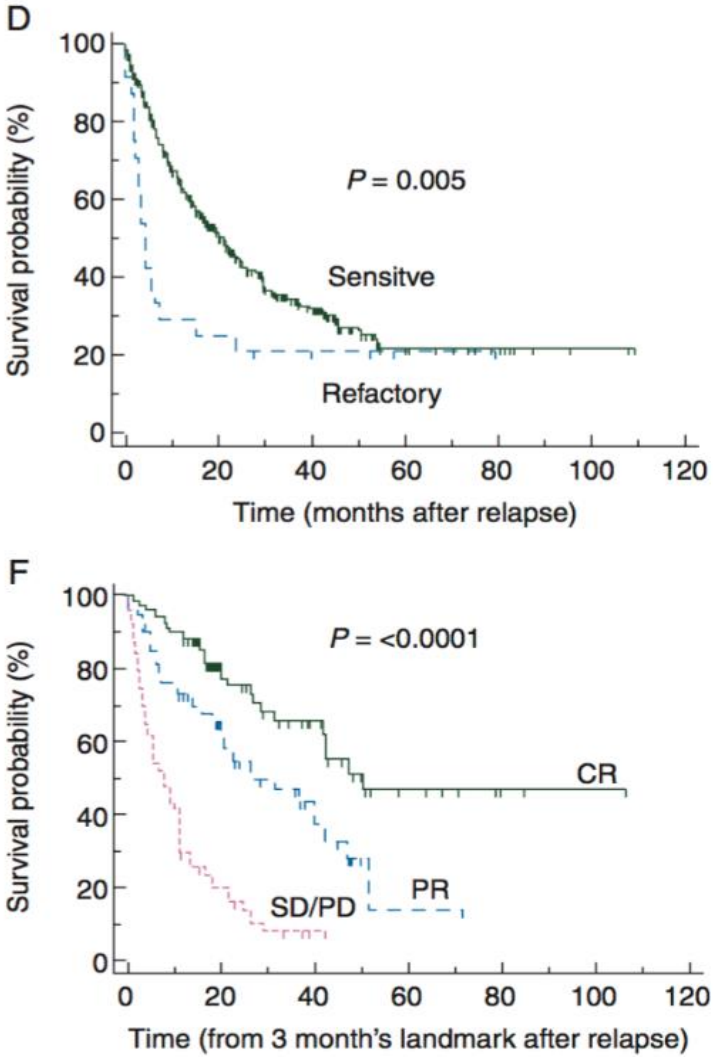


Figure 2. Kaplan-Meier estimates of adjusted OS after allo-HCT for mantle cell lymphoma.

Hamadani M, et al. *Biol Blood Marrow Transplant.* 2013;19(5):746-53

Disease characteristics determine outcome after allo SCT



Dietrich et al, Anal Oncol, 25: 1053–1058, 2014

Summary traditional approaches for relapsed MCL

- Chemotherapy
  - Frequently limited responses and especially response duration
  - Ara-C might add benefit for suitable patients
- HighDose Therapy
  - Rather limited benefit in relapse
- Allogeneic SCT
  - Efficacious
  - Not suitable for all patients
  - High TRM

NOVEL TREATMENT OPTIONS

Comparison of drugs licensed for the use in MCL: data as single agents

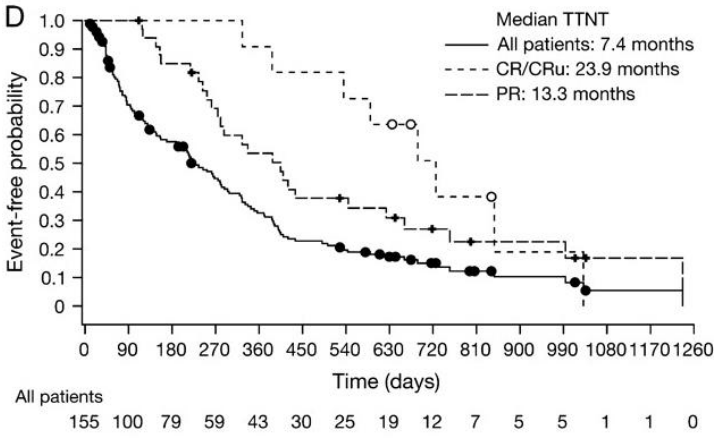
Treatment	No. Patients	ORR	CR	Median DOR (months)	Median PFS (months)	Median OS (months)
Bortezomib	155	33%	8%	9.2	6.5	23.5
Lenalidomide	134	28%	8%	16.6	4	19
Temsirolimus	54[a]	22%	2%	7.1	4.8	12.8

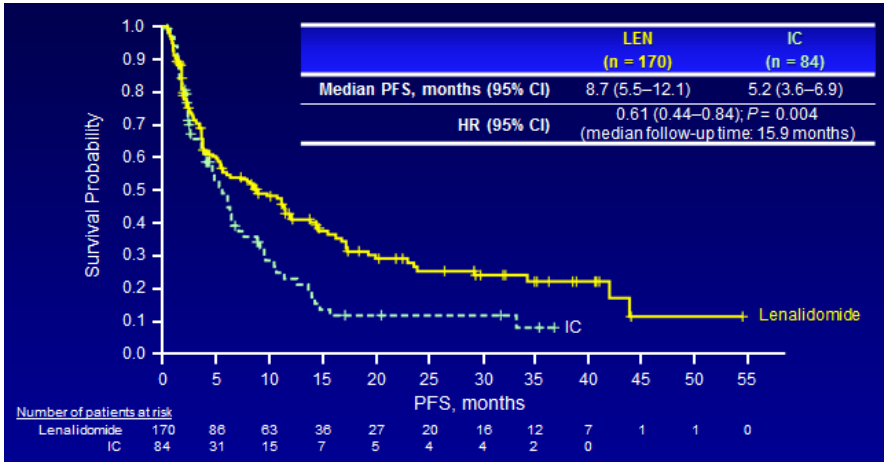
CR=complete response; DOR= duration of response; ORR=overall response rate; OS=overall survival; PFS= progression-free survival; NR=not reported.

[a] Results are presented for temsirolimus 175/75 mg dose group.

Rule S., EHA 2017 (invited oral presentation)

Bortezomib - Lenalidomid





Combinations

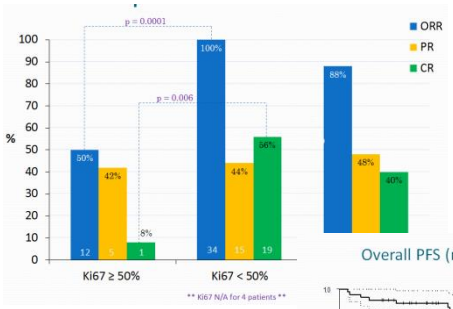
	Rituximab-sensitive patients (n=48)	Rituximab-refractory patients (n=21)	Total (n=69)*
Complete response + partial response	30 (63%; 47–76)	11 (52%; 30–74)	41 (59%)
Complete response	8 (17%; 8–30)	5 (24%; 8–47)	13 (19%)
Partial response	22 (46%; 31–61)	6 (29%; 11–52)	28 (41%)

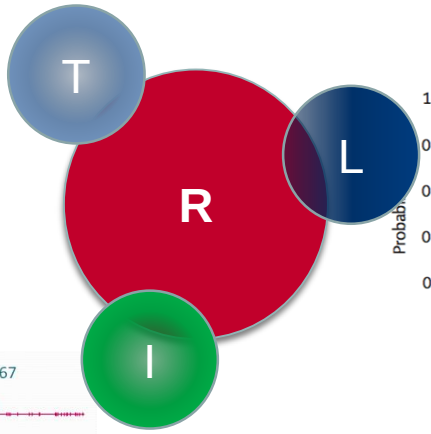
Data are number (%; 95% CI) or number (%). *95% CIs are not appropriate statistically for the whole group because patients in the two cohorts were analysed separately and with different designs.

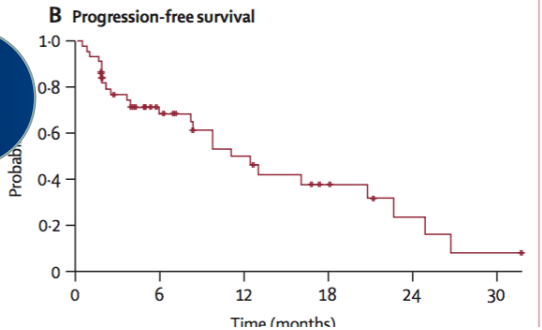
Table 2: **Response rates**

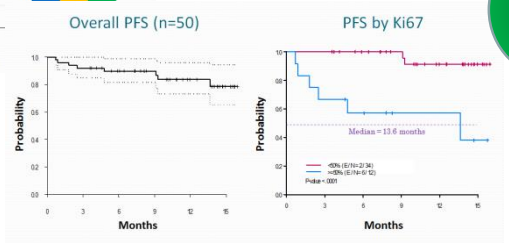
	Phase 2 (n=44)*
Complete response	16 (36%)
Partial response	9 (20%)
Overall response	25 (57%)
Stable disease	10 (23%)
Progressive disease	9 (20%)
Response duration (months)	18·9 (17·0–NR)
Progression-free survival (months)	11·1 (8·3–24·9)
Overall survival (months)	24·3 (19·8–NR)
Time to first response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









