VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

IL RUOLO DEGLI INIBITORI DELLA BRUTON-CHINASI: RAZIONALE, APPLICAZIONI CLINICHE, RESISTENZA

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Disclosures of Alessandro Broccoli

Company name	Research support	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sandoz	X				X	X
Gilead				X	X	X
Merck	X					X
Janssen	X			X	X	X
Takeda		X		X	X	X
Kyowa Kirin	X			X	X	X
Incyte						X
Recordati				X		X
Astra Zeneca				X	X	X
Roche				X		X
GlaxoSmithKline		X		X	X	
BeOne	X			X	X	X
Eli Lilly		X		X		X
SOBI				X		
SERB Pharma		X			X	

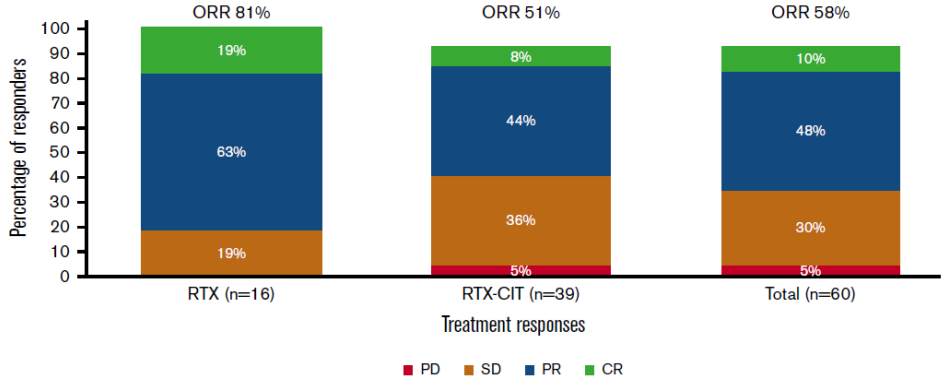
The BTK inhibitors panorama in lymphoid malignancies

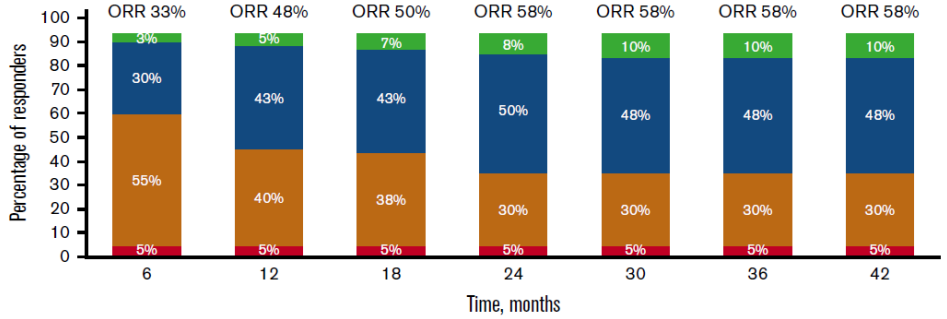
		Pts	ORR	CR	VGPR	PR	SD	PD	PFS	OS
TN-CLL	Ibrutinib	136	92.0	30.0	—	62.0	4.0	NR	59.0 at 84 mos	78.0 at 84 mos
	Acalabrutinib	179	92.2	11.2	—	81.0	2.2	1.7	77.9 at 48 mos	87.6 at 48 mos
	Zanubrutinib	241	94.5	6.6	—	87.9	2.9	0.8	85.5 at 24 mos	94.3 at 24 mos
RR-CLL	Ibrutinib	195	90.0	8.0	—	82.0	NR	NR	40.0 at 60 mos	Median NR
	Ibrutinib	265	79.9	3.0	—	76.9	10.2	2.3	Median 38.4 mos	Median NR
	Acalabrutinib	268	83.2	1.9	—	81.3	10.8	0.7	Median 38.4 mos	Median NR
	Zanubrutinib	327	90.6	4.0	—	86.6	6.1	0.9	78.4 at 24 mos	Median NR
	Ibrutinib	325	82.8	2.5	—	80.3	10.8	2.2	65.9 at 24 mos	Median NR
TN-Mantle cell	R-CHOP+Ibr/R-DHAP ± ASCT	559	99.0	45.0	—	54.0	0.5	1.0	87.0 at 31 mos	91.0 at 30 mos
	BR + Acalabrutinib	299	91.0	66.6	—	24.4	NR	NR	66.4 at 50 mos	Median NR
RR-Mantle cell	Ibrutinib	111	67.0	23.0	—	44	NR	NR	31.0 at 24 mos	47 at 24 mos
	Acalabrutinib	124	81.0	40.0	—	41.0	9.0	8.0	49.0 at 24 mos	72.4 at 24 mos
	Zanubrutinib	112	84.8	NR	—	NR	NR	NR	51.4 at 24 mos	75.9 at 24 mos
Waldenström	Zanubrutinib	102	81.4	0	36.3	45.1	2.9	1.0	78.3 at 42 mos	87.5 at 42 mos
	Ibrutinib	99	79.8	0	25.3	54.5	3.0	2.0	69.7 at 42 mos	85.2 at 42 mos
	Acalabrutinib	106	93.0	0	7.8	72.9	NR	NR	82.0 at 24 mos	89.0 at 24 mos
RR-Marginal zone	Ibrutinib	60	58.0	10.0	—	48.0	30.0	5.0	32.0 at 33 mos	72.0 at 33 mos
	Acalabrutinib	40	52.5	12.5	—	40.0	47.5	0	67.0 at 12 mos	91.4 at 12 mos
	Zanubrutinib	66	68.2	25.8	—	42.4	19.7	9.1	70.9 at 24 mos	85.9 at 24 mos

