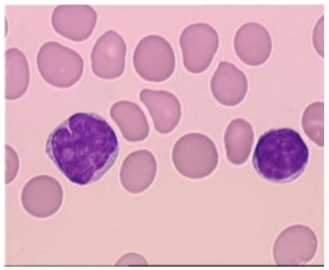
LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
MEDIZINISCHE KLINIK UND POLIKLINIK III
DIREKTOR: PROF. DR. M. VON BERGWELT

MANTLE CELL LYMPHOMA:

BTKI-1: IBRUTINIB



German Lymphoma Alliance

European MCL Network

Mantle Cell Lymphoma
Disclosures

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https://bureaucracyincts.eu

Research Support (institution)	**Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche**
Employee	**-**
Major Stockholder	**-**
Speakers Bureau	**-**
Speakers Honoraria	**Amgen, Astra Zeneca, Bayer, BMS/Celgene, Gilead/Kite, Incyte, Janssen, Novartis, Roche**
Scientific Advisory Board	**Astra Zeneca, Bayer, Beigene, BMS/Celgene, Genmab, Gilead/Kite, Incyte, Janssen, Lilly/Loxo, Morphosys, Novartis, Roche**

Relapsed mantle cell lymphoma
Overall survival (n=404)

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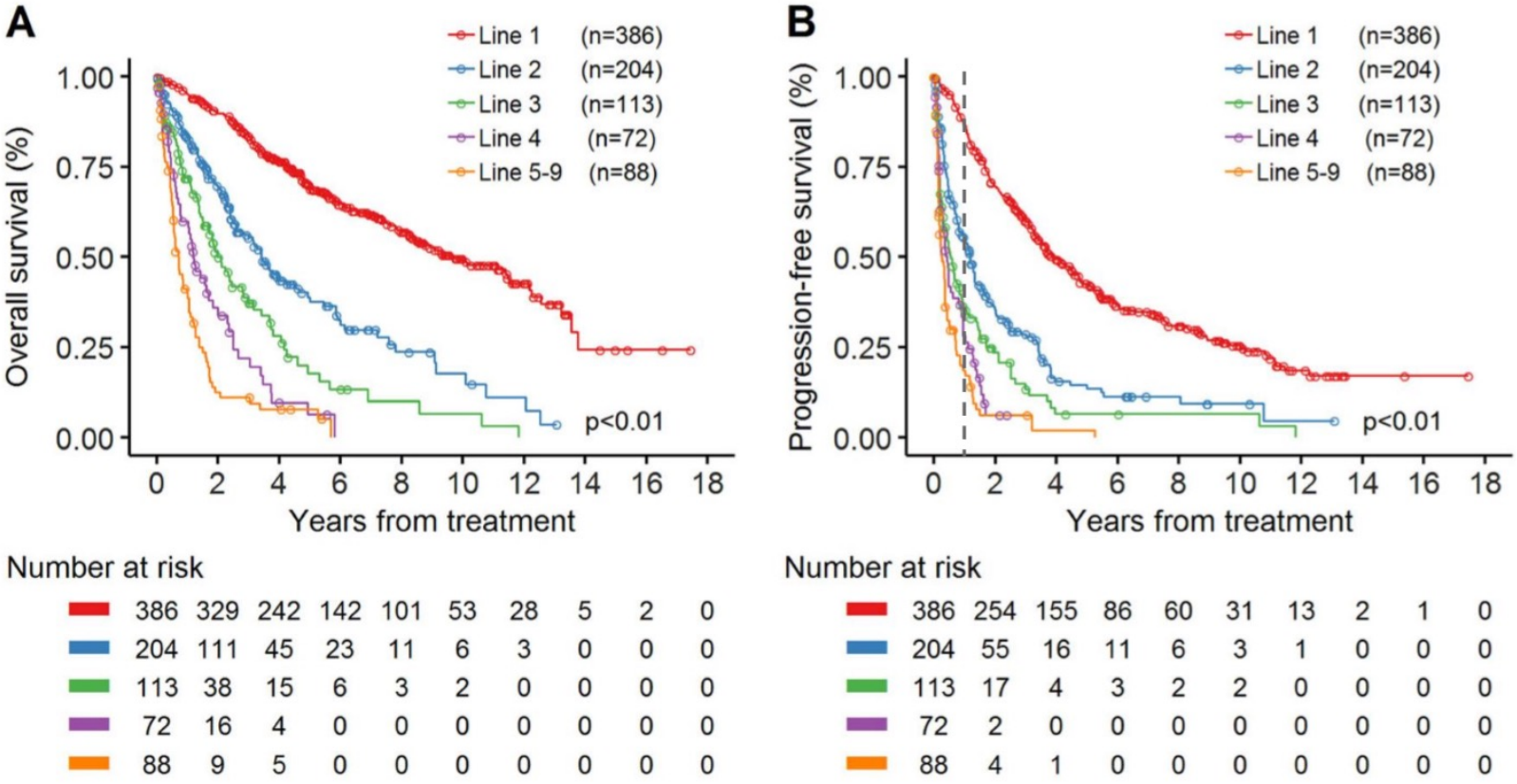

Kumar, Blood Cancer 2019


It was 20 yrs ago today,
When Sgt Pepper taught the band to play
SGT. PEPPERS LONELY HEARTS CLUB BAND,
SGT PEPPER'S LONELY HEARTS CLUB BAND
Cellophane flowers of yellow and green
and Billy plays on
within you and
without you.
I read the news today, oh boy.

Mantle cell lymphoma
Therapeutic algorithm

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young patient (≤65)	elderly patient (>65)	compromised patient
First line treatment		
dose-intensified immuno-chemotherapy (R-CHOP, high dose Ara-C) ⇒ Autologous SCT ⇒ Rituximab maintenance	conventional immuno-chemotherapy (VR-CAP, R-CHOP,BR, R-BAC) ↓ Rituximab maintenance	Best supportive care? R-Chlorambucil BR (dose-reduced) R-CVP
1. relapse		
immuno-chemotherapy (R-BAC, BR) or targeted approaches ↓ discuss: - allogeneic SCT	immuno-chemotherapy (BR, R-BAC) or targeted approaches ↓ discuss: - Rituximab maintenance - radioimmunotherapy	Immuno-chemotherapy (BR) or targeted approaches
higher relapse		
Targeted approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination) Alternatively: repeat previous therapy (long remissions)		

Dreyling, ESMO CR MCL 2017 (updated)

Mantle cell lymphoma
B-cell receptor signal pathway

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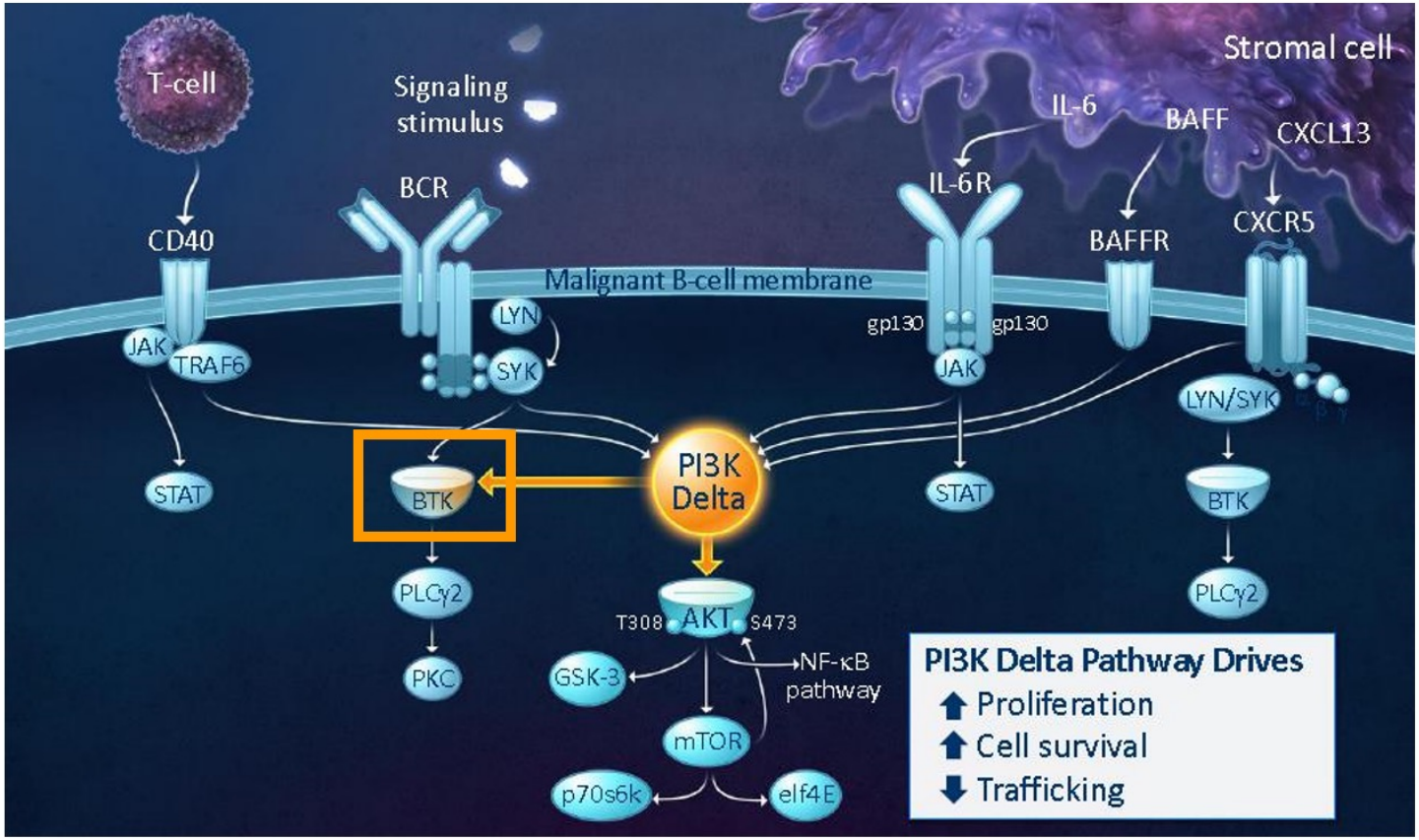
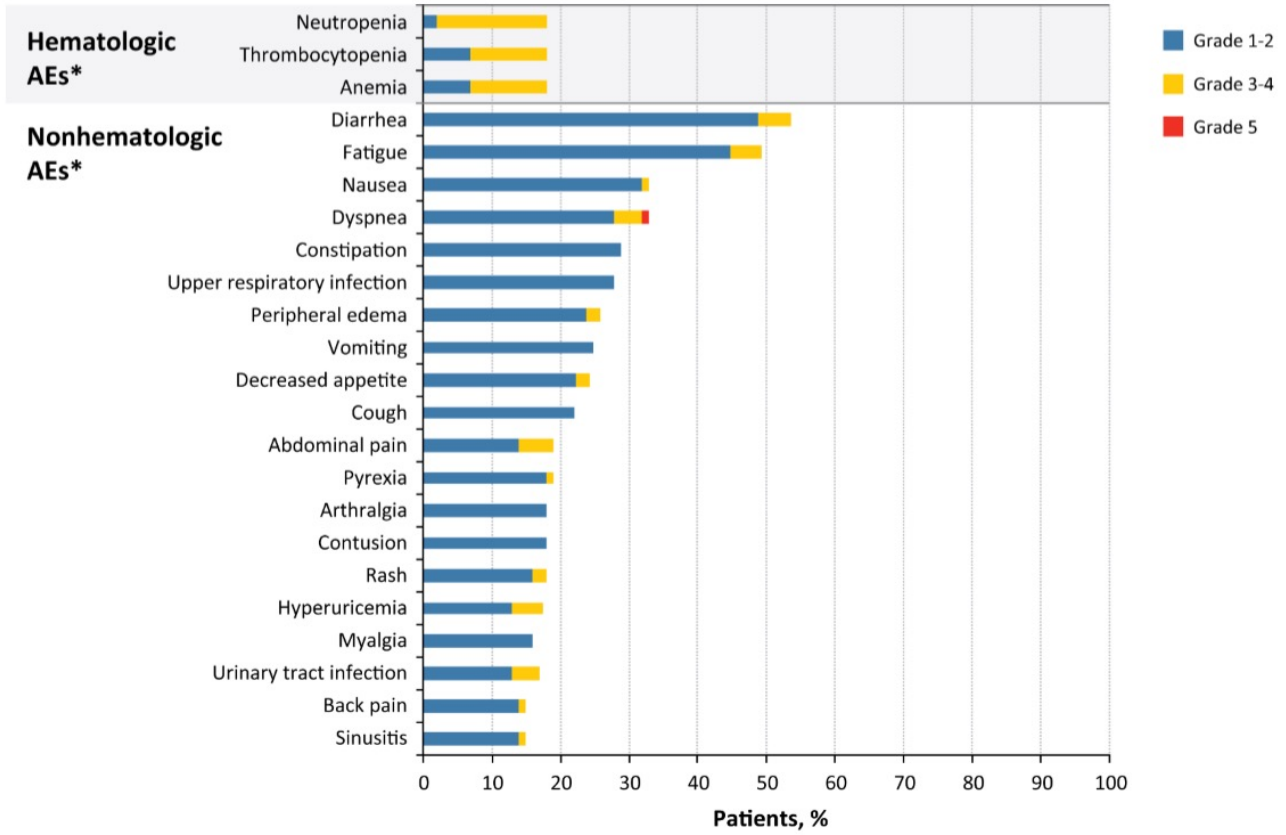


