HIGHLIGHTS IN EMATOLOGIA

TREVISO
7-8 NOVEMBRE 2025

BTKi e nuovi farmaci nei pazienti ricaduti/refrattari

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Ematologia Treviso

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					x		
Astrazeneca					x		
Beone					x		
Janssen					x		

LINFOMA MARGINALE

- III sottotipo di B-LNH più comune, II più frequente tra i B-LNH indolenti

- WHO identifica 3 sottotipi in base alla sede primaria di coinvolgimento
  61% LNH marginale (MZ) extranodale (EMZL)
  30% LNH marginale nodale (NMZL)
  9% LNH marginale splenico (SMZL)

- Eterogeneità clinica

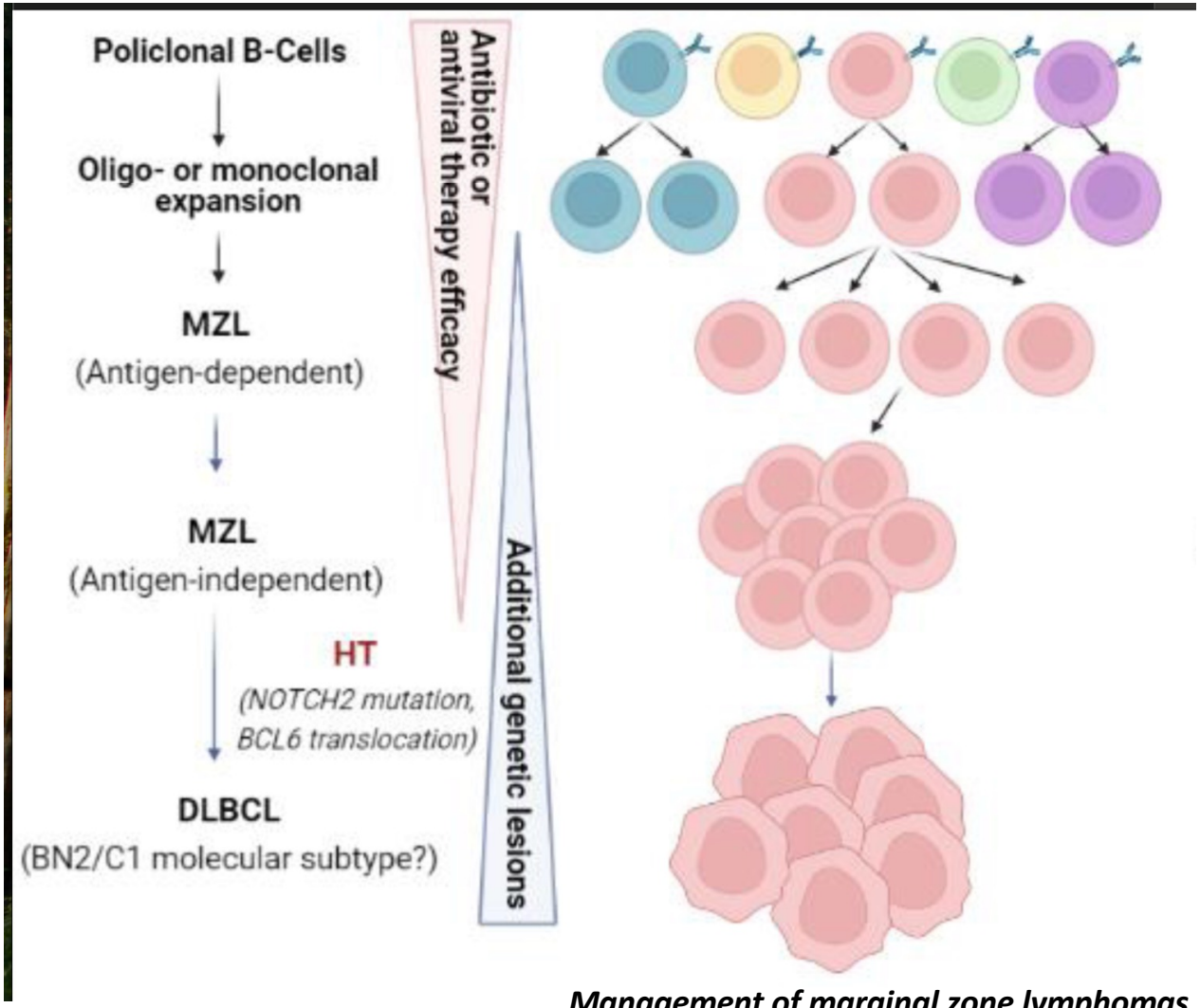
- Incidenza aumenta con età