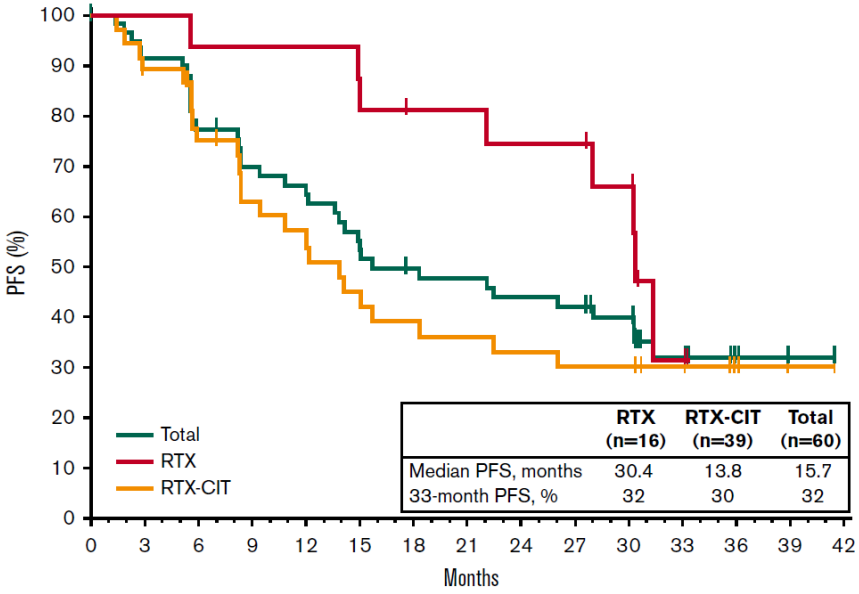
Adapted from: Broccoli A. *J Cell Mol Med*, 2025; 29: e70170

MARGINAL ZONE LYMPHOMA

Durable ibrutinib responses in relapsed/refractory marginal zone lymphoma: long-term follow-up and biomarker analysis







Noy A. *Blood Adv*, 2020; 4: 5773-5784

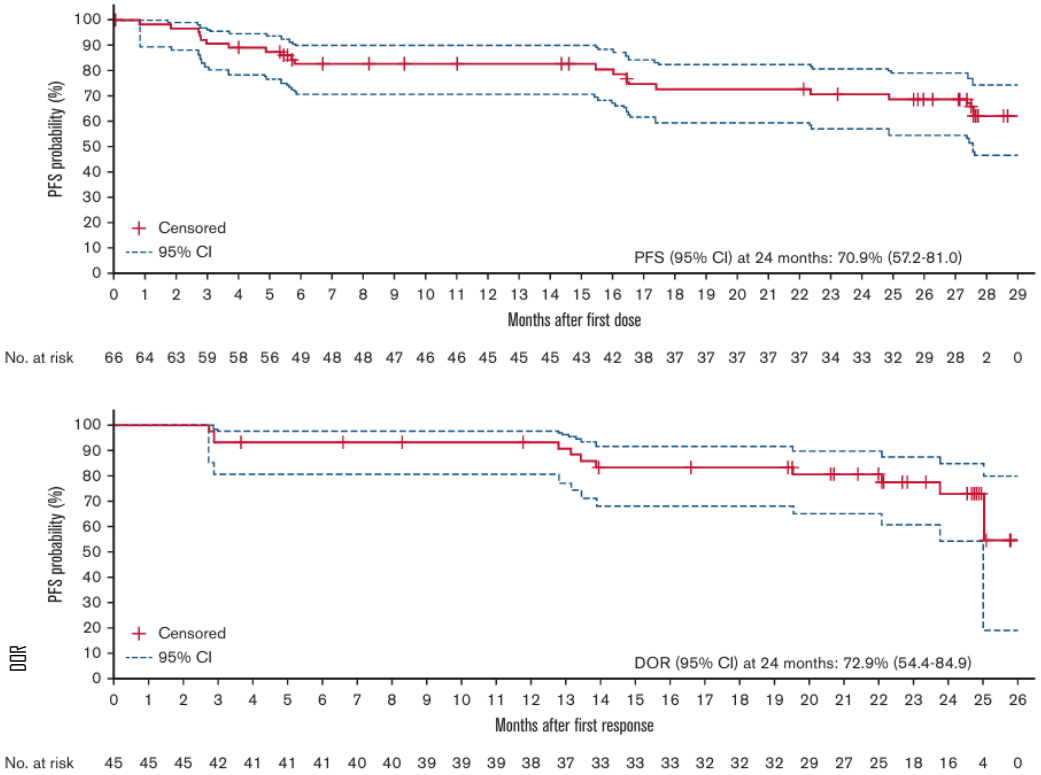
Safety and efficacy of zanubrutinib in relapsed/refractory marginal zone lymphoma: final analysis of the MAGNOLIA study

	Extranodal (MALT) (n = 25)	Nodal (n = 25)	Splenic (n = 12)	Unknown* (n = 4)	Total† (N = 66)
ORR, % (95% CI)‡	64.0 (42.5-82.0)	76.0 (54.9-90.6)	66.7 (34.9-90.1)	50.0 (6.8-93.2)	68.2 (55.6-79.1)
Best overall response, n (%)					
CR	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)	17 (25.8)
PR	6 (24.0)	14 (56.0)	7 (58.3)	1 (25.0)	28 (42.4)
Stable disease	4 (16.0)	5 (20.0)	3 (25.0)	1 (25.0)	13 (19.7)
Progressive disease	3 (12.0)	1 (4.0)	1 (8.3)	1 (25.0)	6 (9.1)
Nonprogressive disease§	1 (4.0)	0	0	0	1 (1.5)
Discontinued study before first assessment	1 (4.0)	0	0	0	1 (1.5)
Median time to response, mo (IQR)	2.8 (2.7-2.9)	2.8 (2.7-3.8)	3.6 (2.7-6.0)	2.7 (2.6-2.8)	2.8 (2.7-3.7)

MALT, mucosa-associated lymphoid tissue.
*These patients presented with both nodal and extranodal lesions; therefore, the study sites were unable to classify the MZL subtype.
†Two patients were excluded from the efficacy analysis set because central review determined their diagnosis as diffuse large B-cell lymphoma.
‡95% CIs were calculated using 2-sided Clopper-Pearson methodology.
§One patient was classified as having "nonprogressive disease" because of a missed PET scan at cycle 3 (CT scan showed stable disease).