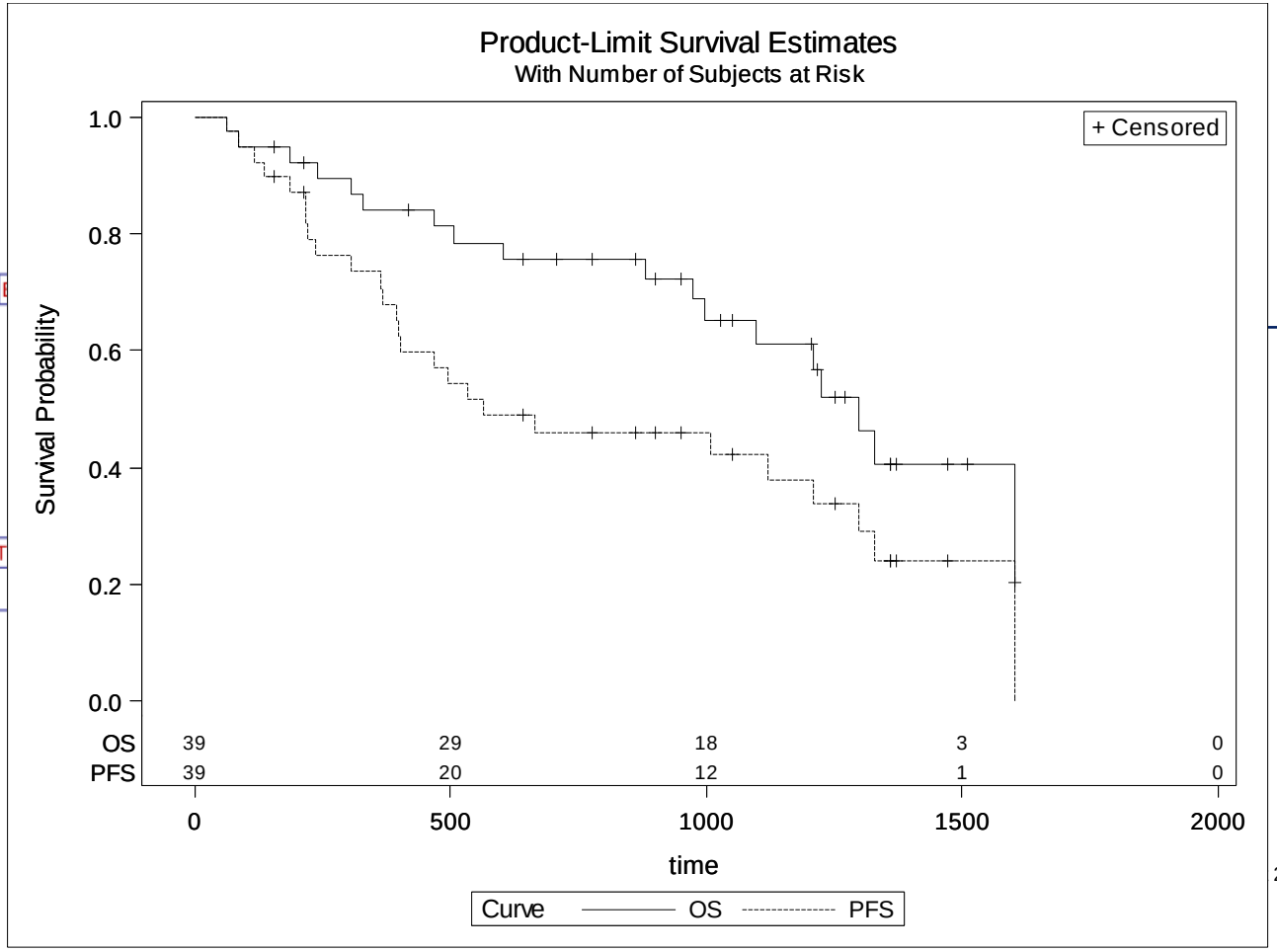
Ansell et al. Lancet Oncology, 2011, DOI: 10.1016/S1470-2045(11)70062-6
Wang et al, Lancet Oncol 2012; 13: 716–2, Wang et al., ASH 2014; abstract 627

Temsirolimus with Bendamustine and Rituximab (BeRT)

BEndamustin
90 mg/m²

Rituximab
375 mg/m²

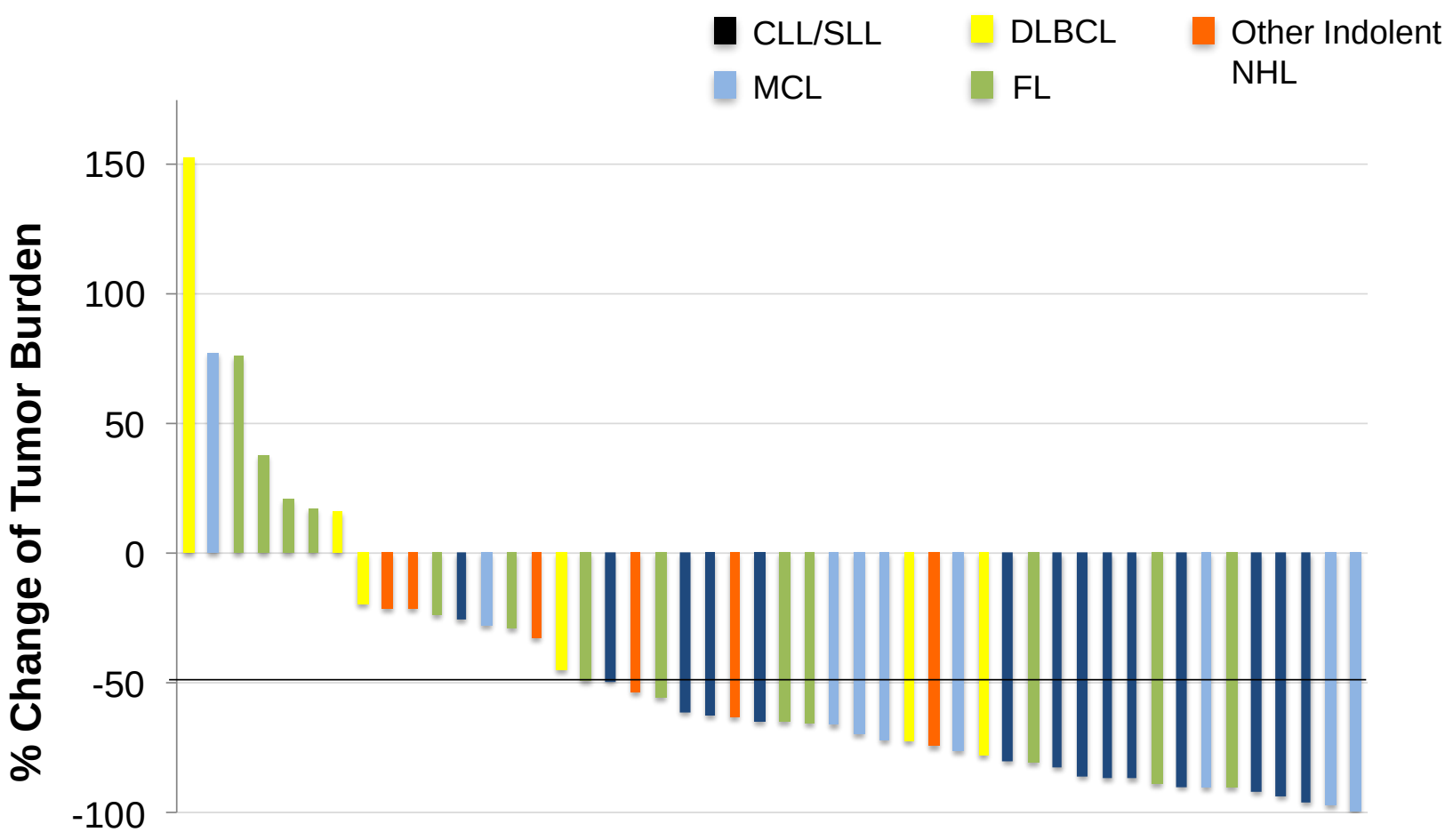
Temsirolimus
25/50/75 mg



	Total (N= 37)
	2 (7%)
	24 (86%)
	2 (7%)
	0 (0%)
	26 (93%)

2977, poster presentation)

Ibrutinib - Phase 1 Study in NHL and CLL



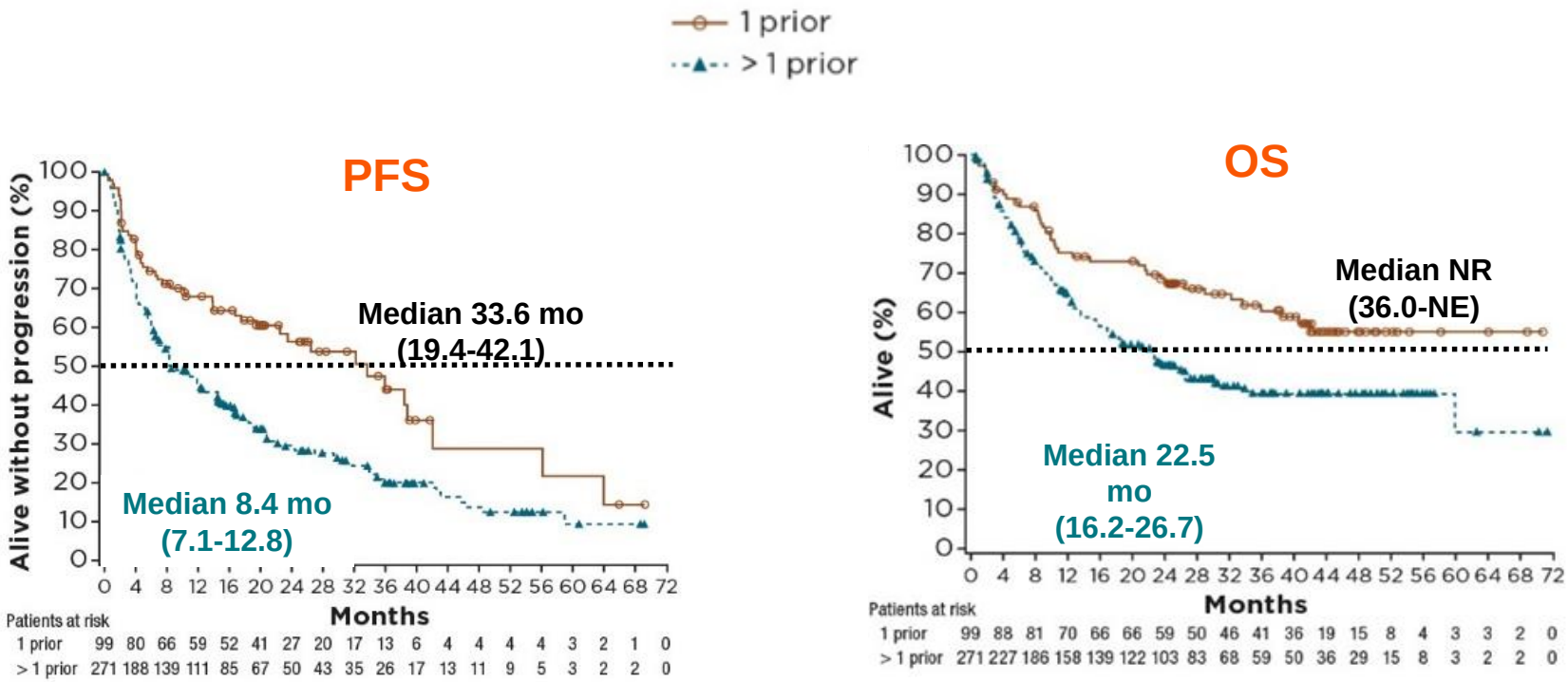
Treatment options for R/R MCL

Treatment	No. patients	ORR	CR	Median DOR (months)	Median PFS (months)	Median OS (months)
Ibrutinib	111	68%	21%	17.5	13.9	Not reached
Bortezomib	155	33%	8%	9.2	6.5	23.5
Lenalidomide	134	28%	8%	16.6	4	19
Temsirolimus*	54	22%	2%	7.1	4.8	12.8

* Results are presented for temsirolimus 175/75 mg dose group

Rule and Campo Blood 2015; 125(1):48-55

Ibrutinib in MCL: PFS and OS by prior line of therapy



Median PFS overall (95% CI): 13.0 (8.4-16.8) months

Median OS overall (95% CI): 26.7 (22.5-38.4) months

Median PFS was nearly 3 years in patients with 1 prior line of therapy

Patients censored from OS analysis upon study discontinuation. CI, confidence interval; NE, not estimable.