CRITERI GELF di TRATTAMENTO = CRITERI PER LF

Any nodal or extranodal tumor mass ≥7 cm
≥ 3 nodal sites, each >3cm
Presence of B symptoms
Splenomegaly
Compression or vital organs compromise
Significant serous effusions
Lymphocyte count >5.0 x 10^9/L
Cytopenias (granulocytes <1.0 x 10^9/L and/or platelets <100 x 10^9/L)

*All presented as a percentage of total B cells normalised to 100%.

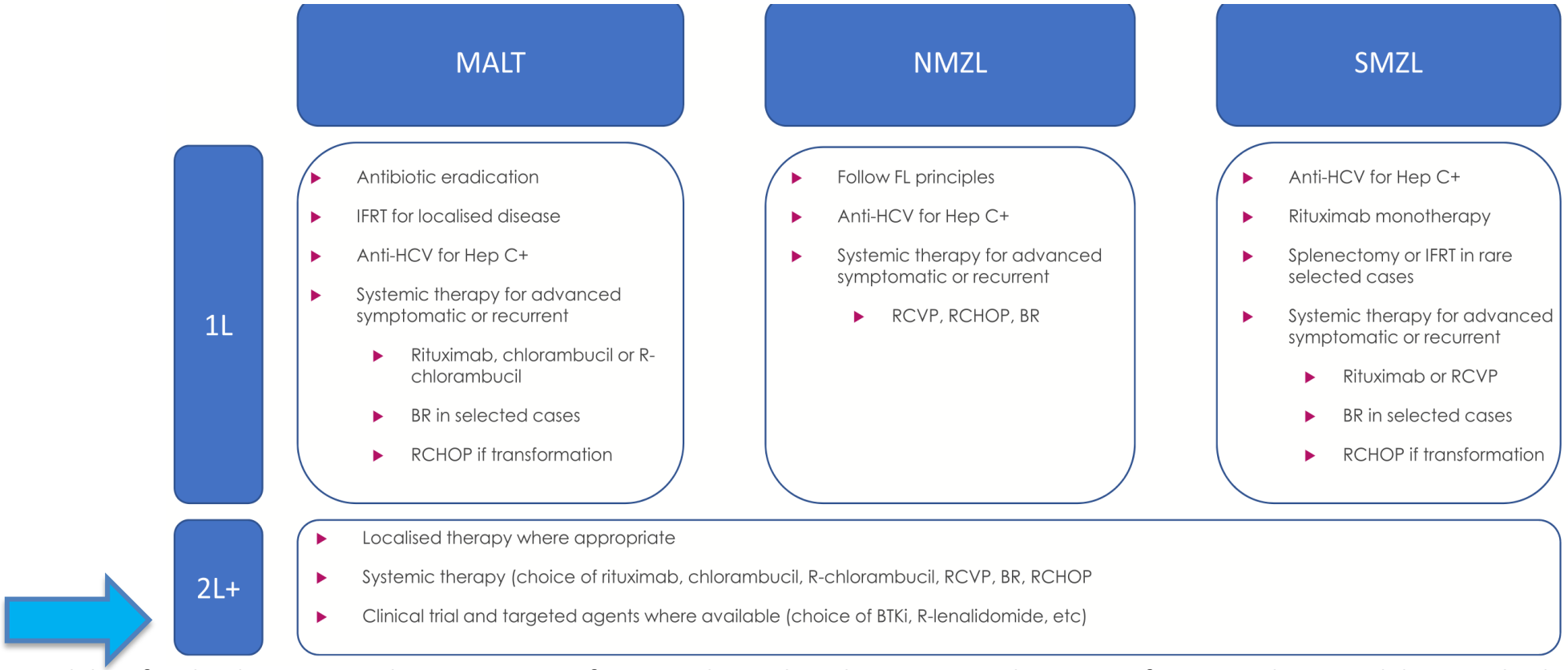
Efficacia di nuove potenziali linee di trattamento si basa prevalentemente su dati derivati da trial clinici randomizzati costruiti per LNH B indolenti e quindi comprendenti per gran parte pazienti affetti da linfoma follicolare e in minima parte da linfoma marginale