BTK inhibitor Ibrutinib

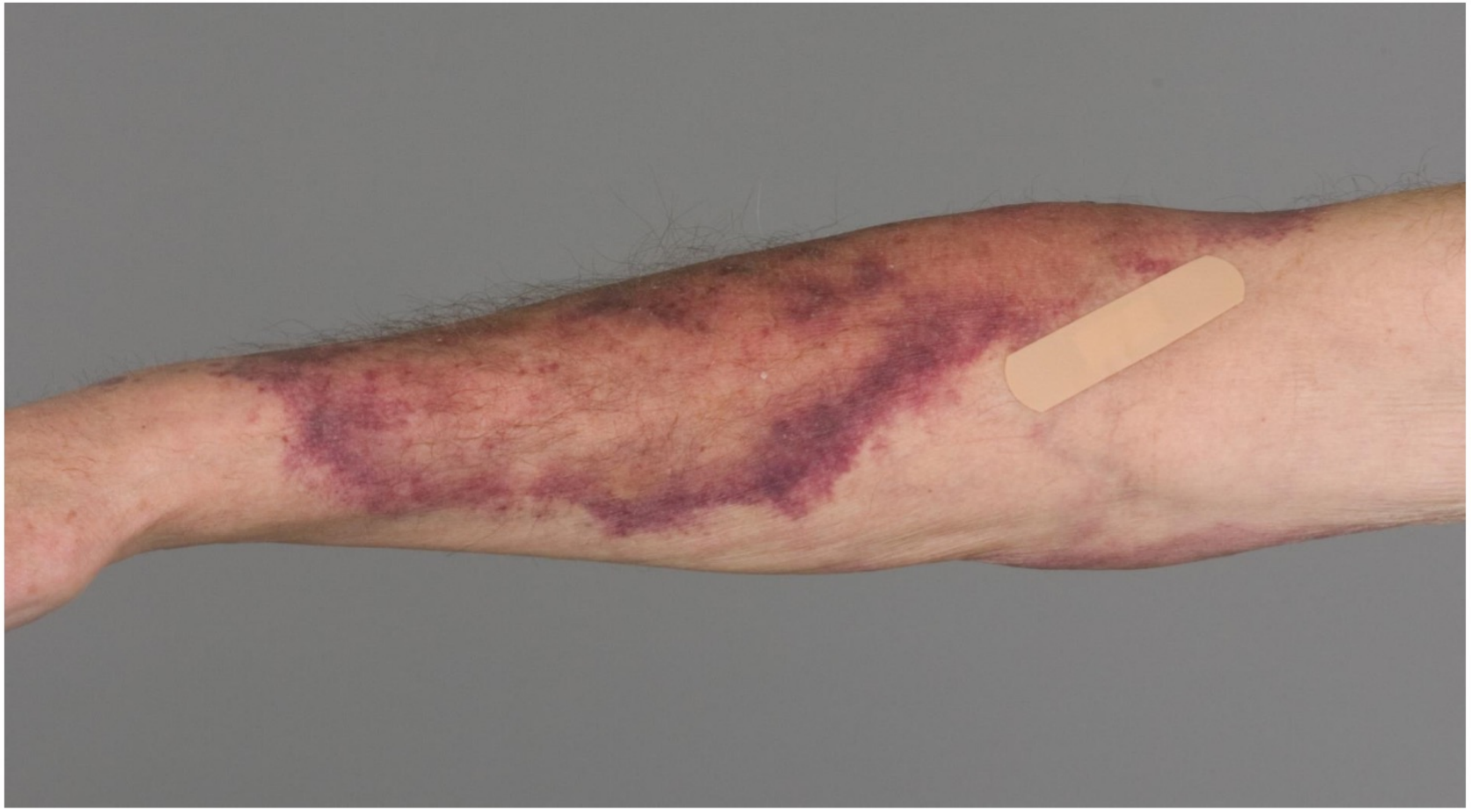
Adverse events (>15%)



Wang, NEJM 2013

Ibrutinib in relapsed MCL

Bleeding events

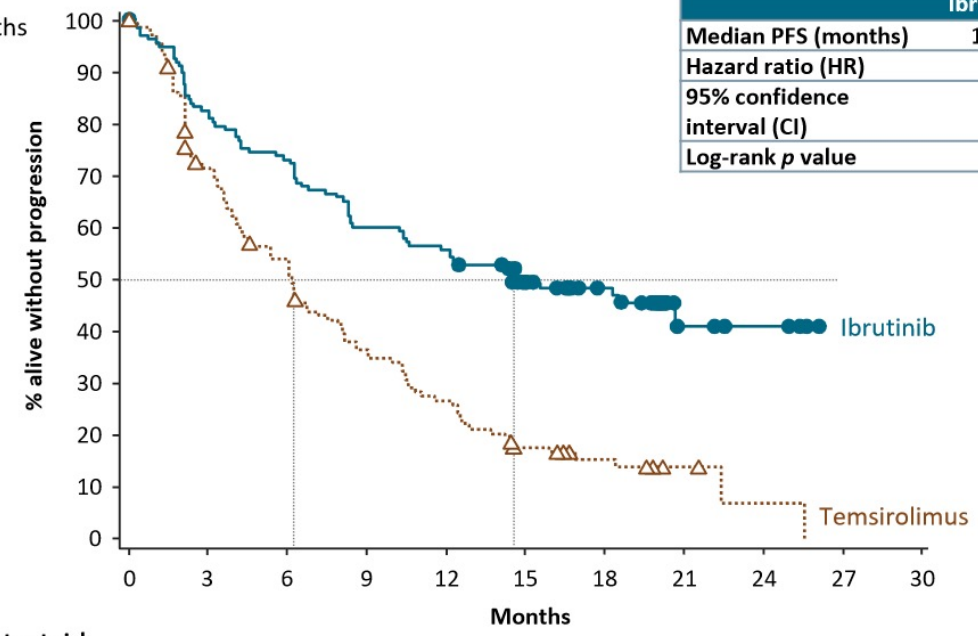


Courtesy of S Rule

Ibrutinib vs. Temsirolimus
Progression-free survival

ITT population
Median follow-up: 20 months

	Ibrutinib	Temsirolimus
Median PFS (months)	14.6	6.2
Hazard ratio (HR)	0.43	
95% confidence interval (CI)	0.32-0.58	
Log-rank *p* value	< 0.0001	



Patients at risk

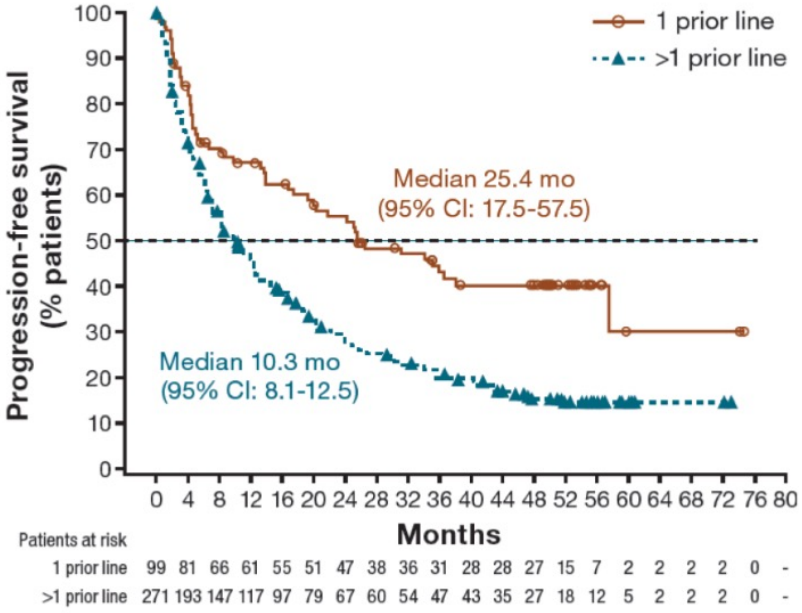
Ibrutinib	139	114	101	83	77	45	34	8	5	0	0
Temsirolimus	141	93	69	45	33	19	11	3	1	0	0