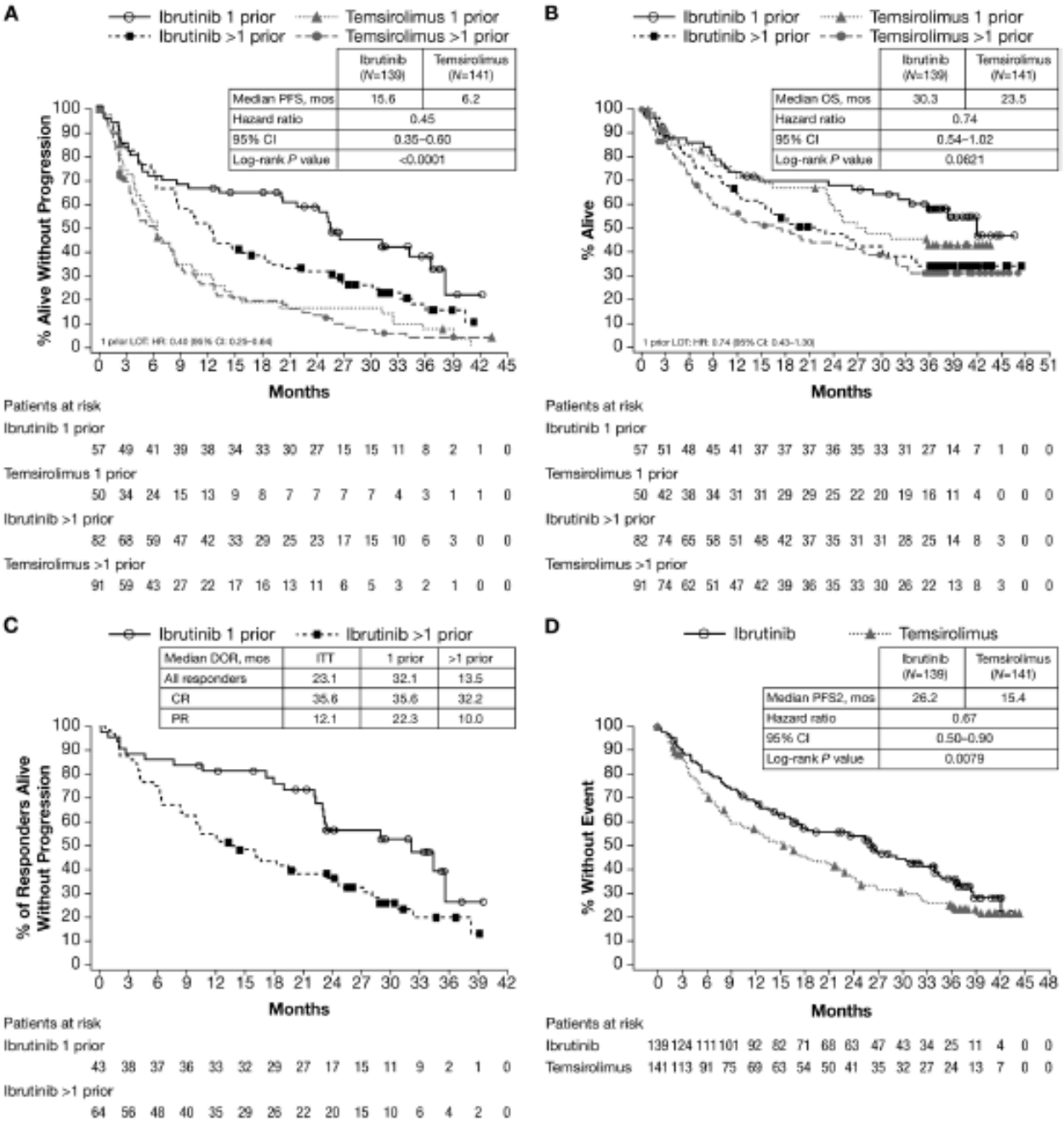
Rule et al., ASH 2017 (abstract 151, oral presentation)

DOR by Best Response and Line of Therapy

		Prior Lines of Therapy	
Median DOR, Months (95% CI)	**Overall (n = 258)**	1 (n = 77)	> 1 (n = 181)
Overall (n = 258)	22.2 (16.5-28.8)	34.4 (23.1-NE)	16.0 (12.9-23.5)
CR (n = 98)	55.7 (55.7-NE)	55.7 (33.1-NE)	NE (40.7-NE)
PR (n = 160)	10.4 (7.7-14.9)	22.1 (10.6-34.4)	8.5 (6.2-12.1)

- Median DOR was 4.5 years in patients achieving a CR
- Patients with 1 prior line had 2× longer DOR than patients with > 1 prior line

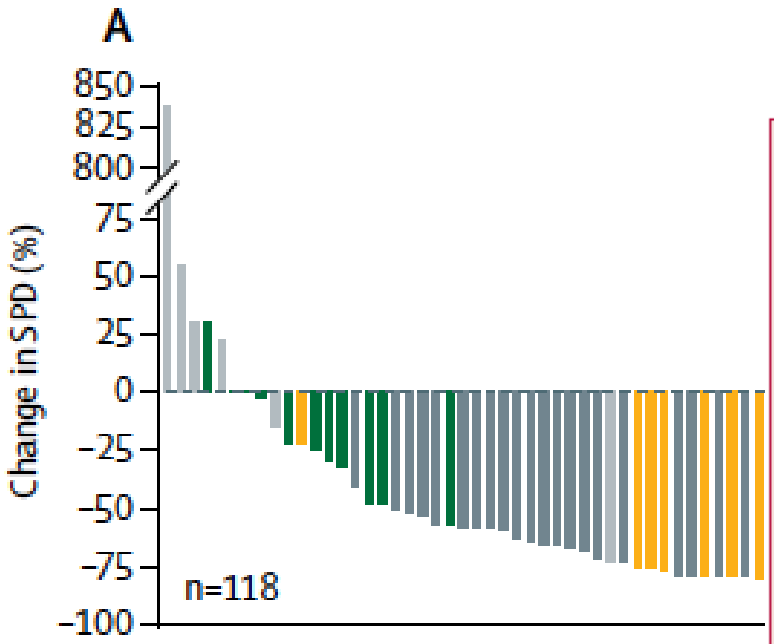
Ibrutinib versus temsirolimus: 3-year follow-up



Rule, S et al, Leukemia, 2018

WHAT ABOUT OTHER BTK‘S?

ACE-LY-004: Response



Progressive disease

	Investigator-assessed response	IRC-assessed response
Overall response (complete response + partial response)	100 (81%; 73–87)	99 (80%; 72–87)
Best response		
Complete response	49 (40%; 31–49)	49 (40%; 31–49)
Partial response	51 (41%; 32–50)	50 (40%; 32–50)
Stable disease	11 (9%; 5–15)	9 (7%; 3–13)
Progressive disease	10 (8%; 4–14)	11 (9%; 5–15)
Not evaluable	3 (2%; 1–7)	5 (4%; 1–9)

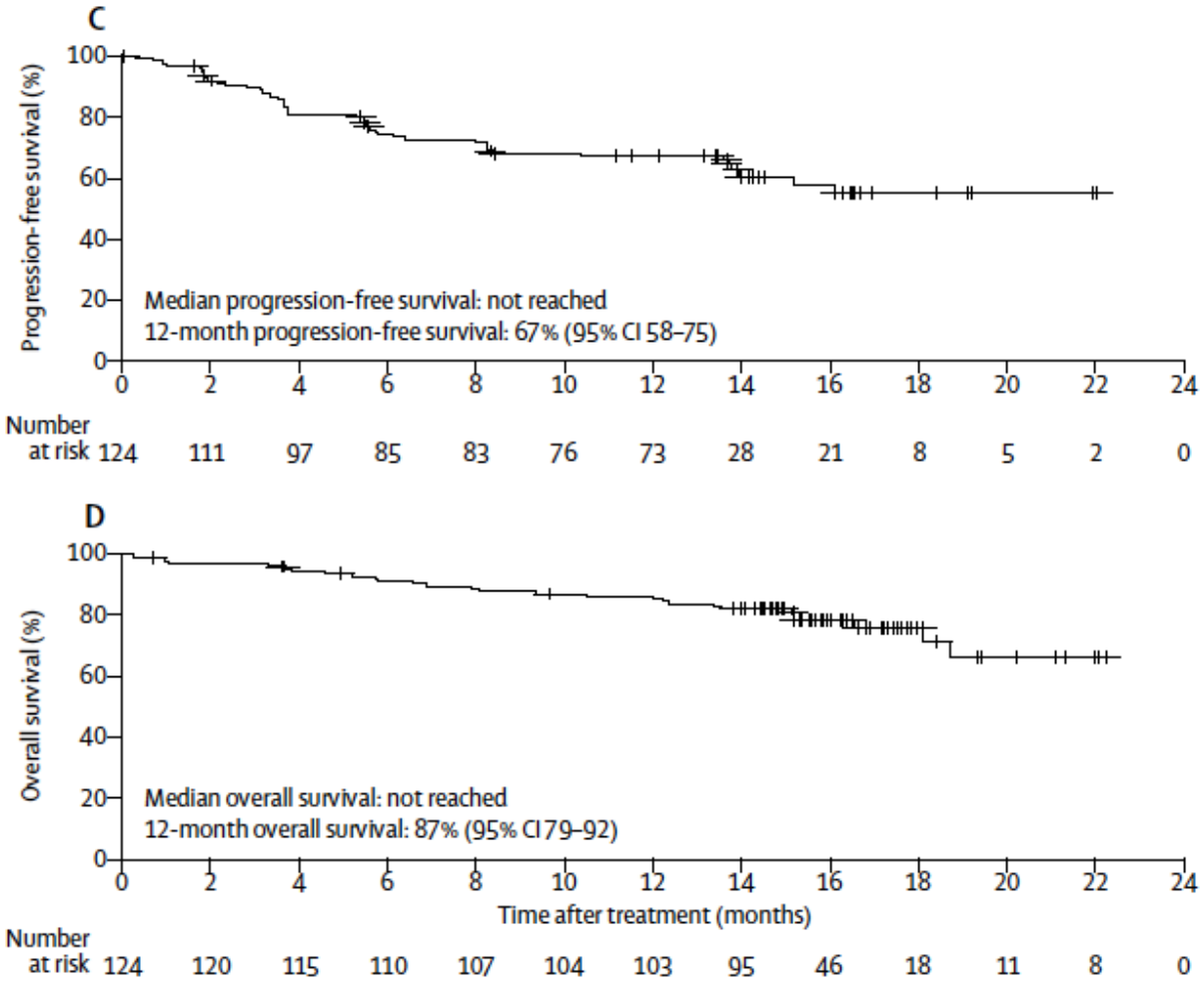
Data are n (%; 95% CI). Overall response and best response according to the Lugano Classification[14] based on assessment by the investigator (primary endpoint) and an independent review committee (secondary endpoint). Patients without post-baseline disease assessment were not evaluable. IRC=independent review committee.