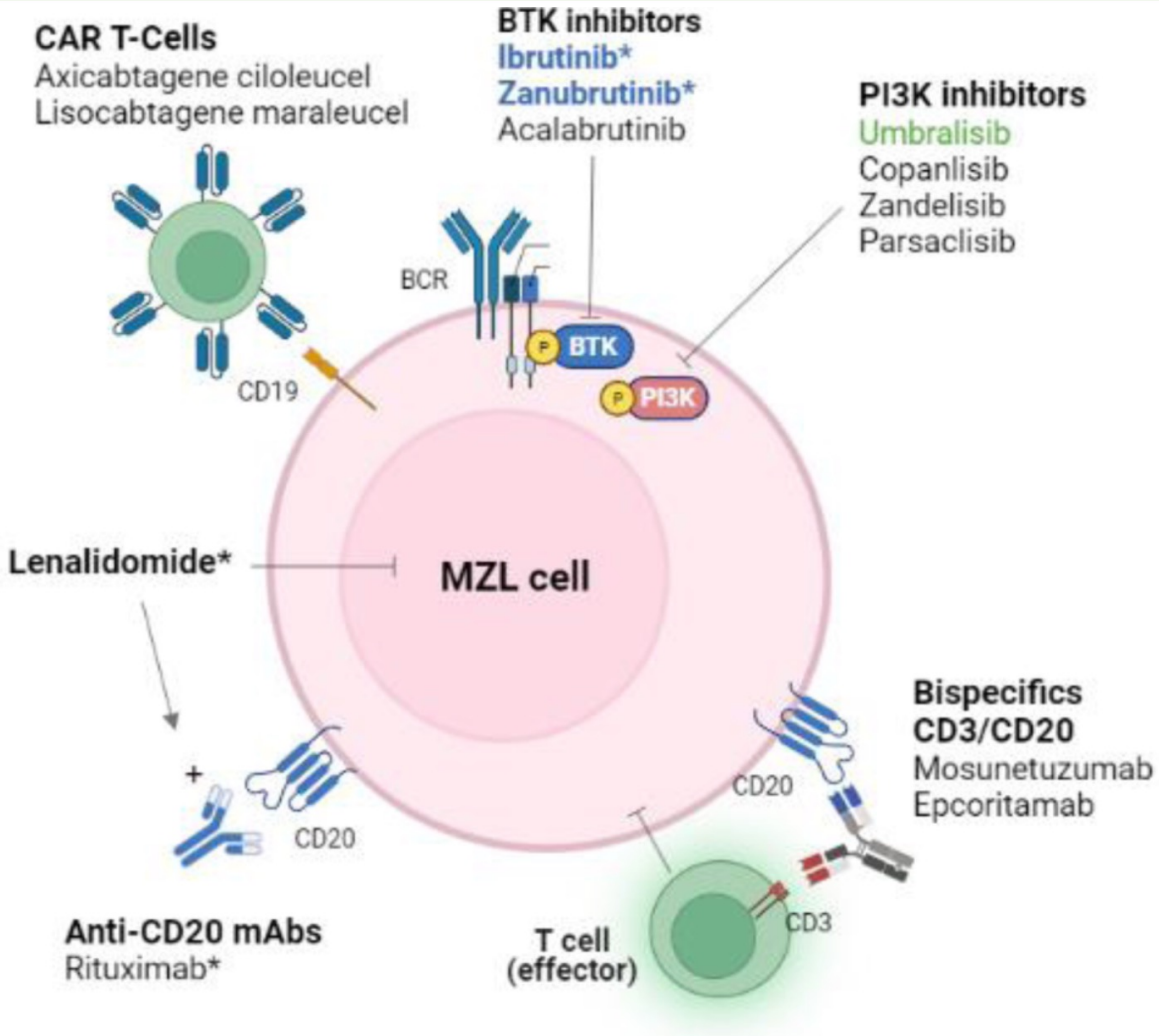
Management of marginal zone lymphomas. Merli M. et al ASH 2022