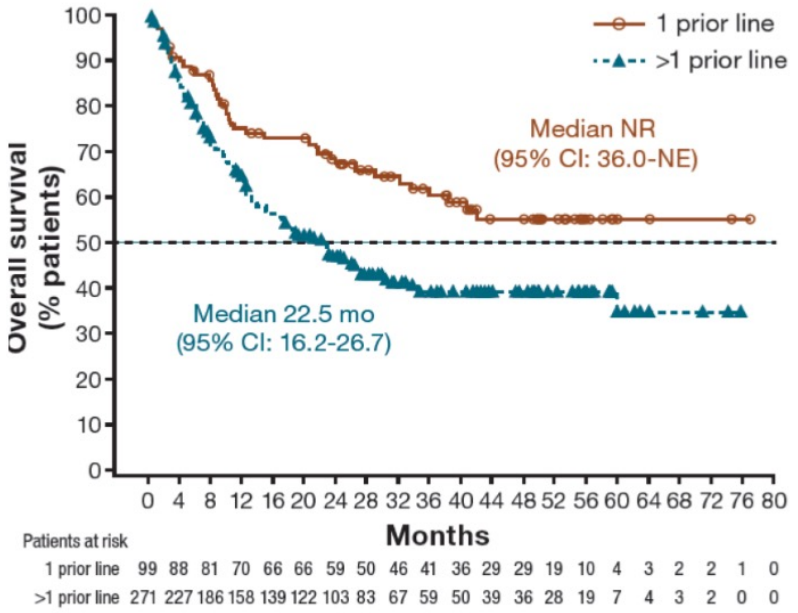
At a 2-year landmark, the PFS rate was 41% for ibrutinib versus 7% for temsirolimus

Investigator-assessed HR for ibrutinib versus temsirolimus was 0.43 (95% CI, 0.32-0.58)

Dreyling, Lancet 2015

Ibrutinib in relapsed MCL
Progression-free survival

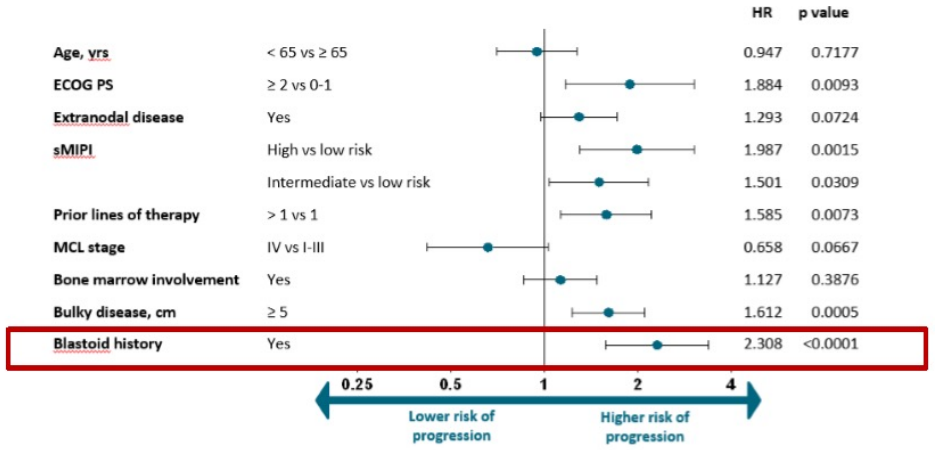




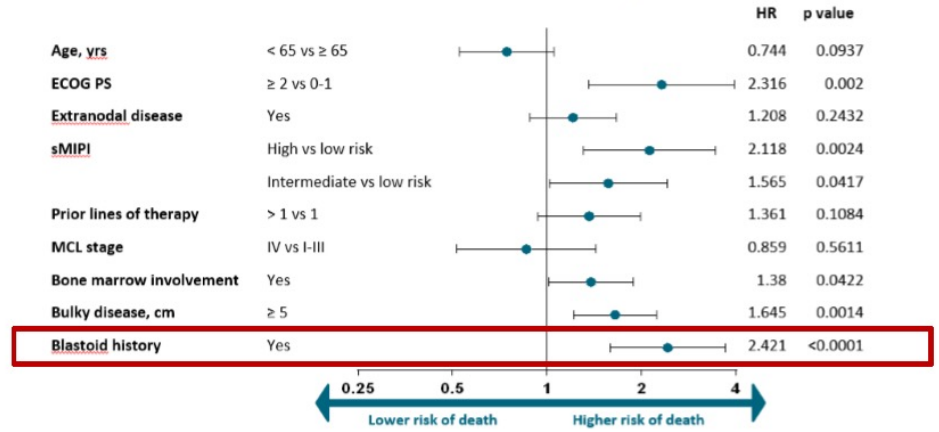
Rule, Haematologica 2019

Ibrutinib in relapsed MCL
Multivariate analysis of prognostic factors

PFS



OS



Rule, Brit J Haematol 2017 (p53: Rule, Haematologica 2019; Ki-67: Wang, Lancet Oncol 2016)

Ibrutinib in relapsed MCL (POD 24)

Progression-free survival

MANTLE-FIRST

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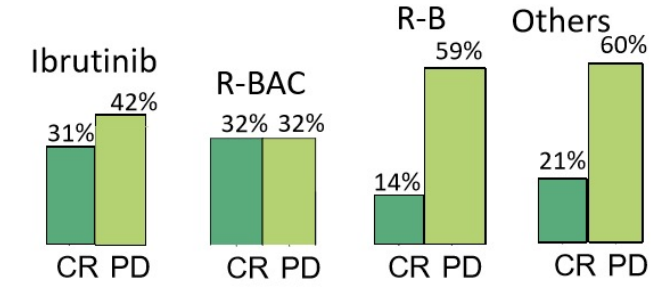
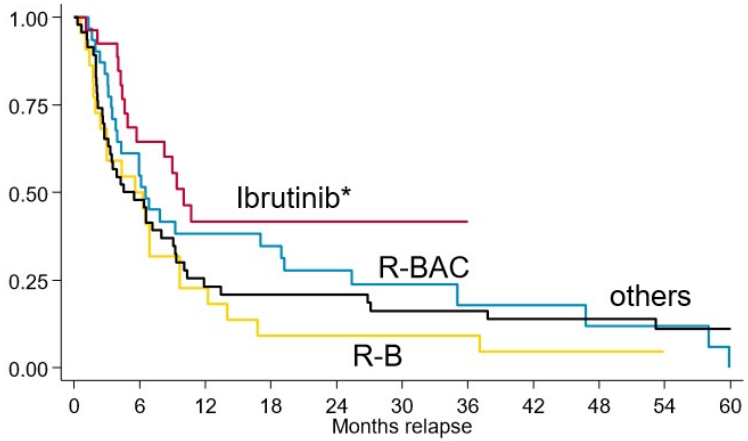
Early POD

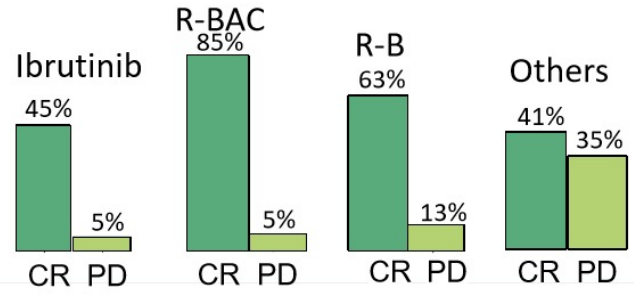


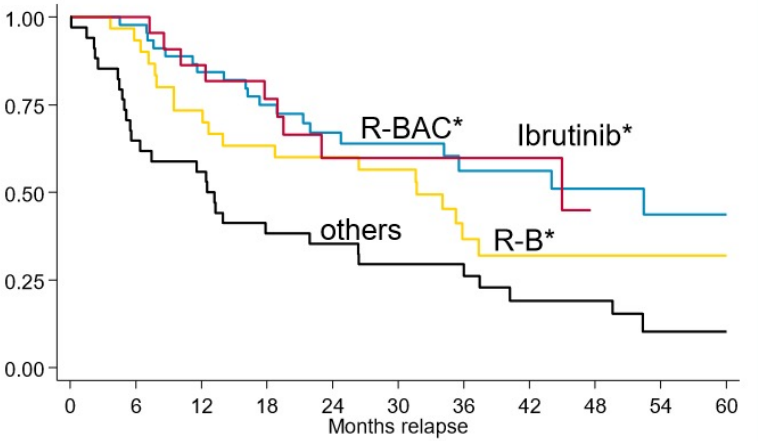


At risk:											
BAC	31	17	11	10	7	6	3	3	2	2	0
BR	22	11	5	2	2	2	2	1	1	0	0
ibru	27	16	8	4	2	1	0	0	0	0	0
other	47	22	10	9	9	7	7	5	5	4	3

*Ibru vs R-B (P=0.01); vs others (P=0.02)

Late-POD





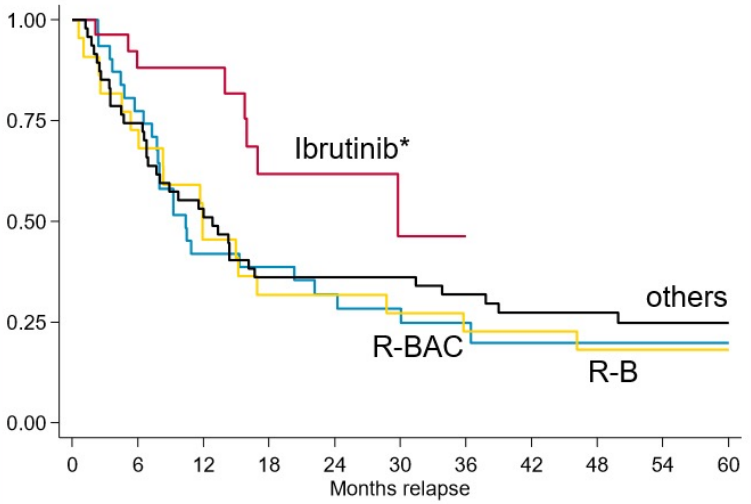
At risk:											
BAC	45	44	37	30	22	20	13	11	10	5	5
BR	32	28	22	19	18	16	8	7	7	6	5
ibru	22	22	19	15	8	6	6	4	0	0	0
other	34	22	19	13	12	10	9	5	5	2	2

*Ibru (P=0.008), R-BAC (P<0.0001) and R-B (P=0.02) vs others

Visco, Leukemia 2020

Ibrutinib in relapsed MCL (POD 24)
Overall survival

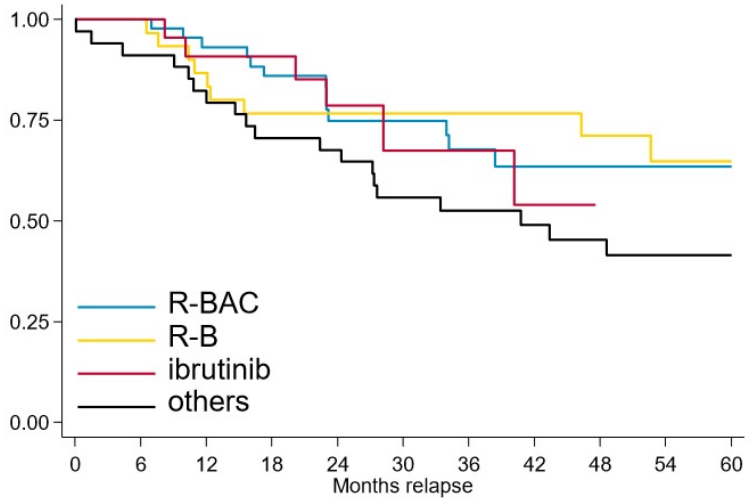
Early POD



At risk:											
BAC	31	24	13	12	9	8	5	4	3	3	3
BR	22	16	10	7	7	6	5	5	4	3	2
ibru	27	21	16	8	5	3	0	0	0	0	0
other	47	35	24	17	17	17	15	11	11	10	6