Table 2: **Investigator-assessed and IRC-assessed responses**

*Per 2014 Lugano Classification. †Best response NE in 3 pts (2
6 pts excluded (n = 4, early PD by evidence other than CT; n =

Wang M, et al. 2018, Lancet Oncol

ACE-LY-004: PFS / OS



Wang M, et al. 2018, Lancet Oncol

ACE-LY-004: AEs of Clinical Interest

	All grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5*
Most common events†						
Headache	47 (38%)	30 (24%)	15 (12%)	2 (2%)	0	0
Diarrhoea	38 (31%)	21 (17%)	13 (10%)	4 (3%)	0	0
Fatigue	34 (27%)‡	24 (19%)	8 (6%)	1 (1%)	0	0
Myalgia	26 (21%)	19 (15%)	6 (5%)	1 (1%)	0	0
Cough	24 (19%)	21 (17%)	3 (2%)	0	0	0
Nausea	22 (18%)	12 (10%)				
Pyrexia	19 (15%)	14 (11%)				
Most common grade 3 or worse events§						
Anaemia	15 (12%)	1 (1%)				
Neutropenia	13 (10%)	0				
Pneumonia	7 (6%)	0				

Data are n (%). *Only one grade 5 event (aortic stenosis) was r
‡Includes one case of fatigue without grading. §Reported in ≥

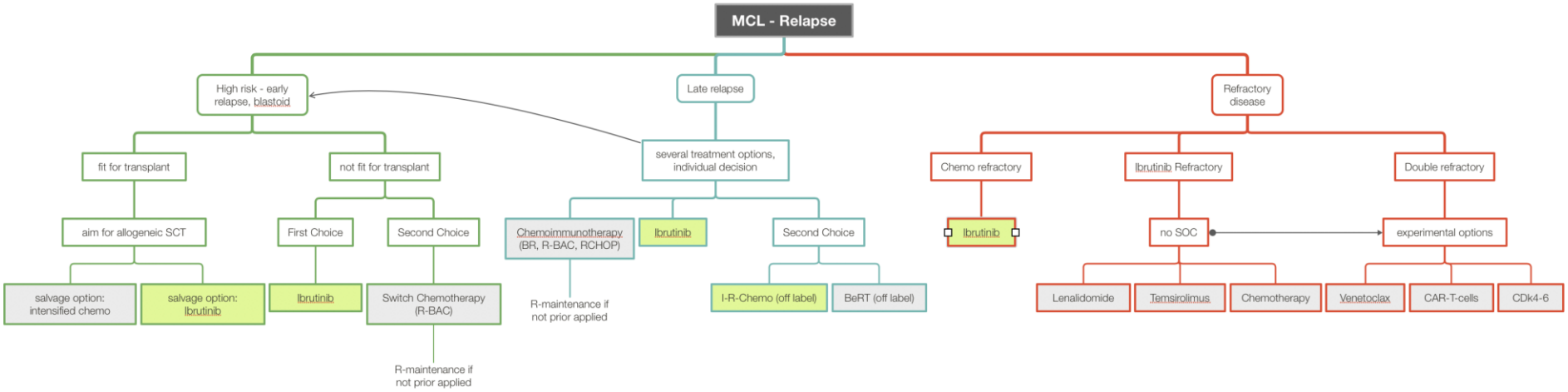
Table 3: **Adverse events**

Adult MCL pts with translocation t(11;14)(q13;q32) and/or cyclin D1 overexpression; relapsed/refractory to 1-5 prior tx; measurable nodal disease (≥ 1 LN with longest diameter ≥ 2 cm); ECOG PS 0-2; **no notable CVD*;**
no concurrent use of warfarin/equivalent vitamin K antagonists, no prior BTK inhibitors
(N = 124)