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

Guideline for the diagnosis and management of marginal zone lymphomas: A British Society of Haematology Guideline



Guideline for the diagnosis and management of marginal zone lymphoma: a British Socitey of Haematology Guideline. Walwska R. et al BJHaem 2024



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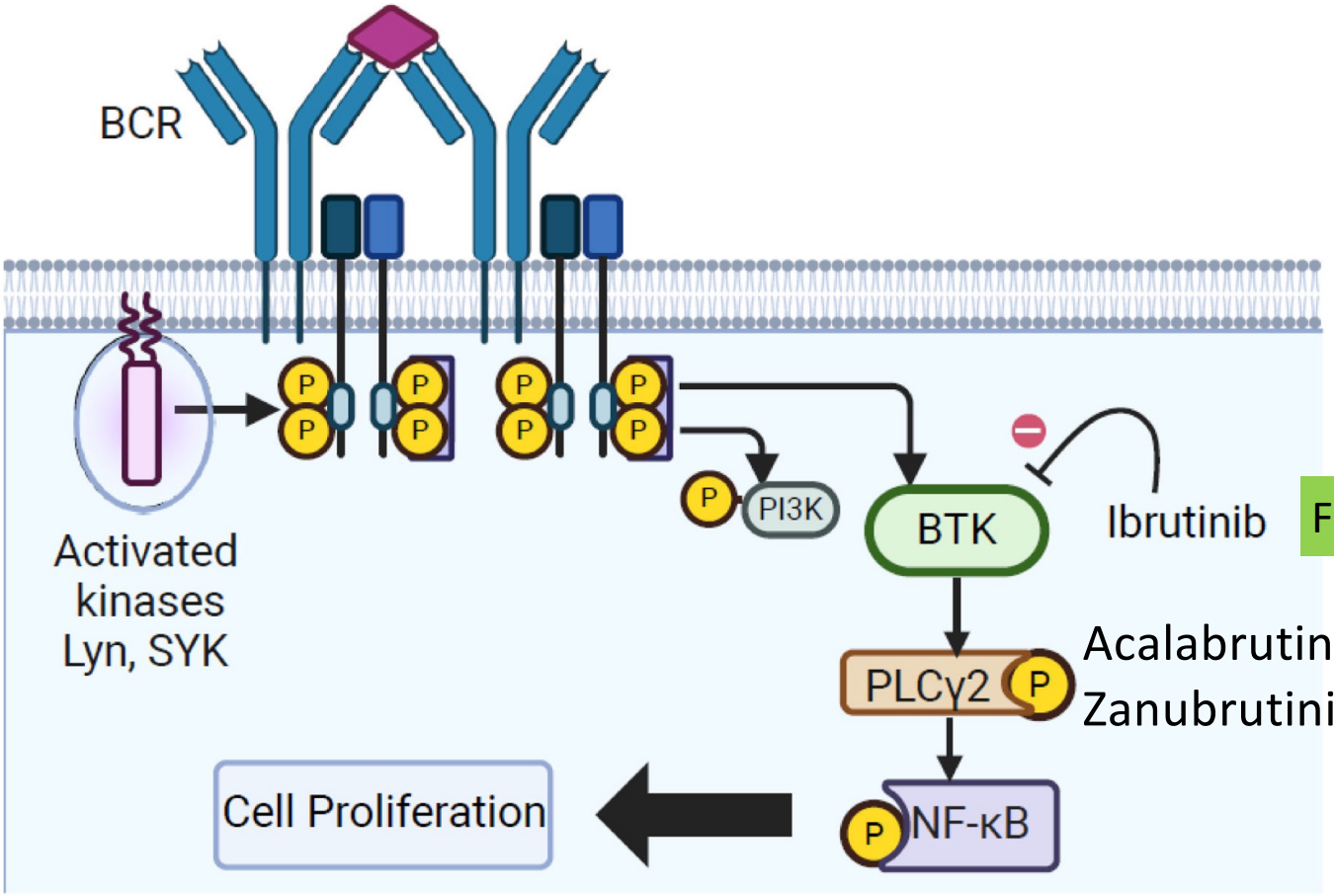
BTK inhibitors covalenti (BTKc)