*Ibru vs R-B and R-BAC (P=0.02); vs others (P=0.03)

Late-POD



At risk:											
BAC	45	45	40	35	26	23	16	14	12	8	7
BR	32	30	26	23	22	20	16	15	13	10	9
ibru	23	22	20	18	10	6	6	4	0	0	0
other	34	31	27	24	23	19	16	13	12	8	7

Visco, Leukemia 2020

Mantle cell lymphoma
The era of combinations

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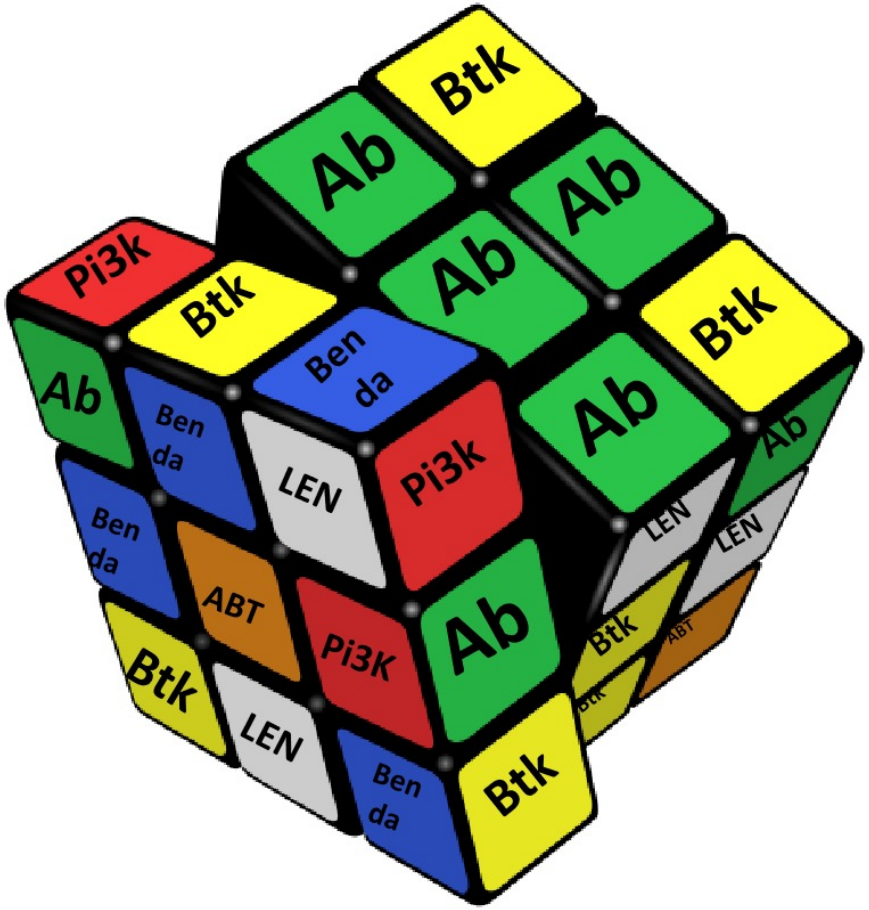

European MCL Network
Study generation 2021

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	< 65 years	> 60 years	> 65 years		
+ chemo	*MCL younger:* R-CHOP/DHAP =>ASCT R-CHOP+I/DHAP =>ASCT => I R-CHOP+I/DHAP => I	*MCL elderly R2:* R-CHOP vs R-CHOP/Ara-C => Rituximab M +/- Lenalidomide	BR +/- BTK ⇒ Rituximab M +/- BTK	*VR-BAC:* R-BAC ⇒ Venetoclax ⇒ (only high risk)	
vs. chemo	?	*ENRICH:* R-CHOP/Benda vs R-Ibrutinib	BR vs. BTK-R	*OASIS 2:* R-Ibrutinib +/- Venetoclax	*MCL elderly 3:* BR (Ibrutinib) vs R-Venetoclax-Ibrutinib

Relapse

R-HAD +/- Bortezomib	Ibrutinib/ Bortezomib	Ibrutinib/ R-Lenalidomide	Venetoclax/ R-Lenalidomide	Ibrutinib +/- ABT-199

The NEW ENGLAND JOURNAL of MEDICINE

Published on June 3, 2022

www.nejm.org/doi/full/10.1056/NEJMoa2201817

ORIGINAL ARTICLE

Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma

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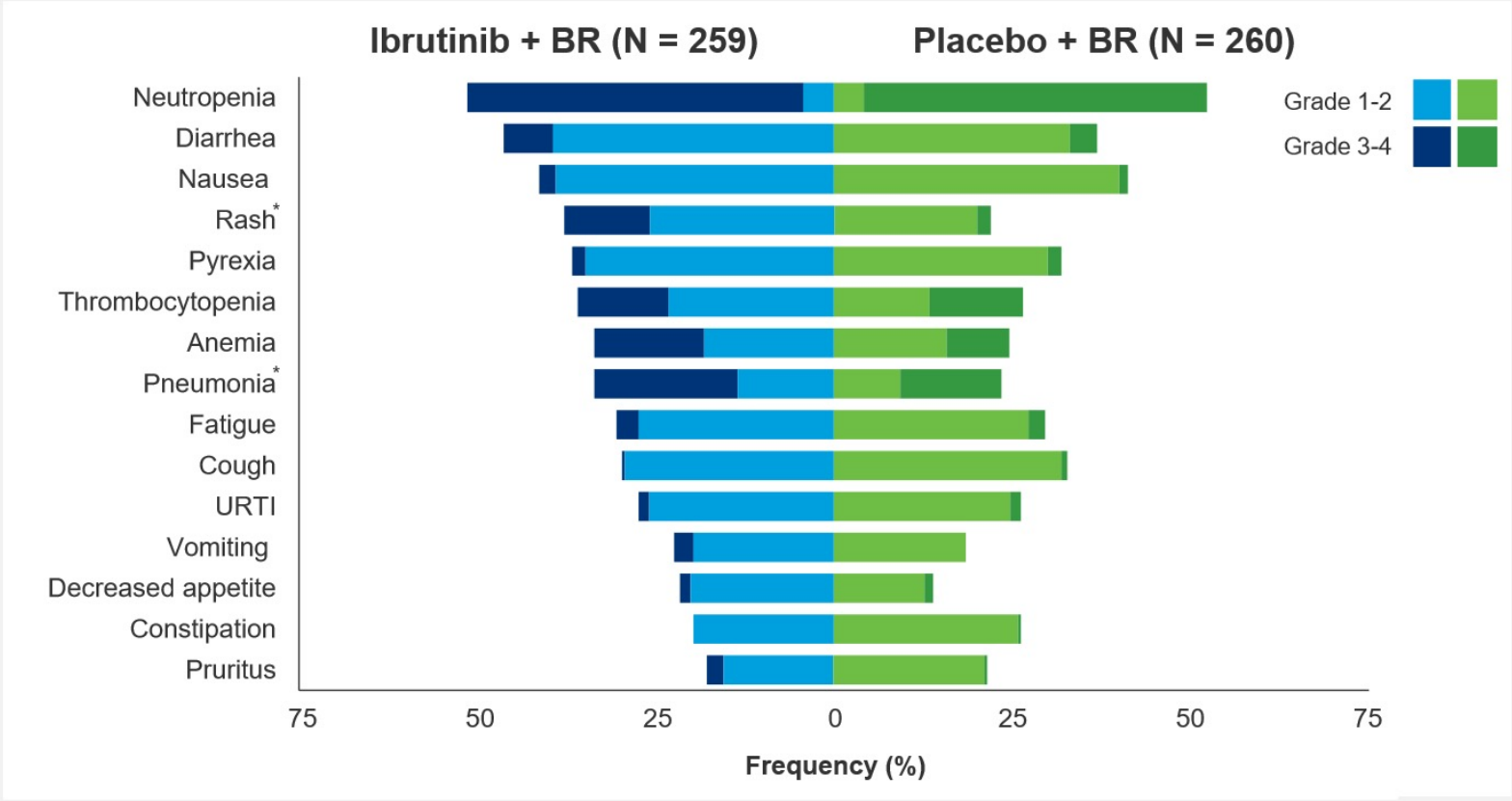
Baseline Characteristics

		Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median age (range), years		71 (65-86)	71 (65-87)
≥ 75 years, n (%)		74 (28.4)	82 (31.3)
Male, n (%)		178 (68.2)	186 (71.0)
ECOG PS 1, n (%)		127 (48.7)	118 (45.0)
Simplified MIPI, n (%)	Low risk	44 (16.9)	46 (17.6)
	Intermediate risk	124 (47.5)	129 (49.2)
	High risk	93 (35.6)	87 (33.2)
Bone marrow involvement, n (%)		198 (75.9)	200 (76.3)
Blastoid/pleomorphic histology, n (%)		19 (7.3)	26 (9.9)
Extranodal, n (%)		234 (89.7)	226 (86.3)
Bulky (≥ 5 cm), n (%)		95 (36.4)	98 (37.4)
TP53 mutated, n (%)		26 (10.0)	24 (9.2)
TP53 mutation status unknown, n (%)		121 (46.4)	133 (50.8)

ECOG PS, Eastern Cooperative Oncology Group performance status; MIPI, Mantle Cell Lymphoma International Prognostic Index.

Common Treatment-Emergent Adverse Events (≥ 20%)



*Difference of ≥ 10% in any grade treatment-emergent adverse event (TEAE).
URTI, upper respiratory tract infection.