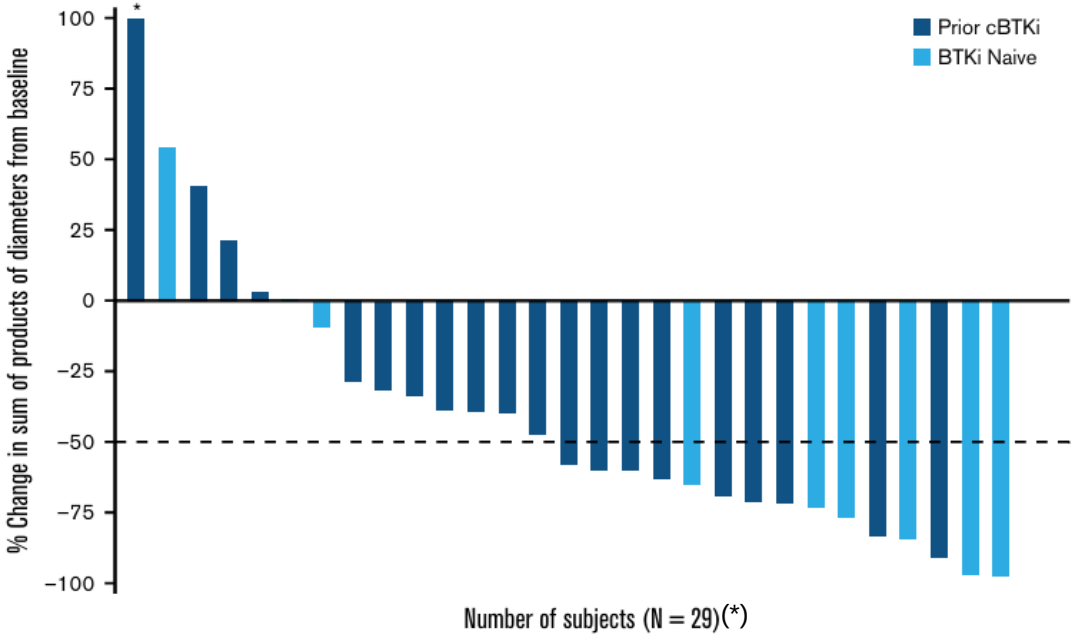
Opat S. *Blood Adv*, 2023; 7: 6801-6811

Safety and efficacy of zanubrutinib in relapsed/refractory marginal zone lymphoma: final analysis of the MAGNOLIA study



Opat S. *Blood Adv*, 2023; 7: 6801-6811

Pirtobrutinib, a highly selective, noncovalent (reversible) BTKi in R/R marginal zone lymphoma: phase 1/2 BRUIN study



PIRTOBRUTINIB 200 mg once daily

36 patients, age: 68 years
- 17% EMZL
- 47% Nodal MZL
- 36% Splenic MZL

Median prior lines: 3 (1-10)
Prior chemotherapy: 86%
Prior cBTKi: 72%
- Discontinued due to progression: 55%
- Discontinued due to toxicity/other: 17%

ORR: 55.6%
- EMZL: 66.7%
- Nodal MZL: 64.7%
- Splenic MZL: 38.5%

CR: 8.3%
PR: 47.2%
SD: 36.1%
PD: 8.3%

Median follow-up: ~ 26 months
mDoR: 17.8 months
mPFS: 16.6 months
2-year OS: 77.0%

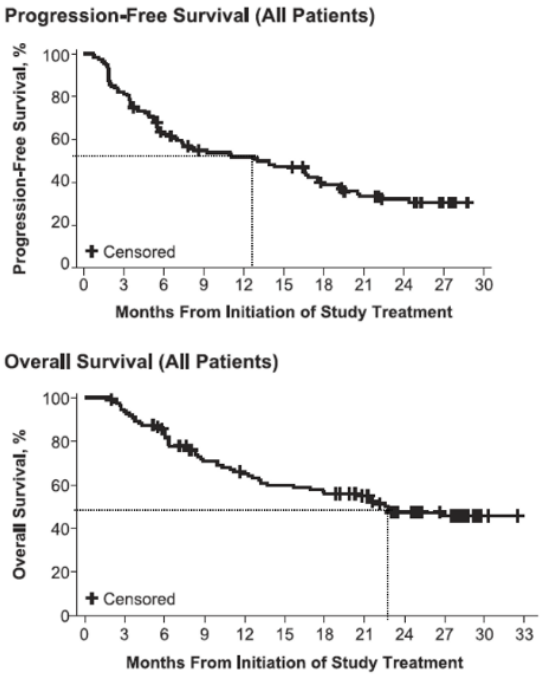
(*) 7 patients with no measurable disease.