BTK inhibitors: Past, Present and Future. Cool A. R. et al Trend Pharmacol Sci 2025

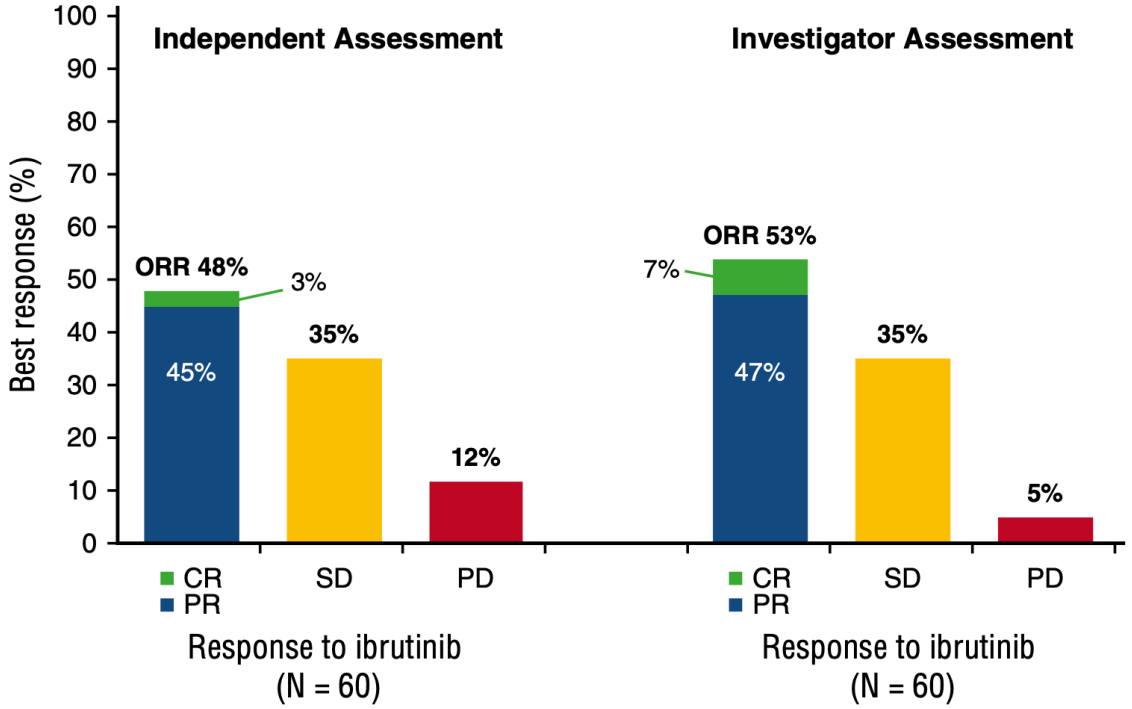
Table 5 Selected features of approved BTK inhibitors and those in later-stage clinical development