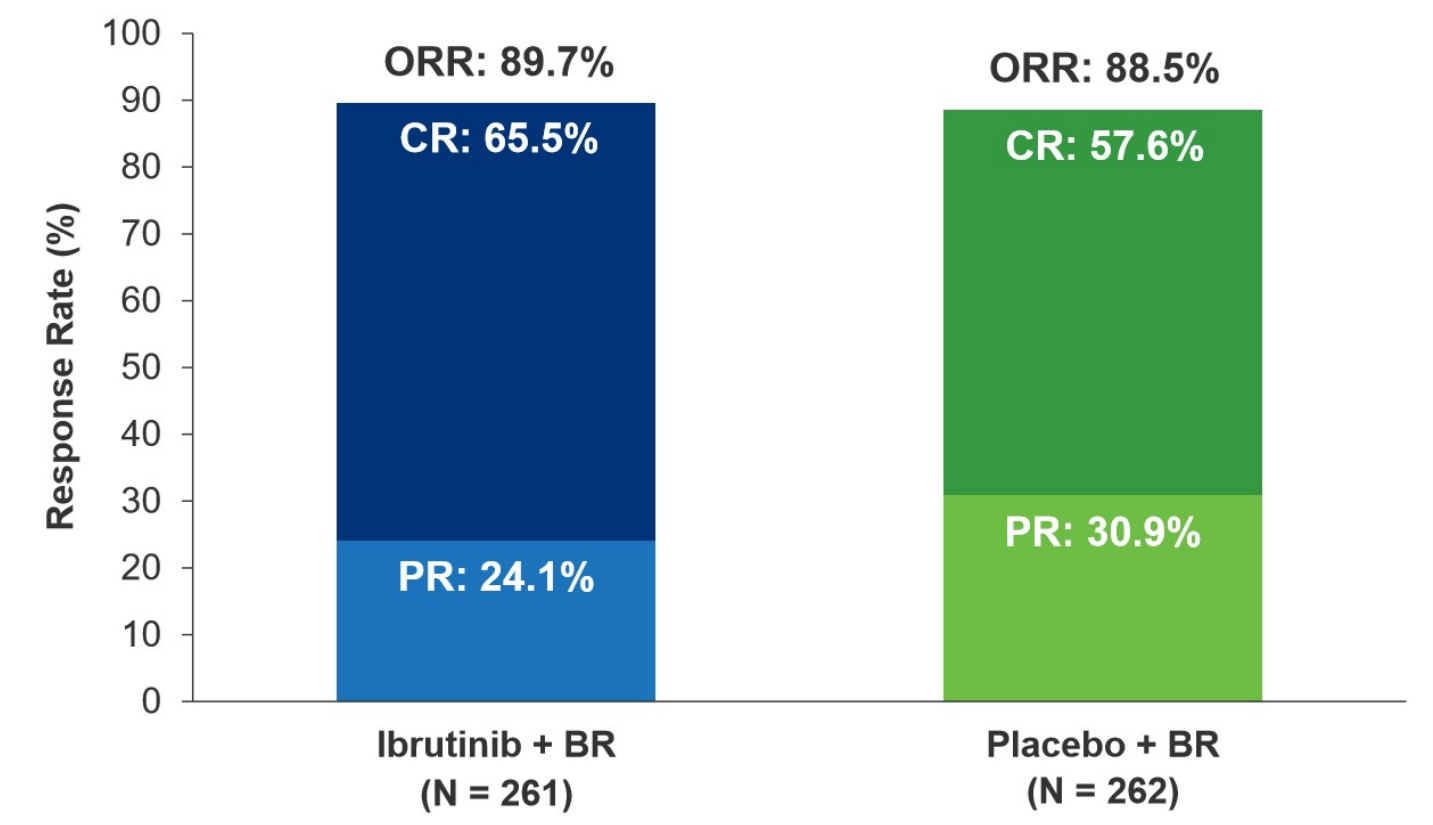
TEAEs of Clinical Interest With BTKis

	Ibrutinib + BR (N = 259)		Placebo + BR (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 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

- These adverse events were generally not treatment limiting
- During the entire study period, second primary malignancies (including skin cancers) occurred in 21% in the ibrutinib arm and 19% in the placebo arm; MDS/AML in 2 and 3 patients, respectively

*Difference of ≥ 5% in any grade TEAE; MDS/AML, myelodysplastic syndromes/acute myeloid leukemia.
Any bleeding is based on Haemorrhage Standardized MedDRA Query (SMQ) (excluding laboratory terms). Major bleeding includes any grade 3 or higher bleeding and serious or central nervous system bleeding of any grade.

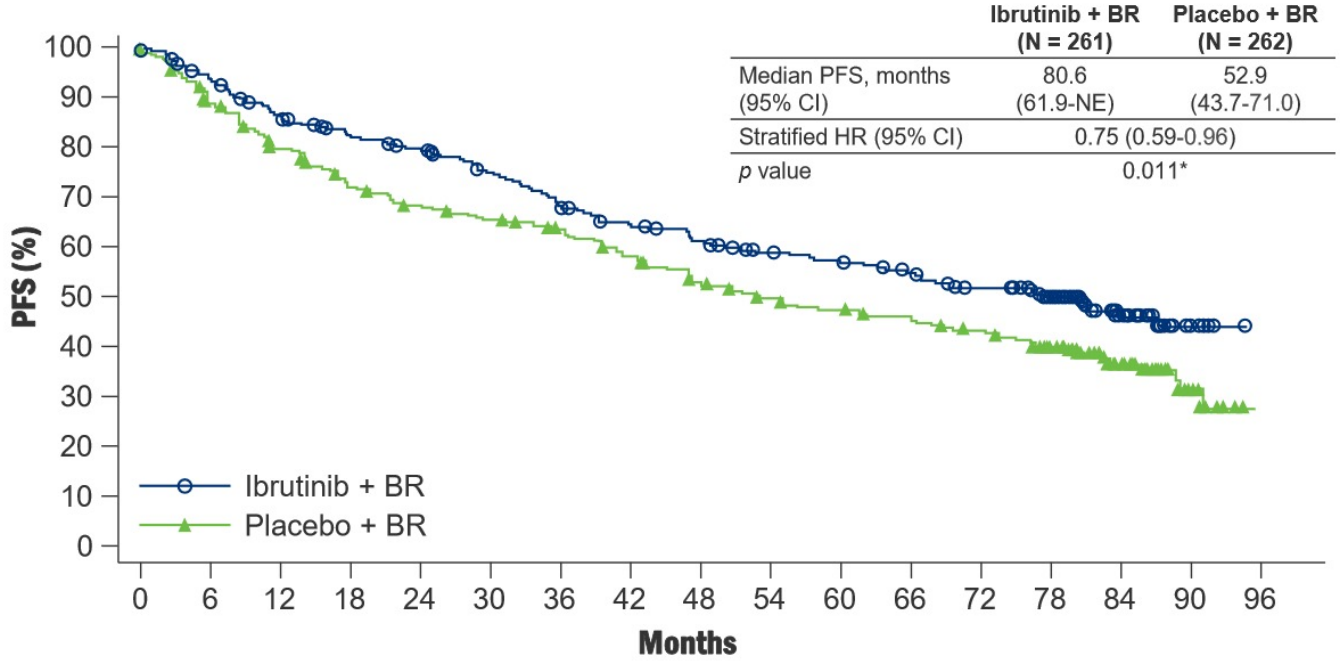
Response Rate



- CR rate was numerically higher in the ibrutinib arm (65.5% vs 57.6%; *p* = 0.057)

CR, complete response; ORR, objective response rate; PR, partial response.

Primary End Point of Improved PFS Was Met



	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median PFS, months (95% CI)	80.6 (61.9-NE)	52.9 (43.7-71.0)
Stratified HR (95% CI)	0.75 (0.59-0.96)	
p value	0.011*	

Patients at Risk

Ibrutinib + BR	261	228	207	191	182	167	152	139	130	120	115	106	95	78	39	11	0
Placebo + BR	262	226	199	177	166	158	148	135	119	109	103	98	90	78	41	11	0

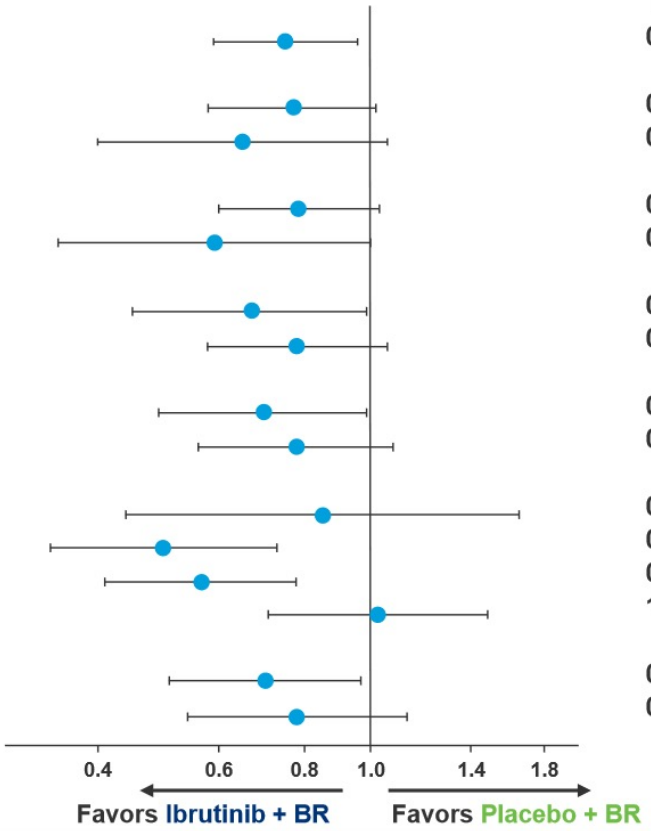
Ibrutinib + BR and R maintenance achieved:

- **Significant improvement in median PFS by 2.3 years** (6.7 vs 4.4 years)
- **25% reduction** in risk of PD or death

CI, confidence interval; HR, hazard ratio; NE, not evaluable.
*Significance boundary for superiority was $p < 0.023$.

PFS Hazard Ratio in Subgroups

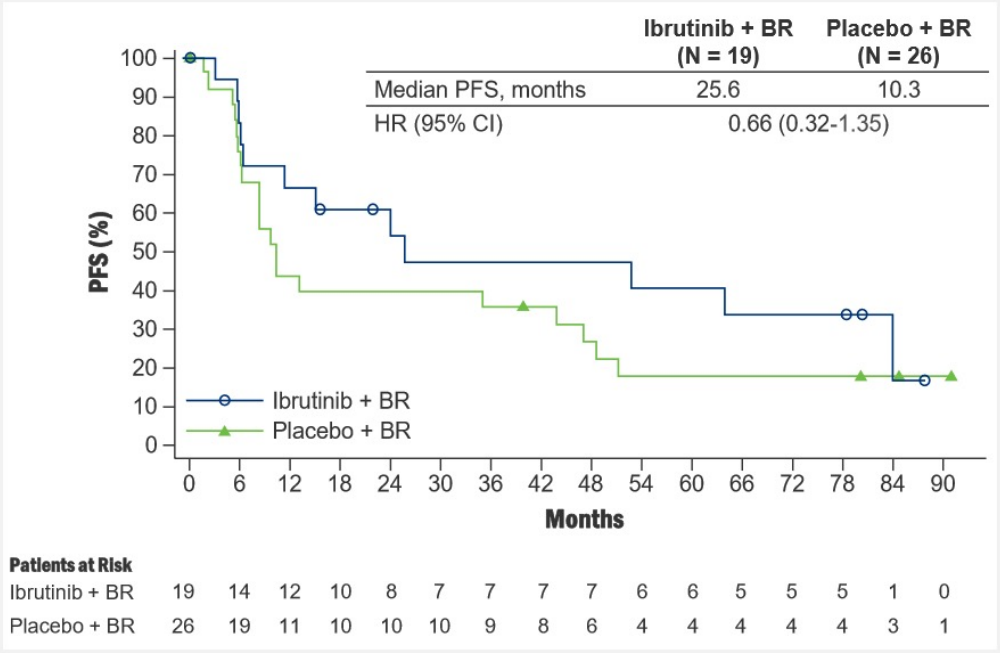
Characteristic, n/N	Ibrutinib + BR	Placebo + BR	HR	95% CI
All patients	116/261	152/262	**0.75**	0.59-0.96
Sex				
Male	88/178	111/186	**0.77**	0.58-1.02
Female	28/83	41/76	**0.65**	0.40-1.06
Race				
White	92/199	118/206	**0.78**	0.60-1.03
Non-white	24/62	34/56	**0.59**	0.35-1.00
Age				
< 70 years	39/99	62/108	**0.67**	0.45-0.99
≥ 70 years	77/162	90/154	**0.78**	0.58-1.06
ECOG PS				
0	53/134	72/141	**0.69**	0.49-0.99
1-2	63/127	80/121	**0.77**	0.56-1.08
Simplified MIPI at baseline				
Low risk (0-3)	15/44	21/46	**0.85**	0.44-1.65
Intermediate risk (4-5)	42/124	76/129	**0.50**	0.34-0.73
Low/intermediate risk (0-5)	57/168	97/175	**0.57**	0.41-0.78
High risk (6-11)	59/93	55/87	**1.02**	0.71-1.48
Tumor bulk				
< 5 cm	64/165	90/163	**0.71**	0.51-0.97
≥ 5 cm	51/95	62/98	**0.78**	0.54-1.13



ECOG PS, Eastern Cooperative Oncology Group performance status; MIPI, Mantle Cell Lymphoma International Prognostic Index.