Patel K. *Blood Adv*, 2026; 10: 2441-2451

MANTLE CELL LYMPHOMA

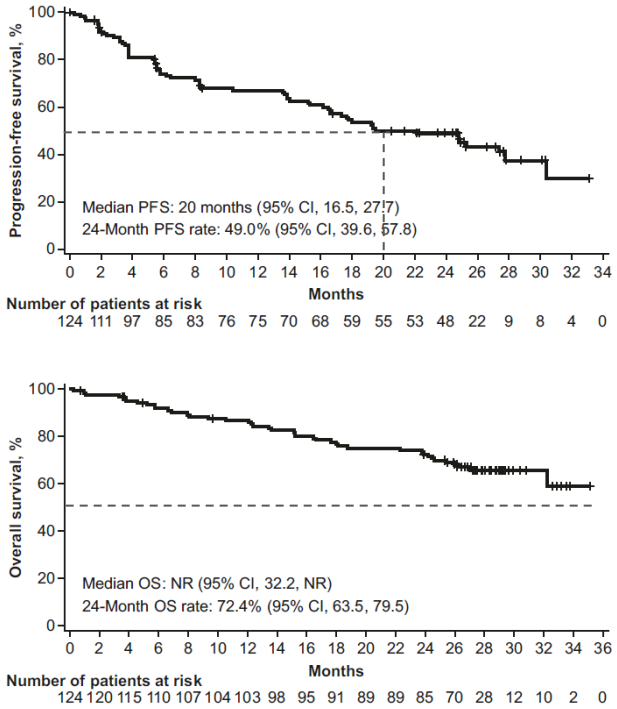
Several covalent BTK inhibitors in the relapsed/refractory setting

Ibrutinib



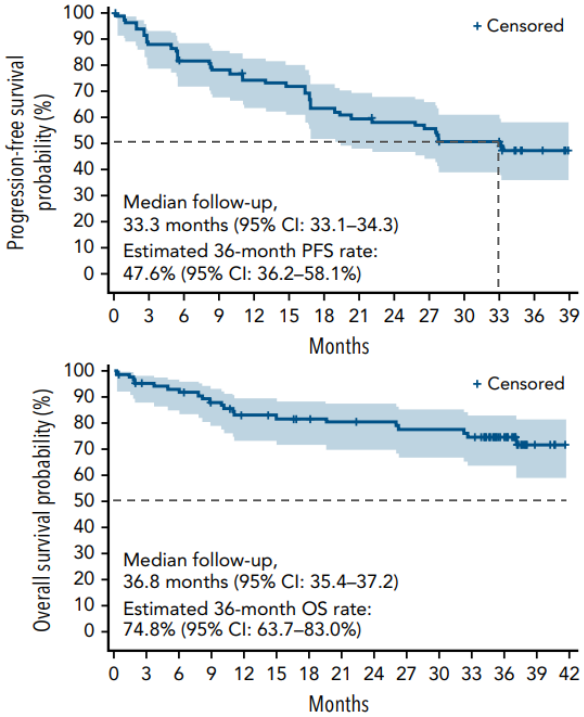
Wang ML. *Blood*, 2015; 126: 739-745

Acalabrutinib



Wang ML. *Leukemia*, 2019; 33: 2762-2766

Zanubrutinib



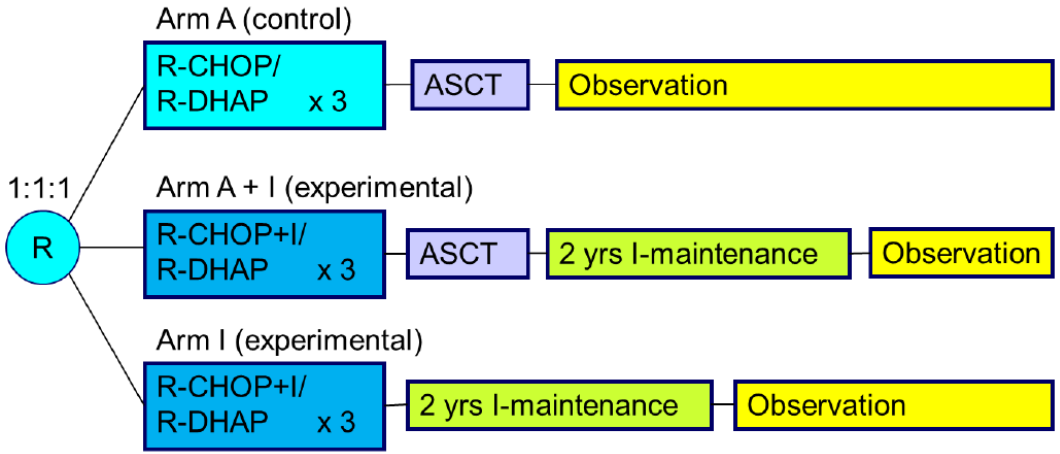
Song Y. *Blood*, 2022; 139: 3148-3158

Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network

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

- Primary outcome: FFS (*)

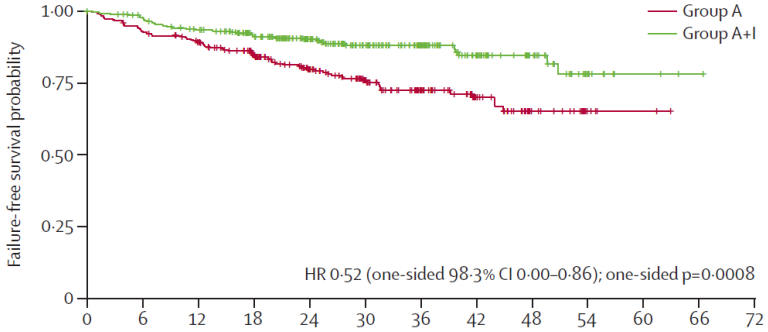
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety



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

(*) from randomization to the occurrence of stable disease, progression or death

Dreyling M. *Lancet*, 2024; 403: 2293-2306



Number at risk (number censored)