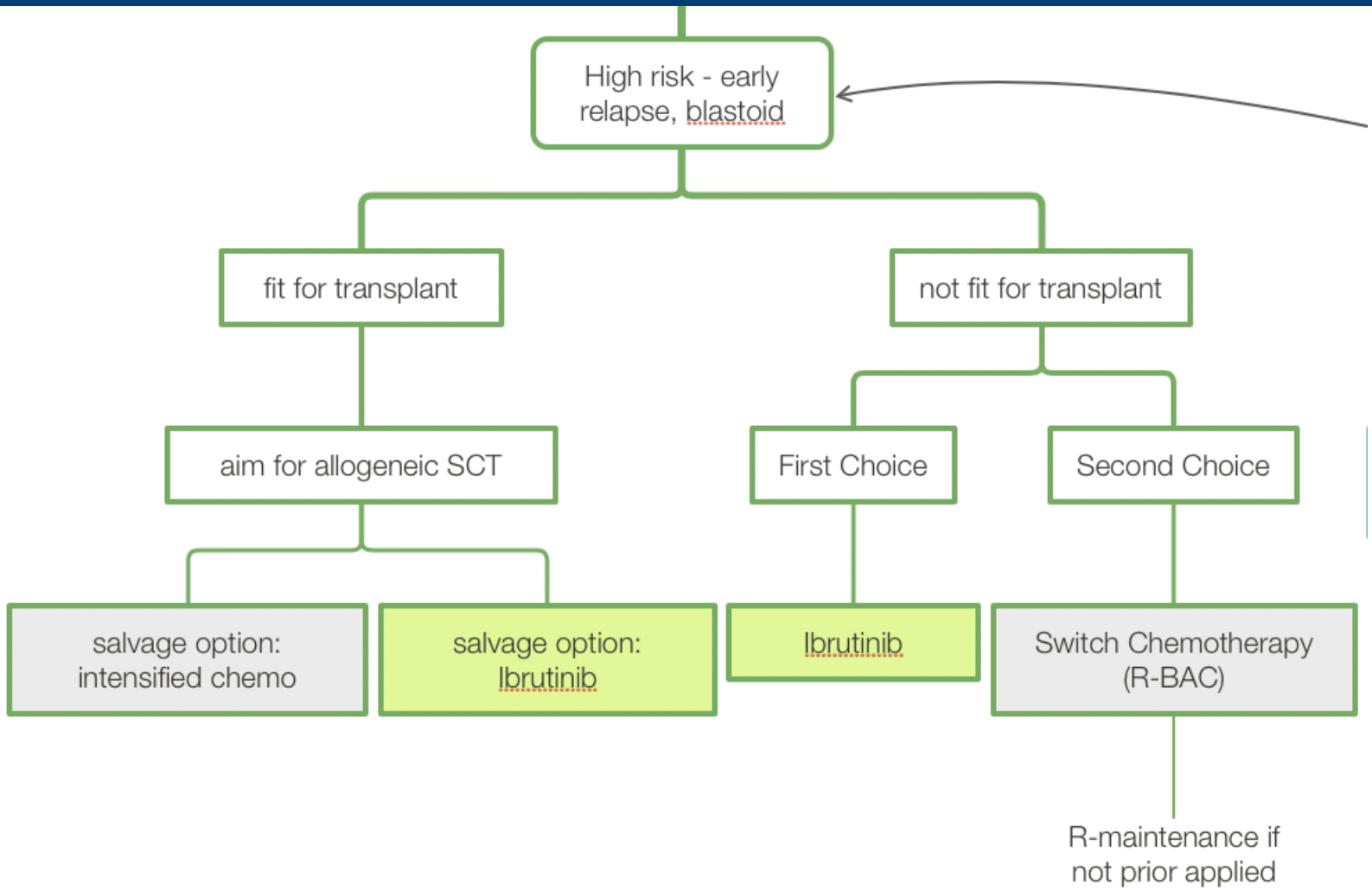
Wang M, et al. 2018, Lancet Oncol

CONSEQUENCES

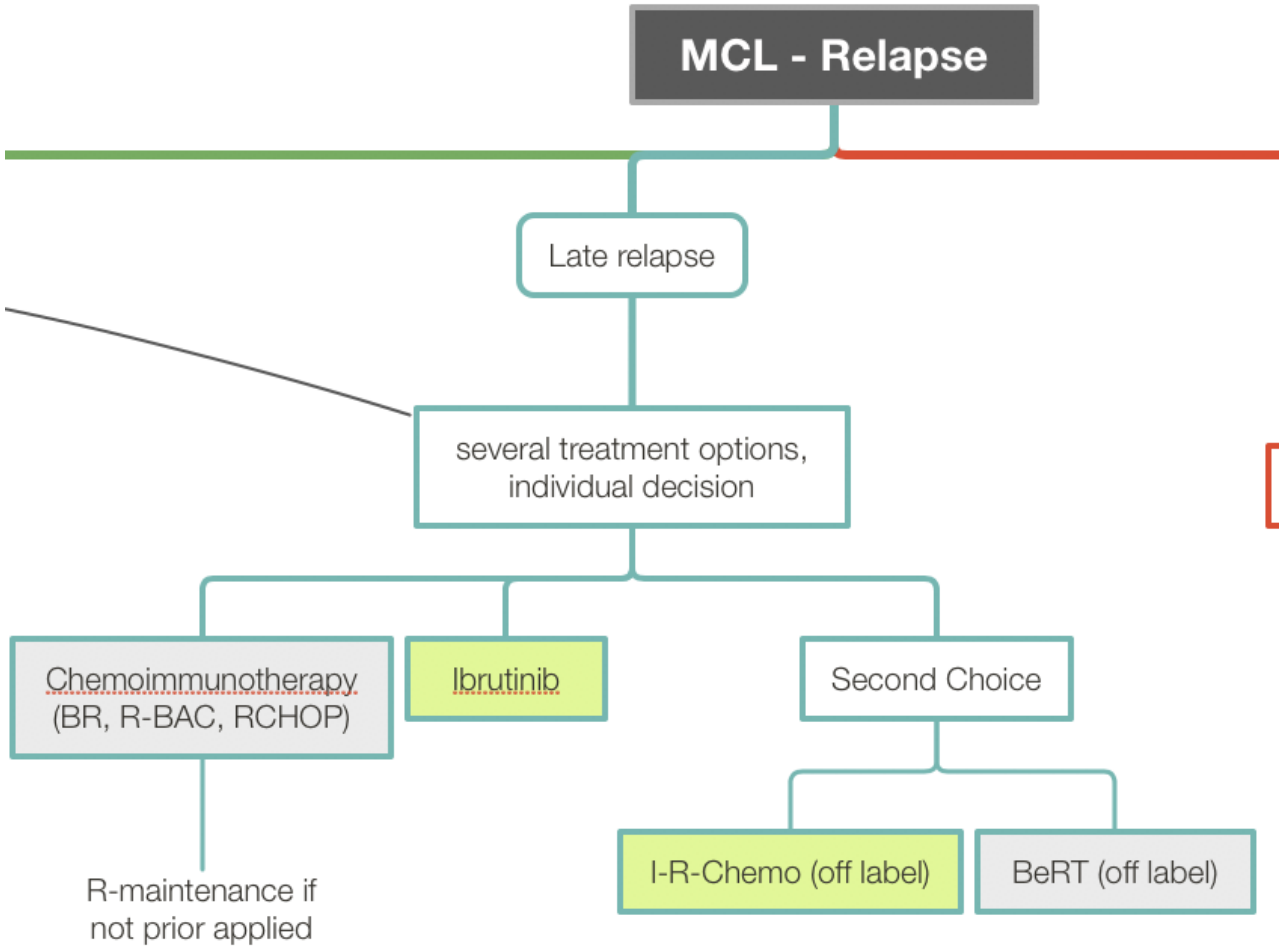
Different relapse strategies



Early / High risk relapse

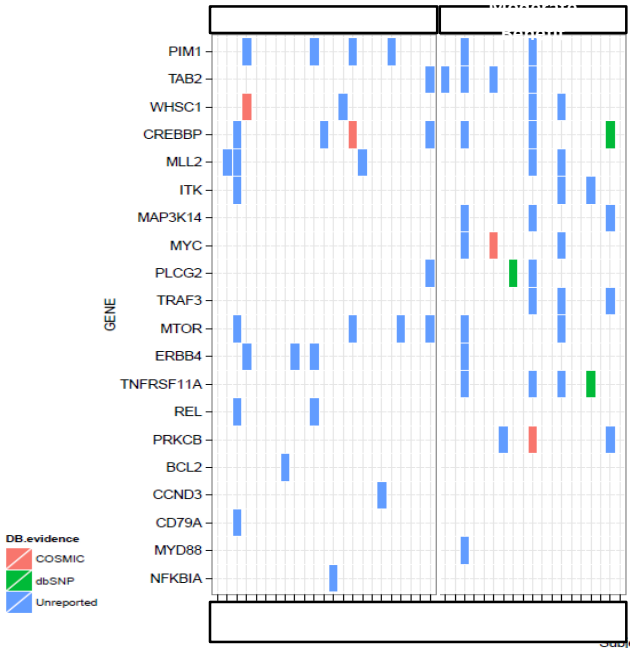


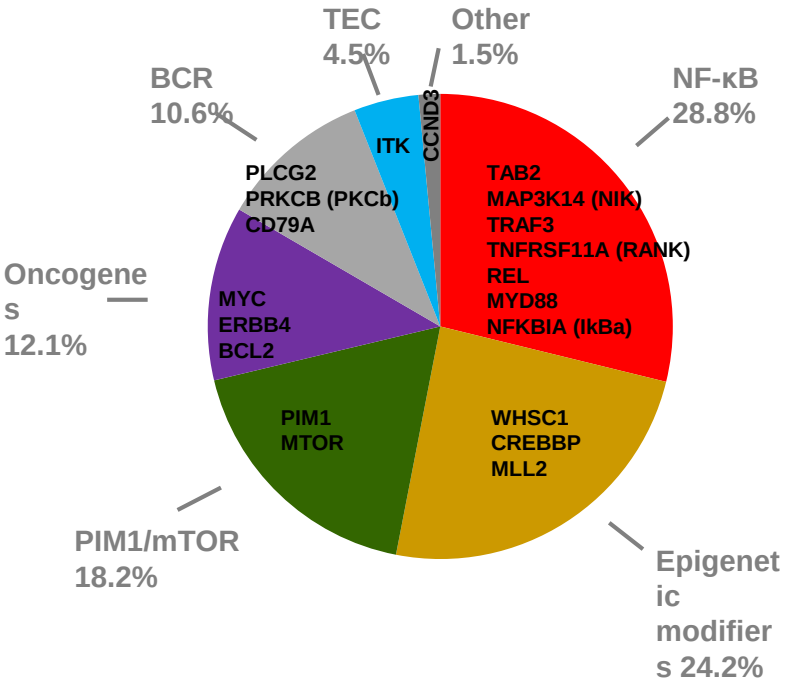
Late relapse



IBRUTINIB FAILURE / REFRACTORY DISEASE

Mutations in patients with moderate/missing clinical benefit





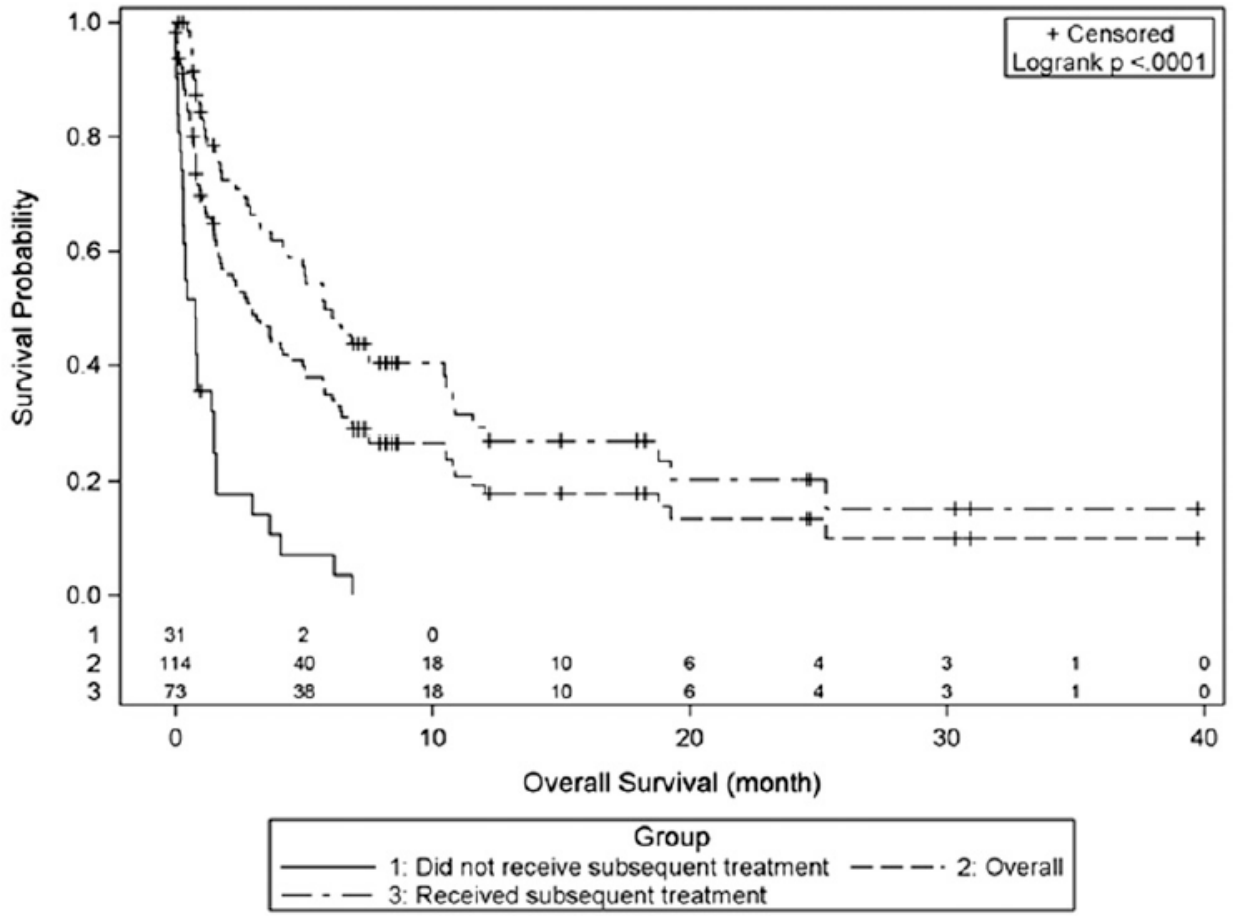
Sequencing analyses revealed a number of novel mutations in patients with primary resistance

Most included several genes involved in NF-κB signaling, PIM1 kinase/mTOR pathway, or epigenetic modifiers

Balasubramanian et al., ASH 2014; abstract 78 (oral presentation)