PFS in High-Risk Subgroups

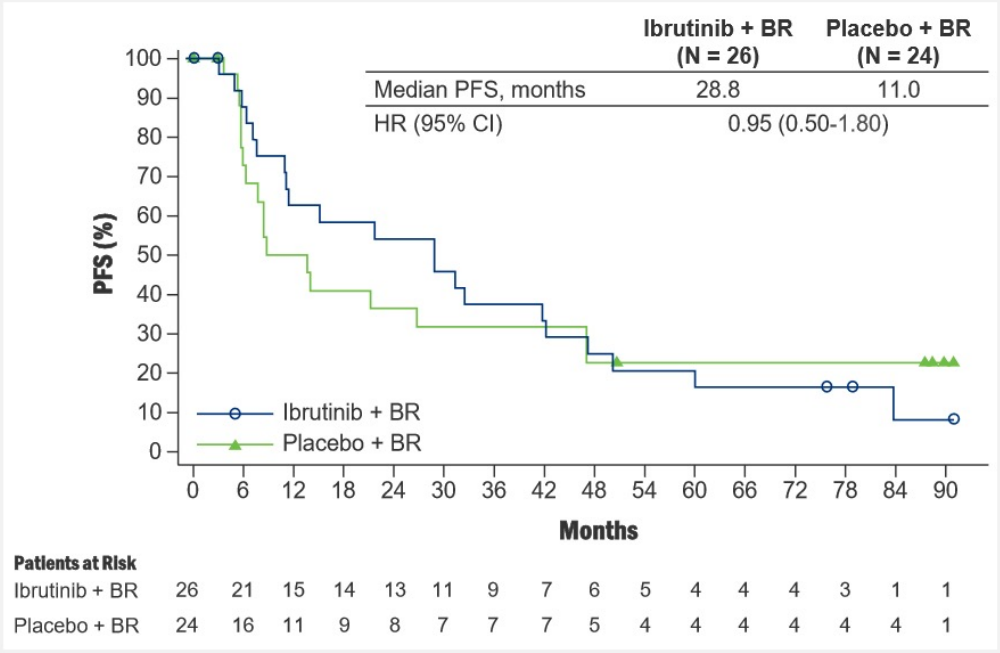
Blastoid/pleomorphic histology



Patients at Risk

Ibrutinib + BR	19	14	12	10	8	7	7	7	7	6	6	5	5	5	1	0
Placebo + BR	26	19	11	10	10	10	9	8	6	4	4	4	4	4	3	1

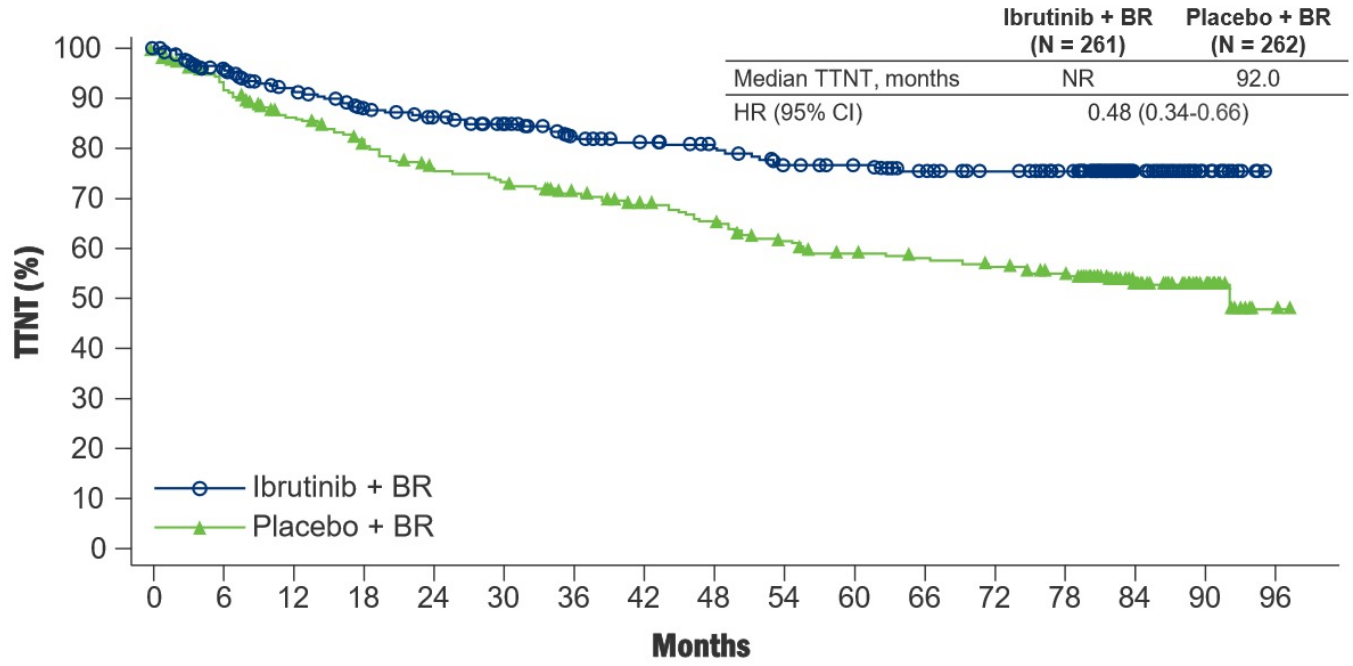
TP53 mutation present



Patients at Risk

Ibrutinib + BR	26	21	15	14	13	11	9	7	6	5	4	4	4	3	1	1
Placebo + BR	24	16	11	9	8	7	7	7	5	4	4	4	4	4	4	1

Time to Next Treatment



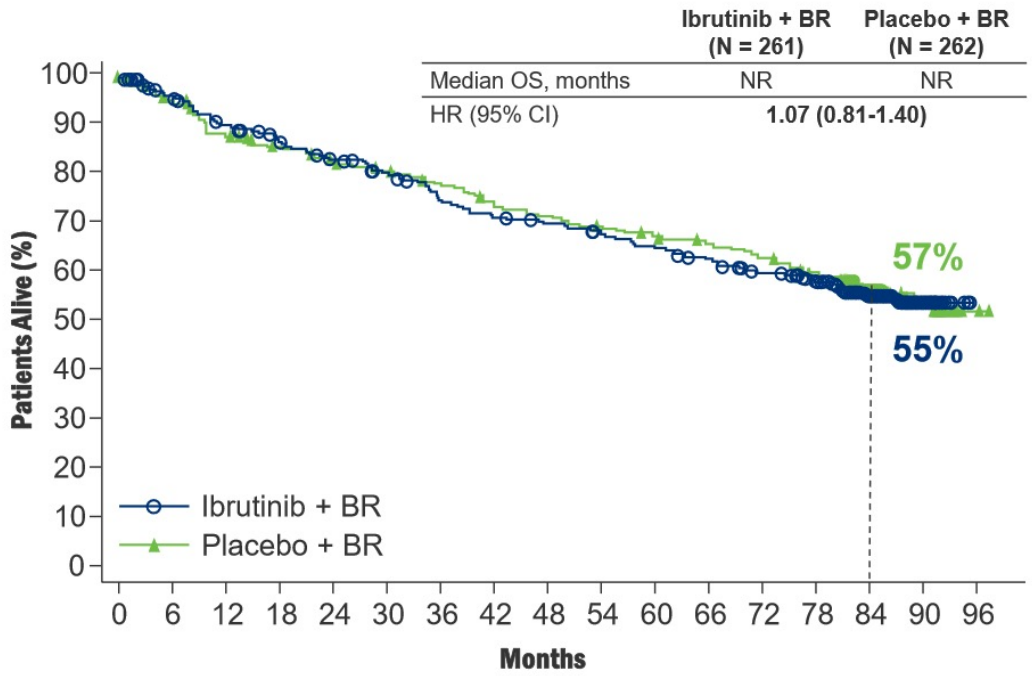
Patients at Risk

Ibrutinib + BR	261	231	209	192	184	174	155	147	140	131	126	119	111	102	60	21	0
Placebo + BR	262	231	203	189	171	167	157	146	137	125	117	113	109	101	67	23	2

- **Subsequent second-line anti-lymphoma treatment:**
  - **Ibrutinib arm: 52/261 (19.9%)**
    - **BTKi: 6/52 (11.5%)**
  - **Placebo arm: 106/262 (40.5%)**
    - **BTKi: 41/106 (38.7%)**

BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; NR, not reached; TTNT, time to next treatment.

Overall Survival



Patients at Risk

Ibrutinib + BR	261	239	221	208	197	187	171	163	158	152	145	138	128	118	70	25	0
Placebo + BR	262	244	223	212	203	197	188	177	171	165	159	154	147	137	90	31	2

Cause of death	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Death due to PD and TEAE	**58 (22.2%)**	**70 (26.7%)**
Death due to PD	**30 (11.5%)**	**54 (20.6%)**
Death due to TEAEs*	**28 (10.7%)**	**16 (6.1%)**
Death during post-treatment follow-up excluding PD and TEAEs	**46 (17.6%)**	**37 (14.1%)**
Total deaths	**104 (39.8%)**	**107 (40.8%)**

- Death due to Covid-19: 3 patients in the ibrutinib arm during the TEAE period and 2 patients in the placebo arm after the TEAE period
- Exploratory analysis of cause-specific survival including only deaths due to PD or TEAEs showed an HR of 0.88

*The most common grade 5 TEAE was infections in the ibrutinib and placebo arms: 9 versus 5 patients. Grade 5 TEAE of cardiac disorders occurred in 3 versus 5 patients, respectively.
CI, confidence interval; HR, hazard ratio; NR, not reached; PD, progressive disease; TEAE, treatment-emergent adverse event.