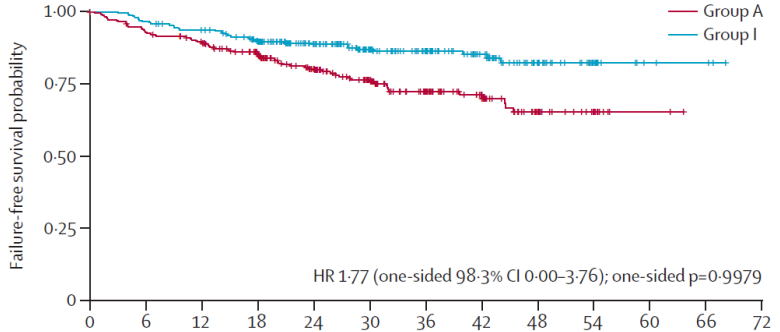
Group A	288	252	237	206	162	126	85	54	27	12	2	0	0
	(0)	(17)	(22)	(43t)	(76)	(105)	(140)	(169)	(193)	(208)	(218)	(220)	(220)
Group A+I	292	270	253	226	184	137	109	65	41	17	3	1	0
	(0)	(16)	(21)	(44)	(82)	(125)	(153)	(194)	(219)	(240)	(254)	(256)	(257)

Median follow-up: 31 months

3y FFS: 88% (A+I)

3y FFS: 72% (A)

Superiority of A+I over A is confirmed



Number at risk (number censored)

Group A	290	269	257	229	180	133	100	68	35	16	4	3	0
	(0)	(12)	(16)	(33)	(80)	(124)	(156)	(187)	(219)	(237)	(249)	(250)	(253)
Group I	288	252	237	206	162	126	85	54	27	12	2	0	0
	(0)	(17)	(22)	(43)	(76)	(105)	(140)	(169)	(193)	(208)	(218)	(220)	(220)

Median follow-up: 31 months

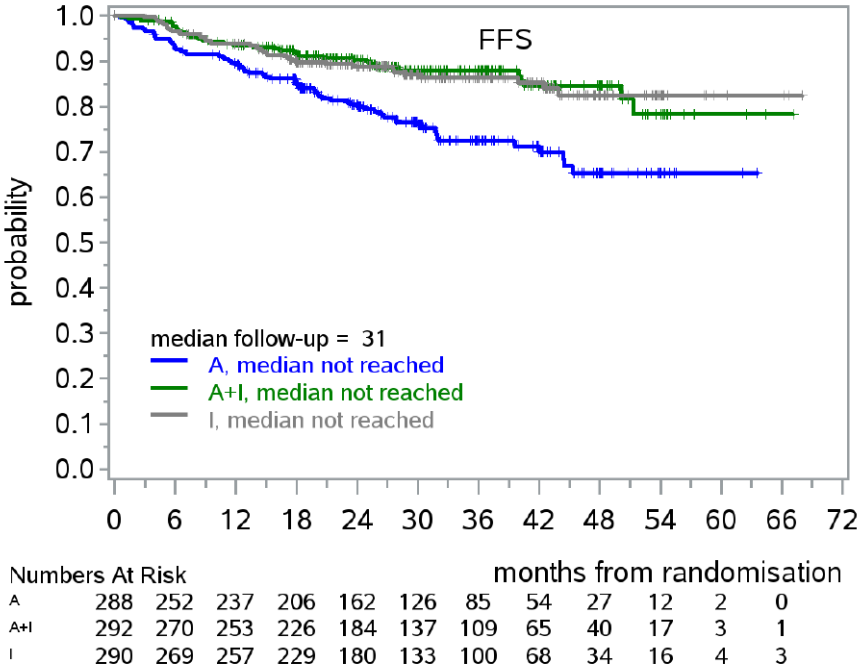
3y FFS: 86% (I)

3y FFS: 72% (A)

Superiority of A vs I is rejected

Conclusion #1: ibrutinib <u>should be</u> part of frontline therapy in younger patients

Dreyling M. *Lancet*, 2024; 403: 2293-2306



A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Median follow-up: 31 months

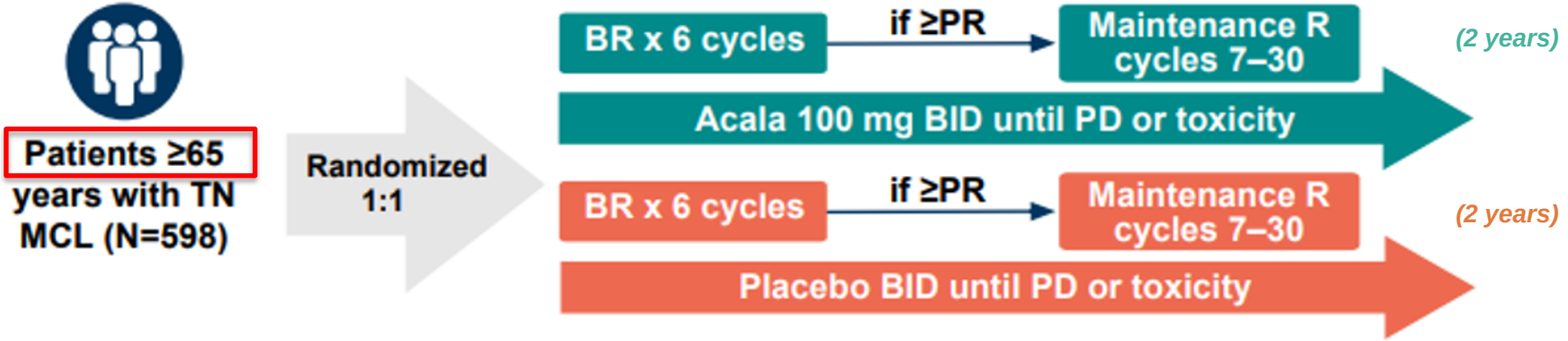
3y FFS (A+I) ~ 3y FFS (I)

Longer follow-up required for confirmation

Conclusion #2: ASCT <u>can be omitted</u> in ibrutinib-treated patients during induction.
ASCT may however maintain a role in high-risk disease (blastoid/pleomorphic, TP53^{mut}, high Ki67) as consolidation.