Table 2. Patient characteristics before first postibrutinib treatment

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		
Unknown		
Ki67 >30%	11	
Subsequent treatment		
Rituximab		
Lenalidomide		
Cytarabine		
Bendamustine		
Bortezomib		
Anthracycline		
PI3K inhibitor		

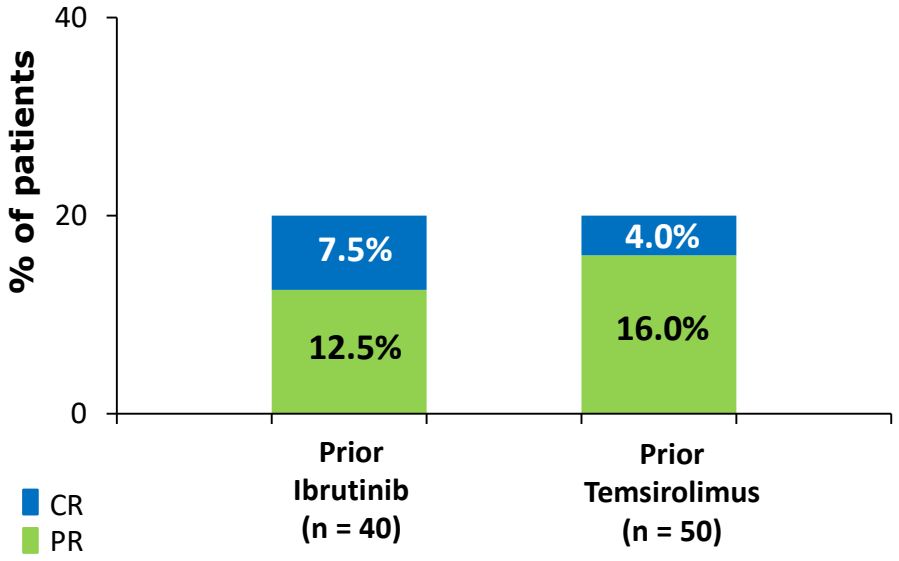


Martin et al, Blood, 2016: Postibrutinib outcomes in patients with mantle cell lymphoma

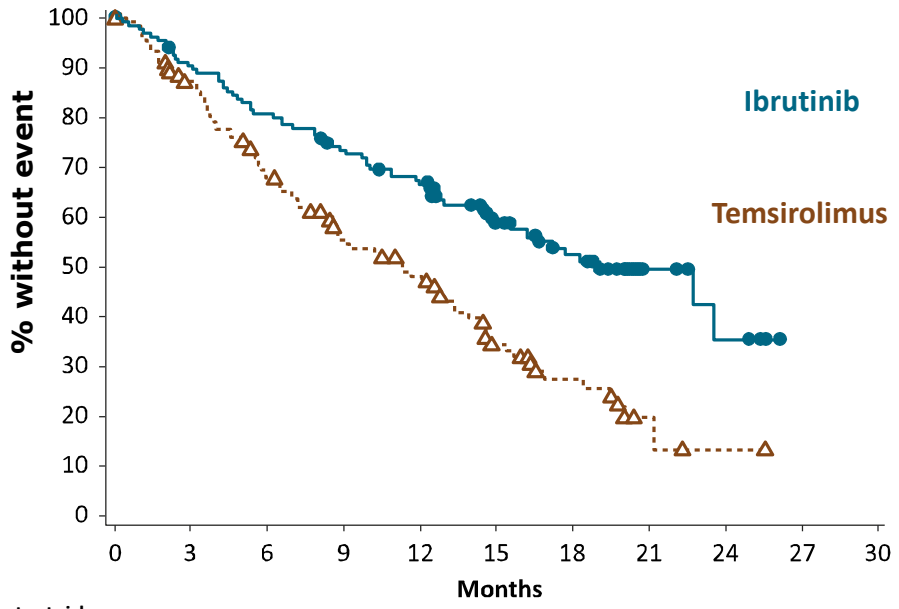
Summary of 1st Subsequent Anti-cancer Therapies in Patients Randomized to Ibrutinib

	N=63
BR	15 (23.8%)
BR + Bortezomib	1 (1.6%)
BR + Chemo + SCT	3 (4.8%)
Bendmustine	3 (4.8%)
Bortezomib	1 (1.6%)
Chemo	15 (23.8%)
Ibrutinib	1 (1.6%)
Lenalidomide	3 (4.8%)
R-chemo + Temsirolimus	1 (1.6%)
R-chemo	9 (14.3%)
R-chemo + Bortezomib	2 (3.2%)
R-chemo + Lenalidomide	1 (1.6%)
Steroid	3 (4.8%)
Temsirolimus	5 (7.9%)

Efficacy of subsequent anticancer therapy in I-failure



Progression-free survival 2 (PFS2)[a]



Patients at risk

Ibrutinib	139	123	110	98	88	54	38	10	5	0	0
Temsirolimus	141	109	84	60	49	28	16	3	1	0	0

	Ibrutinib	Temsirolimus
Median PFS2 (months)	19.1	11.3
HR	0.49	
95% CI	0.36-0.69	
Log-rank *p* value	< 0.0001	

After EXCLUDING patients who received crossover treatment with either drug, ORR was 20% in both groups

Rule et al., ASH 2015 (abstract 469, oral presentation)

Wang et al. Journal of Hematology & Oncology (2017) 10:171
DOI 10.1186/s13045-017-0537-5

Journal of
Hematology & Oncology

RESEARCH Open Access

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[11] and Peter Martin[12]

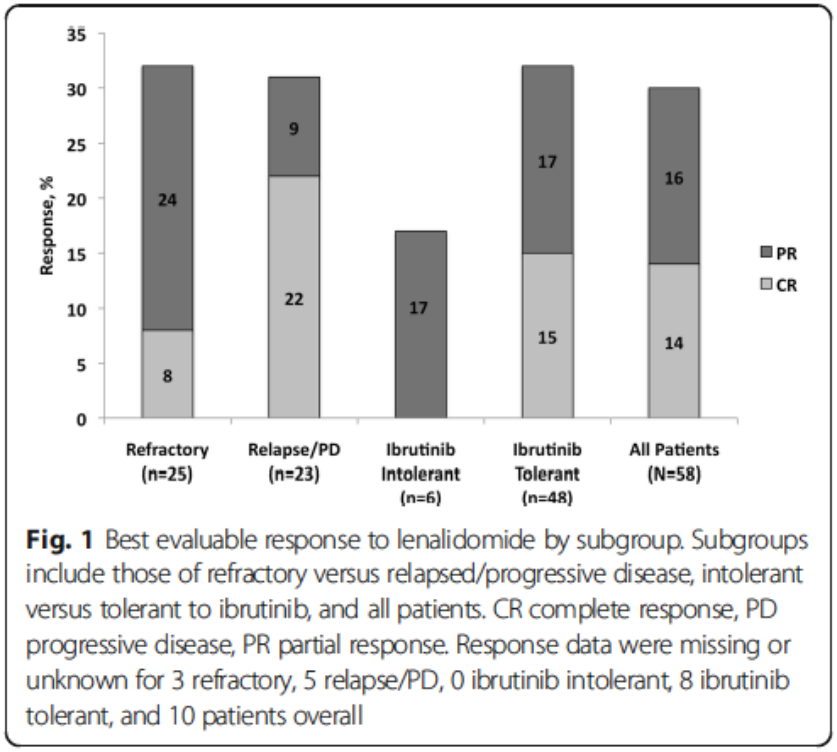


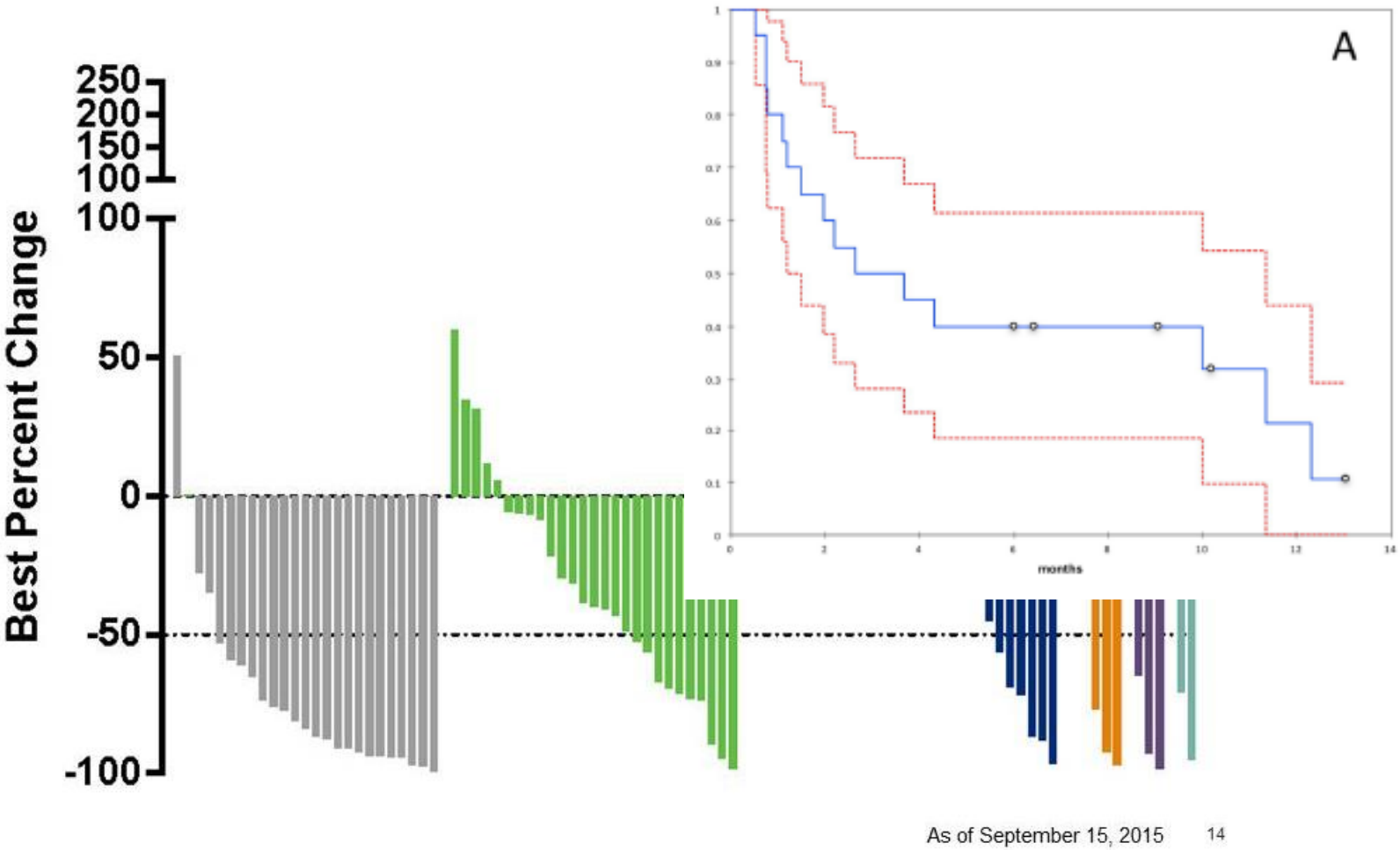
Fig. 1 Best evaluable response to lenalidomide by subgroup. Subgroups include those of refractory versus relapsed/progressive disease, intolerant versus tolerant to ibrutinib, and all patients. CR complete response, PD progressive disease, PR partial response. Response data were missing or unknown for 3 refractory, 5 relapse/PD, 0 ibrutinib intolerant, 8 ibrutinib tolerant, and 10 patients overall