Parameter	Ibrutinib [4, 5]	Acalabrutinib [7, 8]	Zanubrutinib [10]	Tirabrutinib [13, 17]	Orelabrutinib [28, 104]	Pirtobrutinib [20]	Nemtabrutinib [23]
Other names	Imbruvica®; PCI-32765	Calquence®; ACP-196	Brukinsa®; BGB-3111	Velexbru®; ONO-4059	宜诺凯®; ICP 022	LOXO-305	MK-1026; ARQ-531
Phase of development[a]	Marketed	Marketed	Marketed	Marketed	Marketed	Phase III	Phase II
First approval	2013 (USA)	2017 (USA)	2019 (USA)	2020 (Japan)	2020 (China)		
Approved indications[a]	CLL (USA, EU, plus several other countries); MCL (USA, EU, Japan, Mexico); MZL (USA, Canada); WM (USA, EU)	CLL (USA, EU, plus several other countries); MCL (USA, plus several other countries)	CLL (China); MCL (USA, plus several other countries); MZL (USA); WM (USA, Australia, Canada, China)	PCNSL (Japan); WM (Japan)	CLL (China); MCL (China)		
Dosage[b]	420 mg QD in CLL; 560 mg QD in MCL/MZL	100 mg bid	160 mg bid or 320 mg QD	480 mg QD	150 mg QD	200 mg QD	65 mg QD
Use in patients with renal impairment							
Mild	Yes	Yes	Yes	Yes	Yes		
Moderate	Yes	Yes	Yes	Yes	With caution		
Severe	No data	No data	Yes	No data	With caution		
ESRD	No data	No data	No data	No data	No data		
Use in patients with hepatic impairment							
Mild	Reduce dose	Yes	Yes	Yes	Yes		
Moderate	Reduce dose	Yes	Yes	No data	With caution		
Severe	No	No	Reduce dose	No data	No		
Food effect	No	No	No	Yes	No		
Most common adverse events	Thrombocytopenia, diarrhoea, fatigue, musculoskeletal pain, neutropenia, rash	Anaemia, neutropenia, URTI, thrombocytopenia, headache, diarrhoea, musculoskeletal pain	Neutropenia, thrombocytopenia, URTI, leukopenia, anaemia, rash	Rash, neutropenia, leukopenia, stomatitis, thrombocytopenia, nausea	Neutropenia, thrombocytopenia, URTI, leukopenia, anaemia, rash	Fatigue, bruising, diarrhoea, neutropenia, rash, nausea	URTI, back pain, bruising, cough, nausea, diarrhoea

Bruton Tyrosine Kinase inhibitors in B-Cell Malignancies: Their Use and Differantial Features Shirley M. et al Target Oncology 2022

CLINICAL TRIALS AND OBSERVATIONS

Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma



Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Noy A. et al Blood 2017

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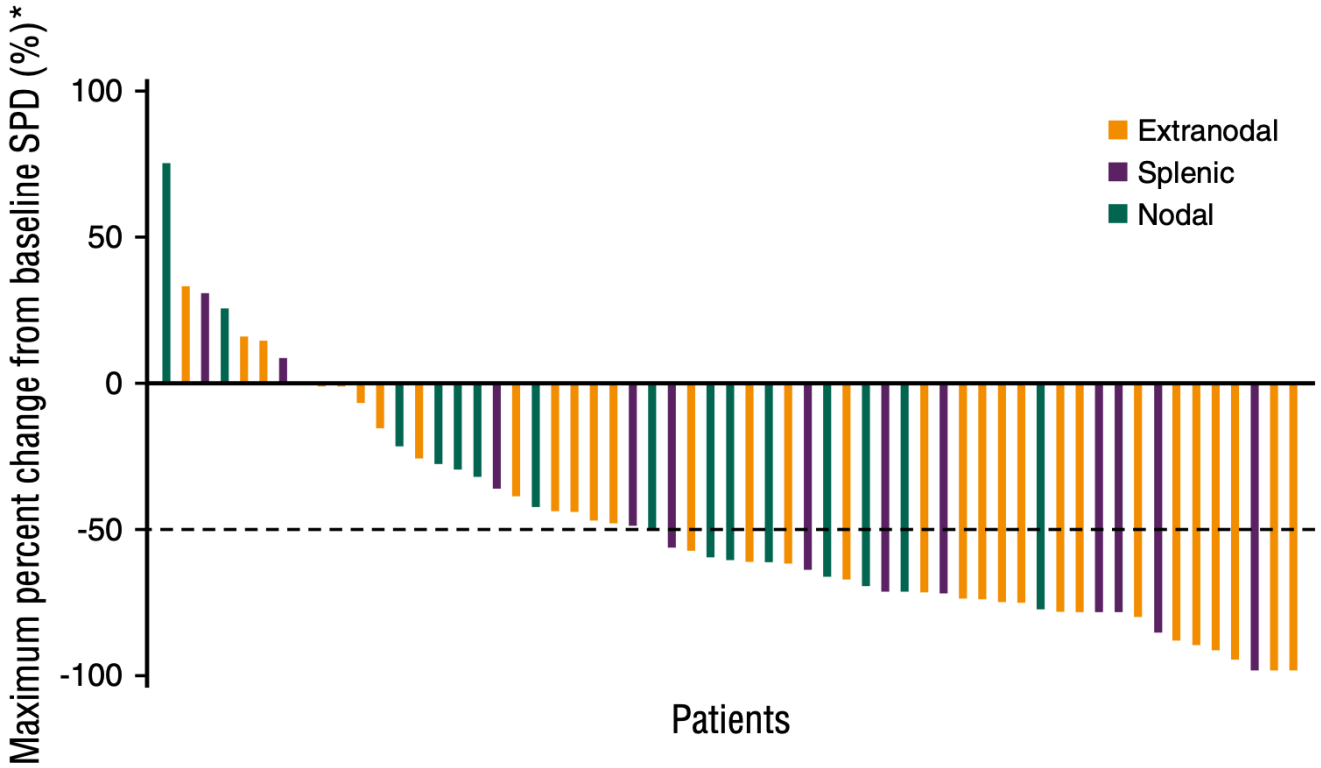