Dreyling M. *Lancet*, 2024; 403: 2293-2306

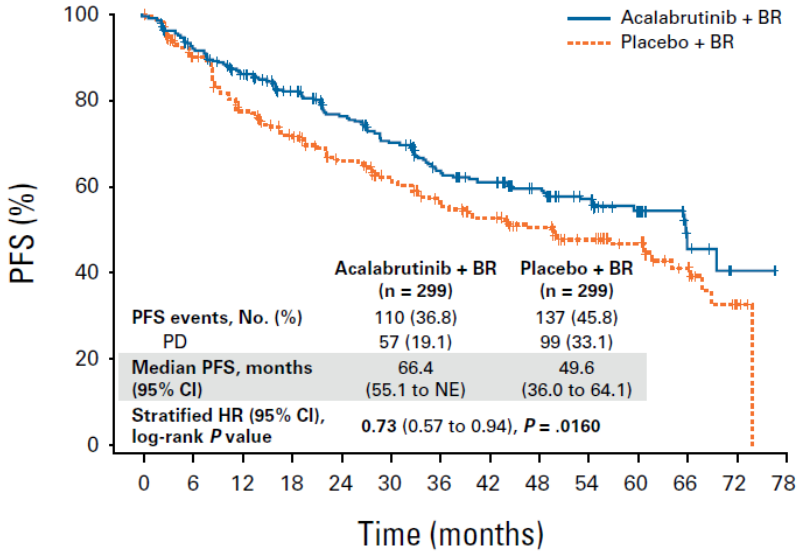
Acalabrutinib Plus Bendamustine-Rituximab in Untreated Mantle Cell Lymphoma



Wang M. *J Clin Oncol*, 2025; 43: 2276-2284

Acalabrutinib Plus Bendamustine-Rituximab in Untreated Mantle Cell Lymphoma

Full Analysis Population

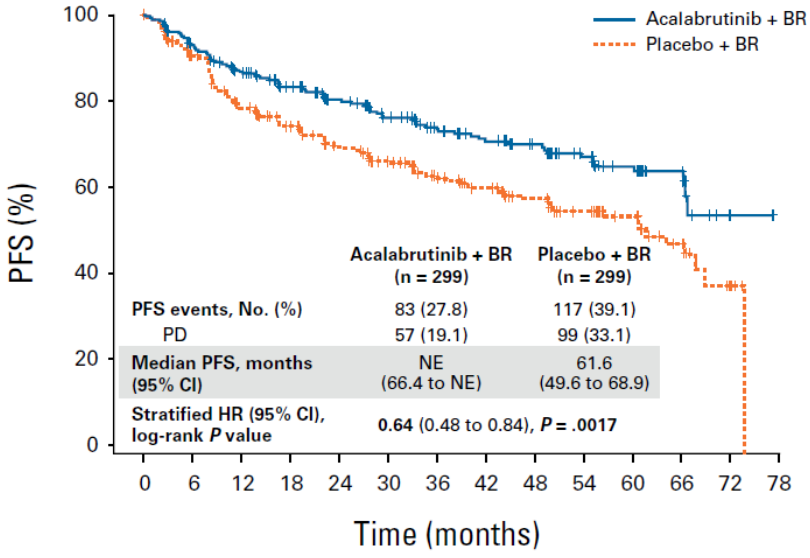


	Acalabrutinib + BR (n = 299)	Placebo + BR (n = 299)
PFS events, No. (%)	110 (36.8)	137 (45.8)
PD	57 (19.1)	99 (33.1)
Median PFS, months (95% CI)	66.4 (55.1 to NE)	49.6 (36.0 to 64.1)
Stratified HR (95% CI), log-rank *P* value	0.73 (0.57 to 0.94), *P* = .0160	

Number at risk

Acalabrutinib + BR	299	258	232	205	182	156	136	122	98	73	53	34	2	0
Placebo + BR	299	243	204	181	159	142	118	102	84	63	44	25	4	0

COVID-19 Deaths Censored



	Acalabrutinib + BR (n = 299)	Placebo + BR (n = 299)
PFS events, No. (%)	83 (27.8)	117 (39.1)
PD	57 (19.1)	99 (33.1)
Median PFS, months (95% CI)	NE (66.4 to NE)	61.6 (49.6 to 68.9)
Stratified HR (95% CI), log-rank *P* value	0.64 (0.48 to 0.84), *P* = .0017	

Number at risk

Acalabrutinib + BR	299	258	232	205	182	156	136	122	98	73	53	34	2	0
Placebo + BR	299	243	204	181	159	142	118	102	84	63	44	25	4	0

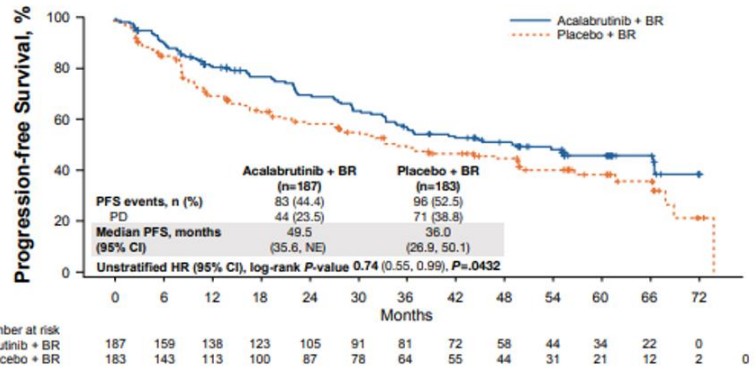
Wang M. *J Clin Oncol*, 2025; 43: 2276-2284

Efficacy of Rituximab-Bendamustine With or Without Acalabrutinib in Patients With Untreated, High-risk Mantle Cell Lymphoma: An Analysis of the Phase 3 ECHO Trial

Best Response of CR Significantly Higher With ABR in Patients With High-risk MCL

	ABR (n=187)	PBR (n=183)
	ORR	**CR**
Difference (ABR vs PBR)	5.1%	20.4%
95% CI	-1.7, 12.1	10.4, 30.0
P-value	.1382	**<.0001**