Triangle

add on vs head to head comparison

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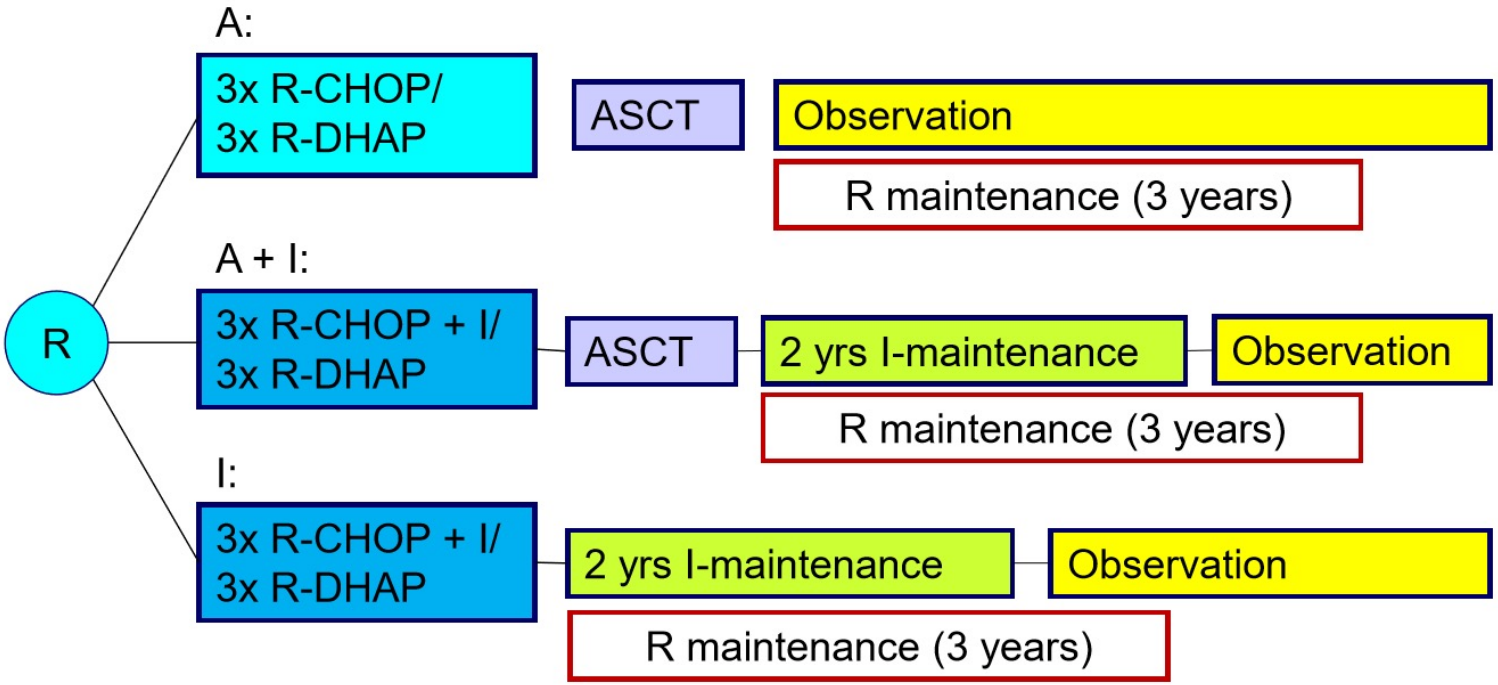

superiority/non-inferiority: time to treatment failure
HR: 0.60; 65% vs. 77% vs. 49% at 5 years

Triangle
Patient recruitment

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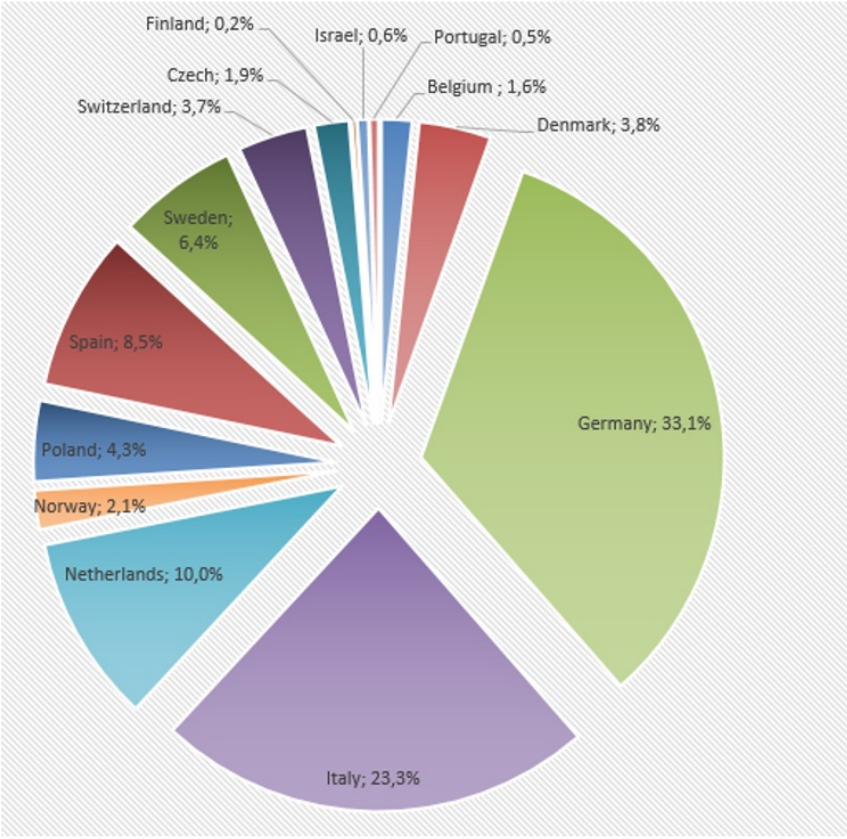
Countries active	Number of Sites		Patients randomized	Patients
	planned	actively recruiting	total per country	in percent
Belgium	8	5	**14**	1,6%
Denmark	6	6	**33**	3,8%
Germany	60	50	**285**	33,1%
Italy	34	31	**201**	23,3%
Netherlands	25	22	**86**	10,0%
Norway	5	5	**18**	2,1%
Poland	7	7	**37**	4,3%
Spain	14	14	**73**	8,5%
Sweden	8	8	**55**	6,4%
Switzerland	13	8	**32**	3,7%
Czech	4	4	**16**	1,9%
Finland	3	1	**2**	0,2%
Israel	7	4	**5**	0,6%
Portugal	1	1	**4**	0,5%
14 countries	195	166	**861**	100,00%



DESIGN

- ***Phase I***: 3+3 design
  (Sample size: 4-18)

Level	Bortezomib s.c. [1] days 1,4,8,11 q21d	Ibrutinib p.o continously
-1	*1.3 mg/m²*	*(280 mg/day)*
1	*1.3 mg/m²*	*420 mg/day*
2	*1.3 mg/m²*	*560 mg/day*

→ 6 cycles, followed by Ibrutinib maintenance *(until progression or unacceptable toxicity)*

- ***Phase II***

→ s.c. Bortezomib at labeled dose and Ibrutinib

→ 6 cycles of this combination *(later amended to at least 4 cycles)*

followed by Ibrutinib maintenance *(until progression or unacceptable toxicity)*

[1] Gerecitano, BJH 2009

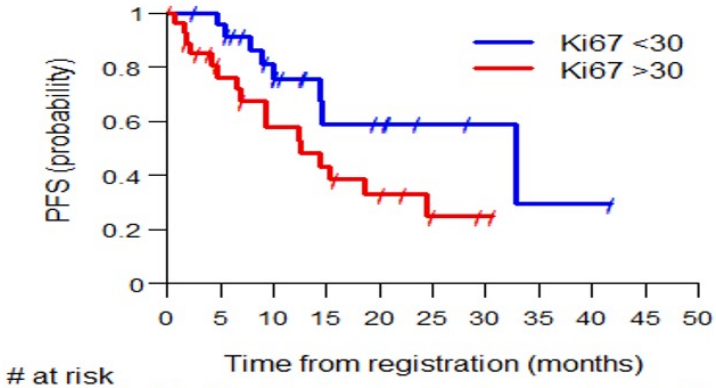
Novak, ICML 2021

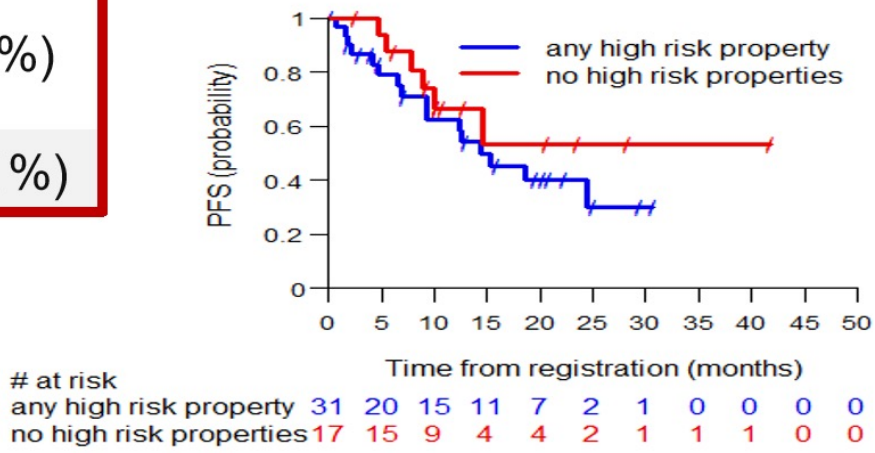
SAKK
WE BRING PROGRESS TO CANCER CARE

EFFICACY IN HIGH RISK PATIENTS

31/55 (56.4%) with ≥1 high risk feature [1]

	Low risk		High risk [1]	
Characteristic	**N**	**OR [2]**	**N**	**OR [2]**
Ki67 (<30 vs. >30)	24	23 (96%)	28	22 (79%)
p53 (<50 vs. >50)	35	32 (91%)	11	8 (73%)
blastoid (normal vs. blastoid/pleomorph)	46	42 (91%)	9	6 (67%)
any of the above	17	16 (94%)	31	25 (81%)





Overlapping time to best response *(data not showi*

[1] Jain, JCO 2020; [2] during trial treatment

Novak, ICML 2021

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Relapsed mantle cell lymphoma
AIM: ABT-199/Ibrutinib