Table 4 Lenalidomide treatment exposure (safety population)

	L (n = 13)	L + R (n = 11)	L + other (n = 34)	Overall (N = 58)
Lenalidomide treatment duration, weeks				
Median	8.4	14.0	7.0	8.4
Range	0.4 to 30.0	0.9 to 37.9	1.1 to 77.9	0.4 to 77.9
Number of lenalidomide cycles				
Median	2.0	2.0	1.0	2.0
Range	1.0 to 7.0	1.0 to 9.0	0.0 to 11.0	0.0 to 11.0
Duration of other therapy combined with lenalidomide, weeks				
Median	NA	8.3	7.2	7.4
Range	NA	0.1 to 35.9	0.7 to 77.7	0.1 to 77.7

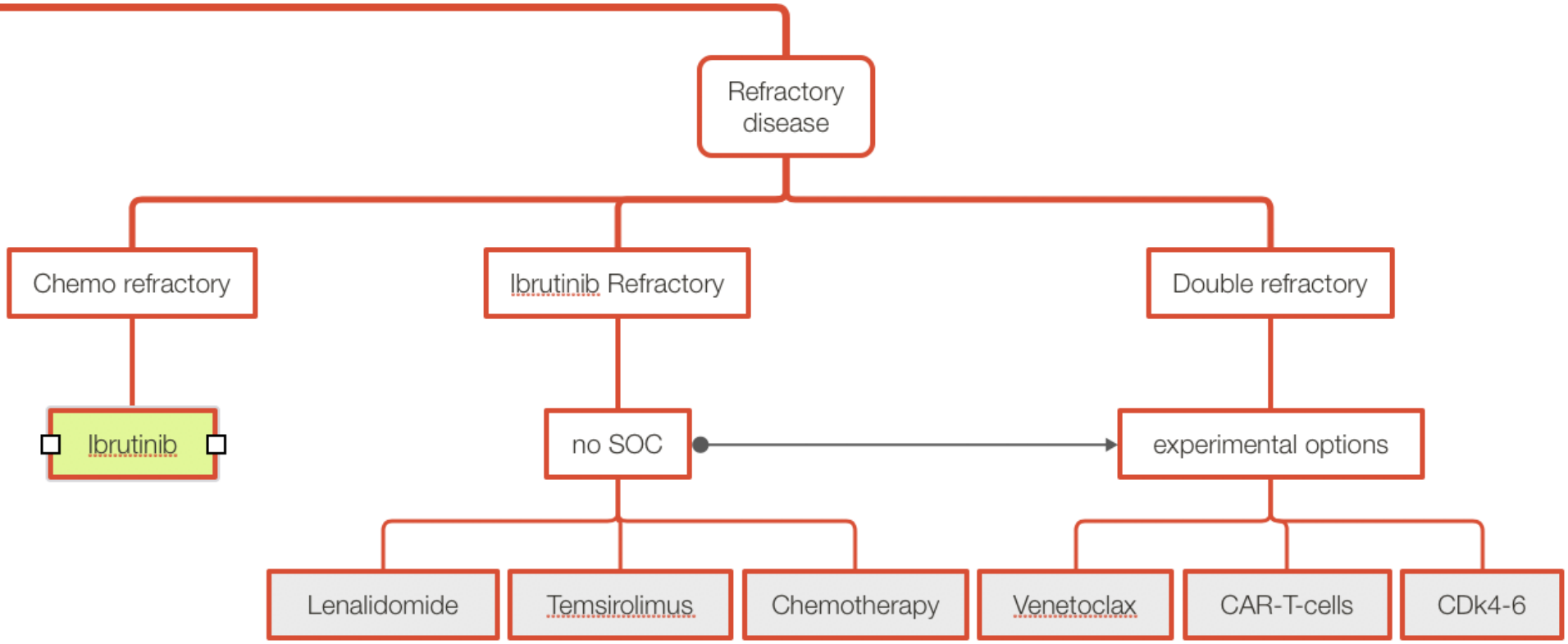
L lenalidomide, *L + R* lenalidomide plus rituximab, *NA* not applicable

ABT-199



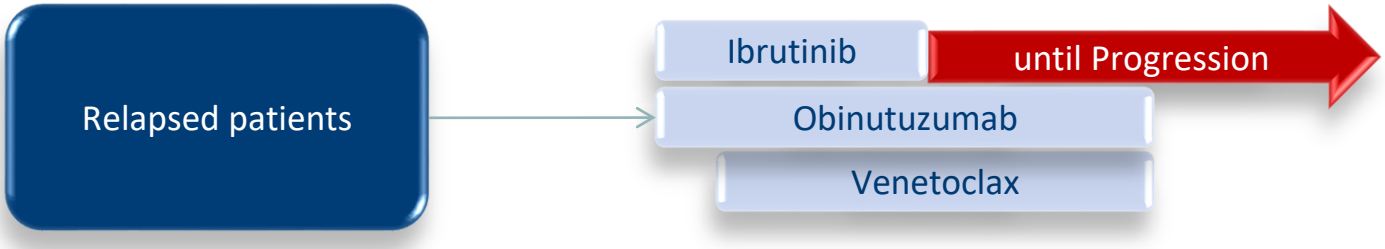
De Vos S et al. Abstract No. 255
Eyre et al, 2018, Haematogica

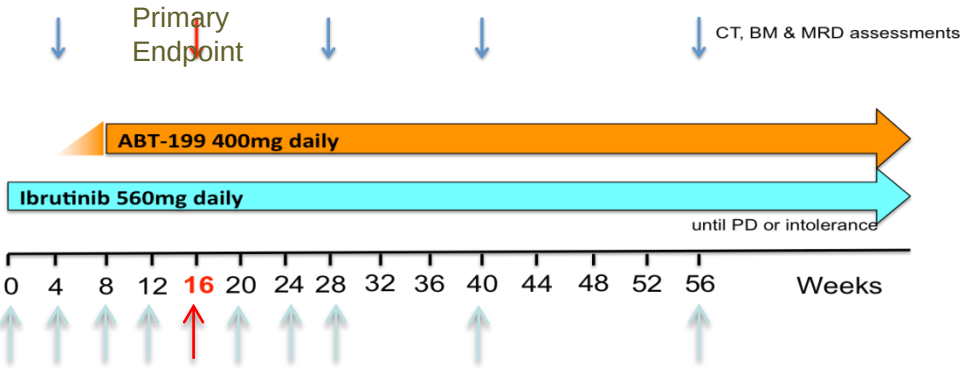
Refractory disease



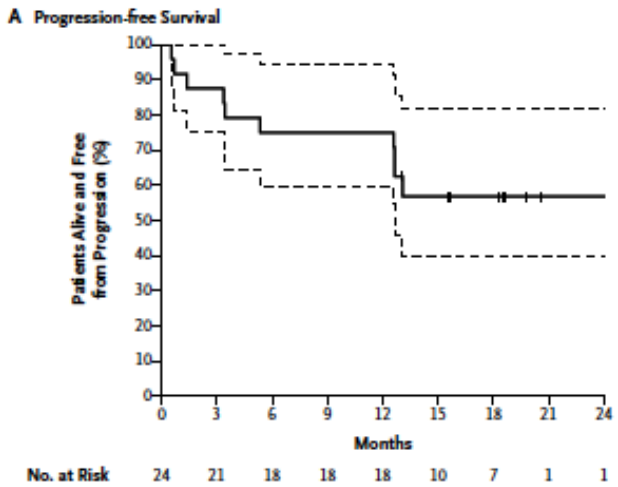
UPCOMING STRATEGIES

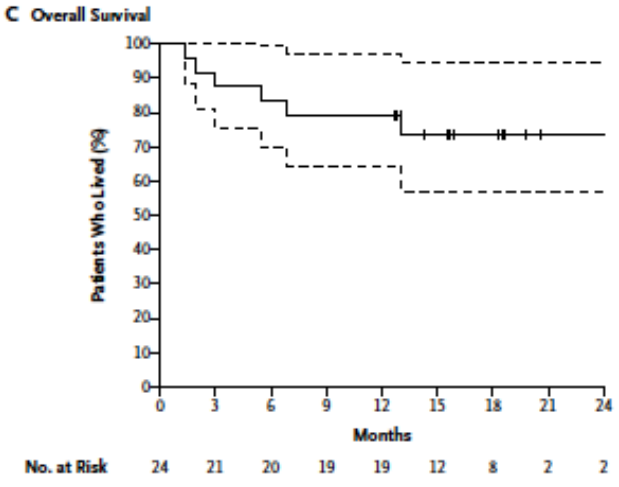
Key Trials: OASIS – AIM -->

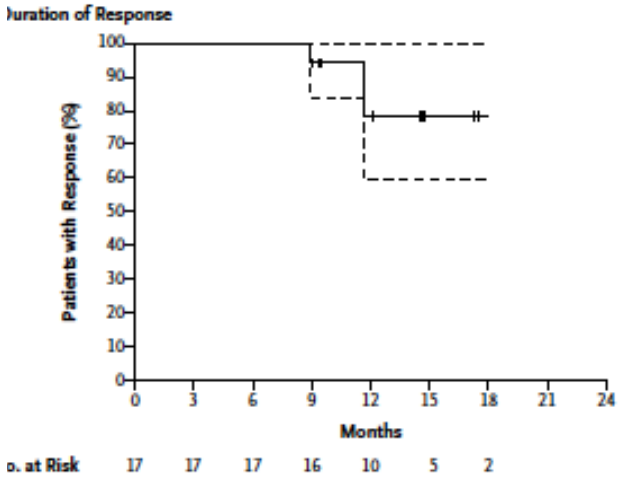




Results







Tam et al, NEJM, 2018

Current protocols

Kinom I	Kinom II	Phase	Site	Author
ABT199	Ibrutinib	preclinical	SWOG	Davids
ABT199	Ibrutinib	I	Melborne	Tam
ABT 199	Ibrutinib, Obinutzumab	I/II	LYSA, BNLI	LeGouill
Palbociclib	Ibrutinib	I	MSKCC	Martin
Ibrutinib	Lenalidomid, Rituximab	I	Nordic	Jerkeman
Ibrutinib	Carfilzomib	I	MDA	Wang
Ibrutinib	Rituximab	I	SAKK	Gine
ABT199	Ibrutinib, Rituximab	II	EMCL	Dreyling, Heß
CAR				