Significantly Longer PFS With ABR in Patients With High-risk MCL



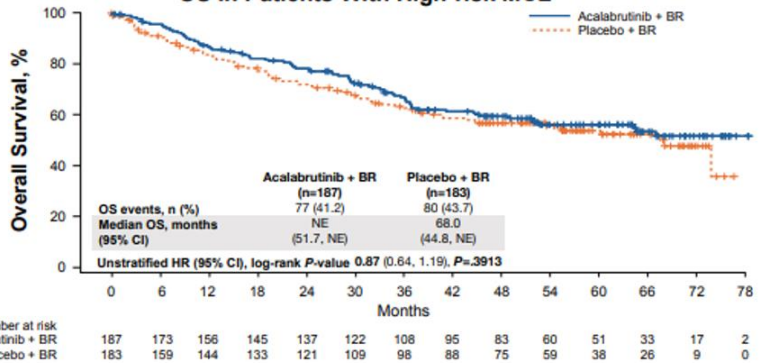
	Acalabrutinib + BR (n=187)	Placebo + BR (n=183)
PFS events, n (%)	83 (44.4)	96 (52.5)
PD	44 (23.5)	71 (38.8)
Median PFS, months (95% CI)	49.5 (35.6, NE)	36.0 (26.9, 50.1)

Unstratified HR (95% CI), log-rank *P*-value 0.74 (0.55, 0.99), ***P*=.0432**

Number at risk

Acalabrutinib + BR	187	159	138	123	105	91	81	72	58	44	34	22	0
Placebo + BR	183	143	113	100	87	78	64	55	44	31	21	12	2

OS in Patients With High-risk MCL



	Acalabrutinib + BR (n=187)	Placebo + BR (n=183)
OS events, n (%)	77 (41.2)	80 (43.7)
Median OS, months (95% CI)	NE (51.7, NE)	68.0 (44.8, NE)

Unstratified HR (95% CI), log-rank *P*-value 0.87 (0.64, 1.19), ***P*=.3913**

Number at risk

Acalabrutinib + BR	187	173	156	145	137	122	108	95	83	60	51	33	17	2
Placebo + BR	183	159	144	133	121	109	98	88	75	59	38	26	9	0

When considering only patients with any of 3 biological factors (*TP53* mutation, Ki-67 index ≥30%, and/or blastoid/pleomorphic histology), ABR demonstrated longer PFS vs PBR (HR 0.66; 95% CI 0.48, 0.91; *P*=.0119)

Patients with individual biological high-risk features had a numerically more pronounced benefit in PFS (blastoid/pleomorphic: HR 0.59; Ki-67 ≥30%: HR 0.63) compared with the total study population (HR 0.73)

However, data on *TP53* status were missing for >60% of patients, which did not allow for meaningful analysis as an individual risk factor

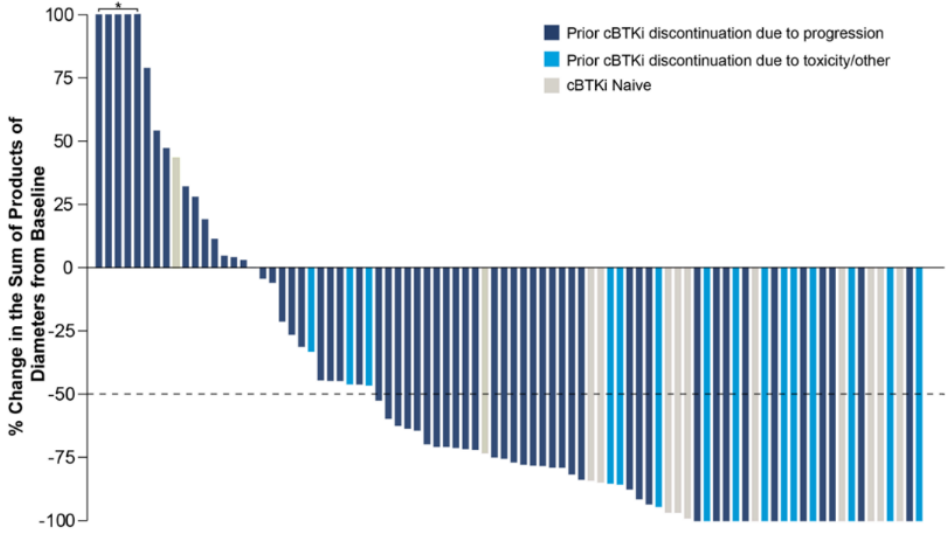
Dreyling M. *Hematol Oncol (18 ICML abstracts)*, 2025; 43(S3): 046a

Pirtobrutinib in Covalent Bruton Tyrosine Kinase Inhibitor Pretreated Mantle-Cell Lymphoma

Characteristics	cBTKi pre-treated MCL (n=90)	cBTKi Naïve MCL (n=14)
Median age, years (range)	70 (46-87)	67 (62, 72)
Male, n (%)	72 (80)	10 (71)
Histology, n (%)		
Classic/Leukemic	70 (78)	11 (79)
Pleomorphic/Blastoid	20 (22)	3 (21)
ECOG PS, n (%)		
0	61 (68)	5 (36%)
1	28 (31)	8 (57%)
2	1 (1)	1 (7%)
Median number prior lines of systemic therapy (range)	3 (1-8)	2 (1, 3)
sMIPI Score, n (%)		
Low risk (0-3)	20 (22)	3 (21)
Intermediate risk (4-5)	50 (56)	5 (36)
High risk (6-11)	20 (22)	6 (43)
Tumor Bulk (cm), n (%)		
<5 / ≥5	65 (72) / 24 (27)	9 (64) / 5 (36)
<10 / ≥10	80 (89) / 3 (3)	11 (79%)/ 2 (14%)
Bone Marrow Involvement, n (%)		
Yes	46 (51)	4 (29%)
No	44 (49)	10 (71%)
Reason discontinued any prior cBTKi, n (%)		
Progressive disease	74 (82)	-
Toxicity/Other	16 (18)	-
Prior therapy, n (%)		
BTK inhibitor	**90 (100)**	**0 (0%)**
Anti-CD20 antibody	**86 (96)**	**14 (100%)**
Chemotherapy	**79 (88)**	**14 (100%)**
Immunomodulator	19 (21)	1 (7%)
Stem cell transplant	19 (21)	7 (50%)
BCL2 inhibitor	14 (16)	0 (0%)
CAR-T	4 (4)	0 (0%)
PI3K inhibitor	3 (3)	1 (7%)