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Characteristic (N=24)	Value	
Bone marrow involvement by MCL	13	54%
Largest bulk 5 to 10 cm Largest bulk > 10 cm	4 2	17% 8%
MIPI Low MIPI Intermediate MIPI High	1 5 18	4% 21% 75%
Blastic or pleomorphic morphology – no./total no.(%)	1/21	5%
Ki67 ≥ 30% - no/total no (%)	9/21	43%
TP53 status – no (%) Mutated with deletion Mutated without deletion Deletion without mutation	 4 7 1	 17% 29% 4%
NF-kB pathway mutations in CARD11, BIRC3, or TRAF2 – no (%)	6	25%
Tumor lysis category Low risk Intermediate risk High risk	 11 6 7	 46% 25% 29%

Tam, NEJM 2018

Relapsed mantle cell lymphoma
AIM: ABT-199/Ibrutinib

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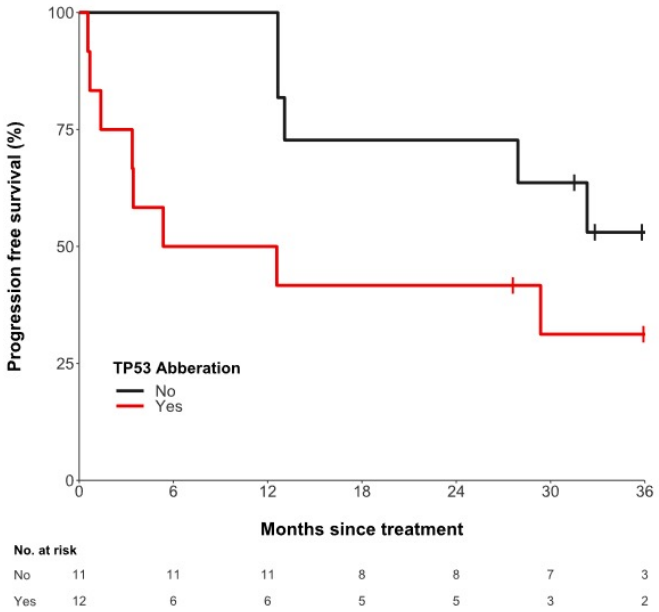
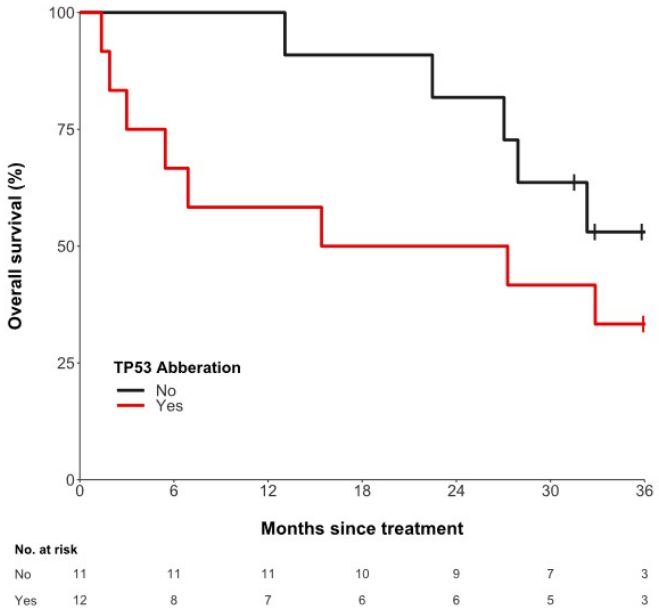
_TP53_ Mutation & PFS



_TP53_ Mutation & OS



The Royal Melbourne Hospital

Handunnetti, ASH 2019

OASIS: TREATMENT SCHEDULE

	Cycle 1				Cycle 1 bis				Cycle 2				cycles	Maintenance	
Baseline	**W1**	**W2**	**W3**	**W4**	**W1**	**W2**	**W3**	**W4**	**W1**	**W2**	**W3**	**W4**	**C3-C6**	**C7-C23**	**until prog**
Ibrutinib (560mg/d)	D2	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Obinutuzumab (1g)	D1	D8	D15		D1				D1				D1 each cycle	D1 every 2 cycles from C8	
Venetoclax (mg/d)					20	50	100	200	400	400	400	400	→	→	

Le Gouill, EHA 2020; Blood 2021

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

EHA 2020- Abstract S228

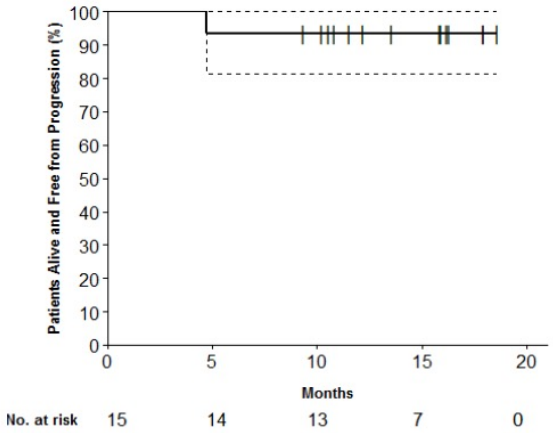
OASIS: Patients' outcome

- mFU = 14 months (range, 5 to 19)
- One patient progressed (not *TP53* mutated nor 17p deleted)
- 14 patients remain in CR and under treatment

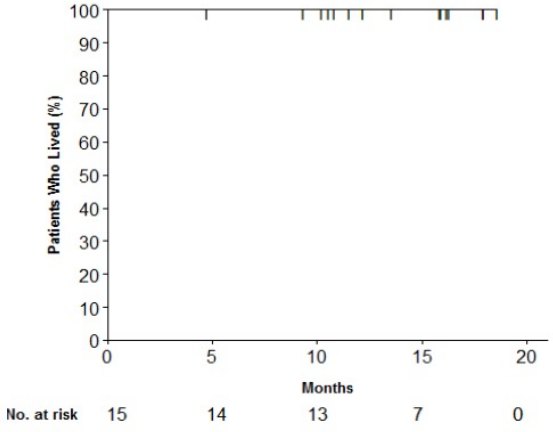
- PFS at one year is 93.3% (95% CI, 81.5- 100%)

- OS at one and two years is 100%

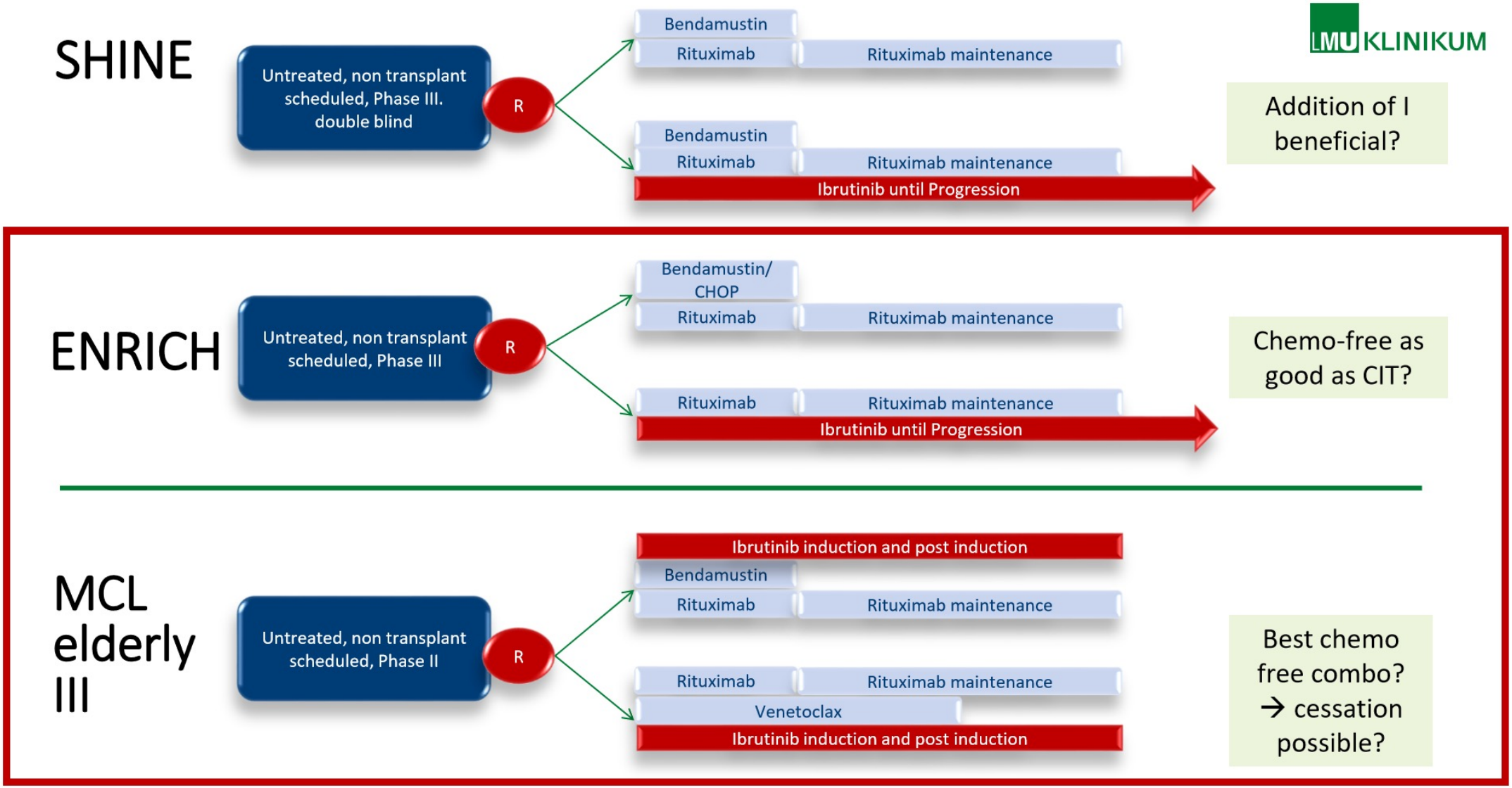
PFS



OS



Le Gouill, EHA 2020; Blood 2021


SHINE
Untreated, non transplant scheduled, Phase III. double blind
R
Bendamustin
Rituximab
Rituximab maintenance
Bendamustin
Rituximab
Rituximab maintenance
Ibrutinib until Progression
Addition of I beneficial?
ENRICH
Untreated, non transplant scheduled, Phase III
R
Bendamustin/ CHOP
Rituximab
Rituximab maintenance
Rituximab
Rituximab maintenance
Ibrutinib until Progression
Chemo-free as good as CIT?
MCL elderly III
Untreated, non transplant scheduled, Phase II
R
Ibrutinib induction and post induction
Bendamustin
Rituximab
Rituximab maintenance
Rituximab
Rituximab maintenance
Venetoclax
Ibrutinib induction and post induction
Best chemo free combo? → cessation possible?

Mantle cell Lymphome
Novel treatments 2022

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- high risk in clinical routine: Ki-67, p53 mut, blastoid

- first line: - younger: R/DHAP-autologous SCT- R-maintenance ?

  Elderly: IR-CHOP/Benda **(+ I)** + R-maintenance

  in studies: **non-chemo (combined) approaches**

- in early relapses: **BTKi (combinations?)**

  - in studies: non-covalent BTKi, CAR –T cells, bispecific antibodies (combinations?)

Acknowledgement