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Safety and tolerability of idelalisib, lenalidomide, and rituximab in relapsed and refractory lymphoma: the Alliance for Clinical Trials in Oncology A051201 and A051202 phase 1 trials

Prof Sonali M Smith, MD, Brandelyn N Pitcher, MS, Prof Sin-Ho Jung, PhD, Prof Nancy L Bartlett, MD, Nina Wagner-Johnston, MD, Steven I Park, MD, Kristy L Richards, MD, Amanda F Cashen, MD, Anthony Jaslowski, MD, Scott E Smith, MD, Prof Bruce D Cheson, MD, Prof Eric Hsi, MD, Prof John P Leonard, MD

Published: 14 March 2017

Interpretation

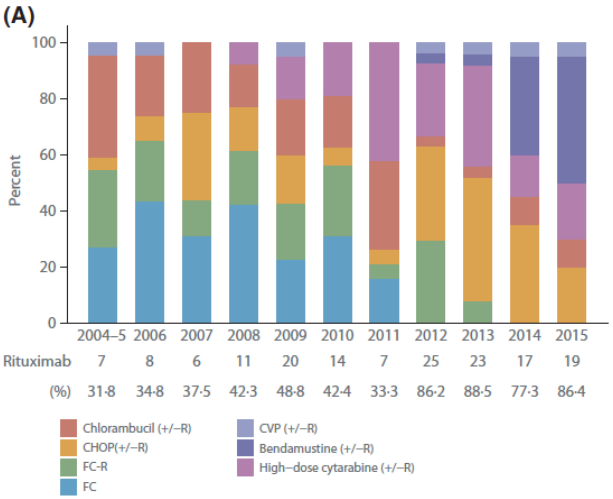
The **combination of idelalisib, lenalidomide, and rituximab** in these trials **is excessively toxic**, and these trials serve as cautionary notes as new combinations are proposed. Off-target effects, drug–drug interactions, and emerging toxicities should be carefully assessed when investigating biological agents in combination and should never be done outside of a clinical trial setting.

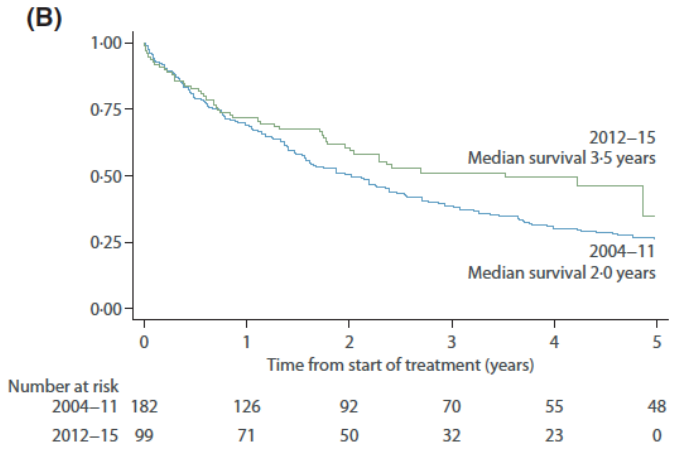
http://www.thelancet.com/journals/lanhae/issue/vol4no4/PIIS2352-3026(17)X0004-5

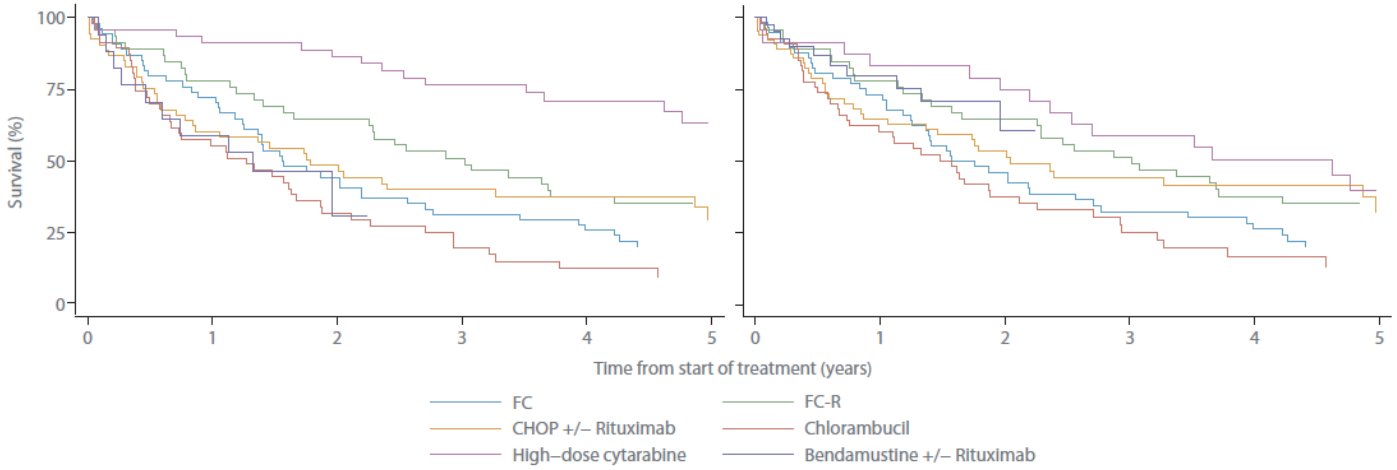
Summary

- First line regimen in MCL have been optimized in recent years with the introduction of AraC, Rituximab, HDT and maintenance
- Novel targeted agents – namely Ibrutinib – have changed the fate of relapsed disease
- Selection of optimal treatment has to be performed on an individual basis – chemo-resistance urges for novel agents
- Evaluation of combination of established and new options is ongoing and may result in further improvement of prognosis

Impact of „novel“ agents in MCL 2004-2015







Smith, A et al, BJH; 2018

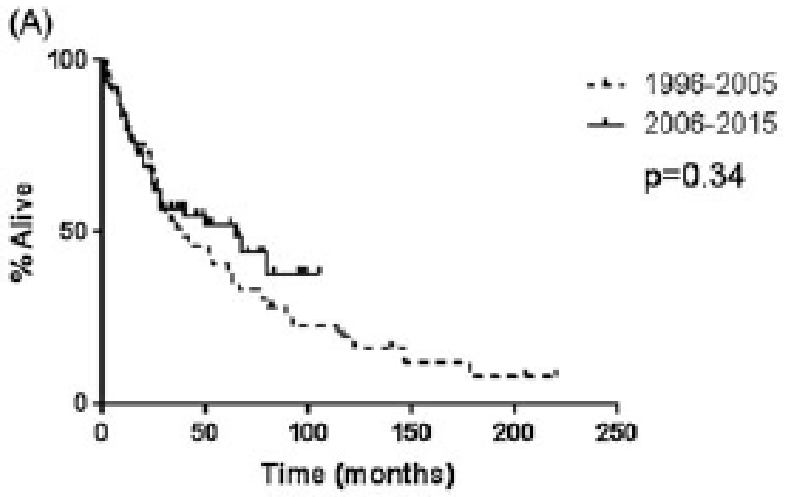
Received: 6 October 2017 | Revised: 28 October 2017 | Accepted: 29 December 2017

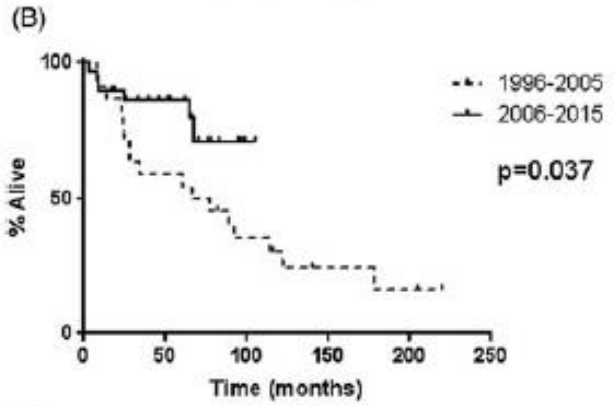
DOI: 10.1002/hon.2495

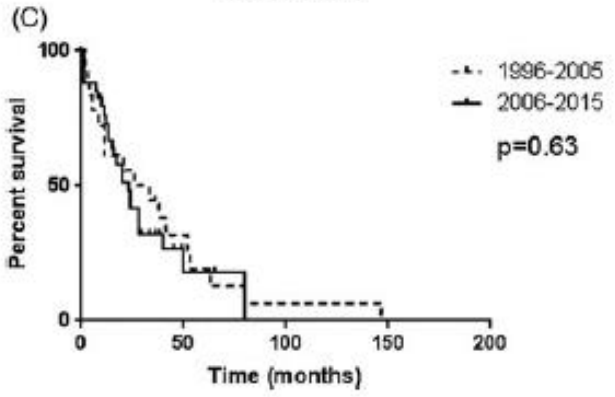
LETTER TO THE EDITOR

WILEY

Population-based study of mantle cell lymphoma:







Joshi et al, Hematol Oncol. 2018 Jan 24. doi: 10.1002/hon.2495.

Thank you – Gracie!