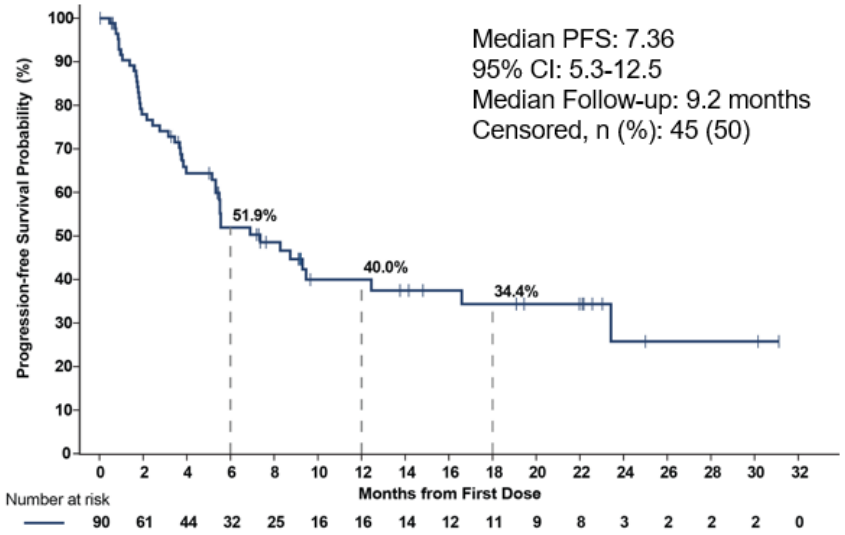
cBTKi pre-treated MCL patients	n=90
Overall Response Rate, %	57.8%
(95% CI)	(46.9-68.1)
Best response	
CR, n (%)	18 (20.0)
PR, n (%)	34 (37.8)
SD, n (%)	14 (15.6)
PD, n (%)	15 (16.7)

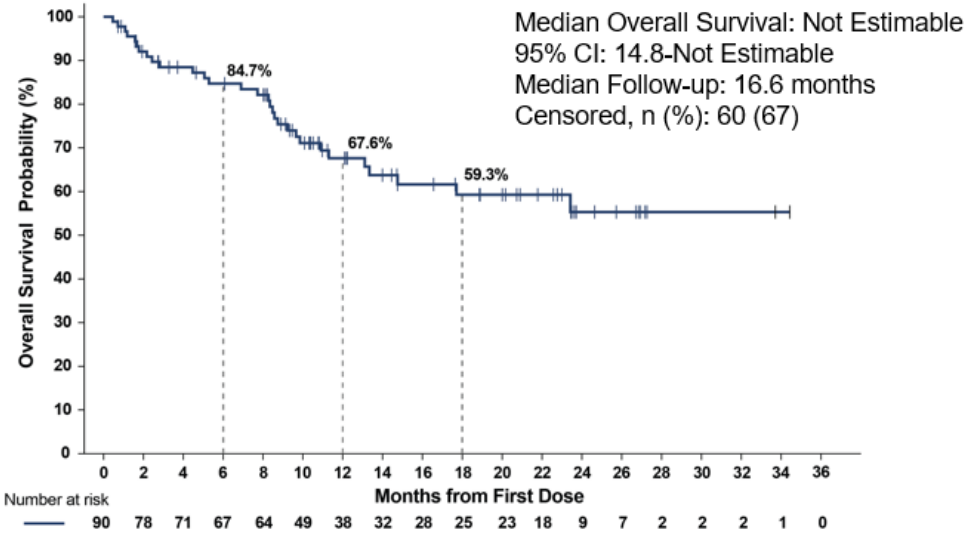
cBTKi Naïve MCL patients	n=14
Overall Response Rate, %	85.7%
(95% CI)	(57.2-98.2)
Best response	
CR, n (%)	5 (35.7)
PR, n (%)	7 (50.0)
SD, n (%)	0 (0.0)
PD, n (%)	1 (7.1)



Wang M. *J Clin Oncol*, 2023; 41: 3988-3997

Pirtobrutinib in Covalent Bruton Tyrosine Kinase Inhibitor Pretreated Mantle-Cell Lymphoma





Wang M. *J Clin Oncol*, 2023; 41: 3988-3997

Take home messages

- Covalent BTK inhibitors currently represent the standard therapy of relapsed and refractory marginal zone lymphoma regardless of prior therapy and disease presentation.

- Ibrutinib and acalabrutinib are now part of frontline treatment of mantle cell lymphoma patients along with chemoimmunotherapy. Post-induction maintenance with both rituximab and covalent BTK inhibitor is always required. Ibrutinib-based frontline treatment reduces (possibly abrogates) the indication of a consolidative autologous stem cell transplantation.

- The non-covalent BTK inhibitor, pirtobrutinib, is indicated whenever patients progress on covalent BTK inhibitors. It is now considered the best salvage therapy in marginal zone lymphoma and the most suitable second line in mantle cell lymphoma previously treated with ibrutinib or zanubrutinib.

- A careful revision of concomitant medications and a close patient monitoring is always necessary when treatment with BTK inhibitors is given.