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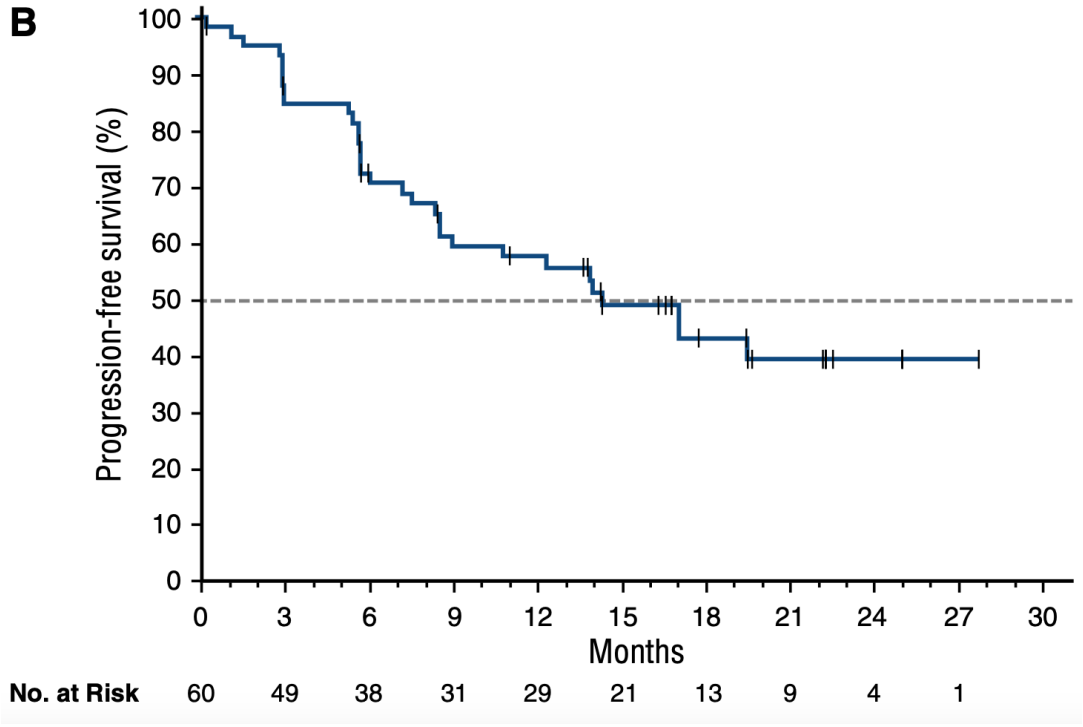


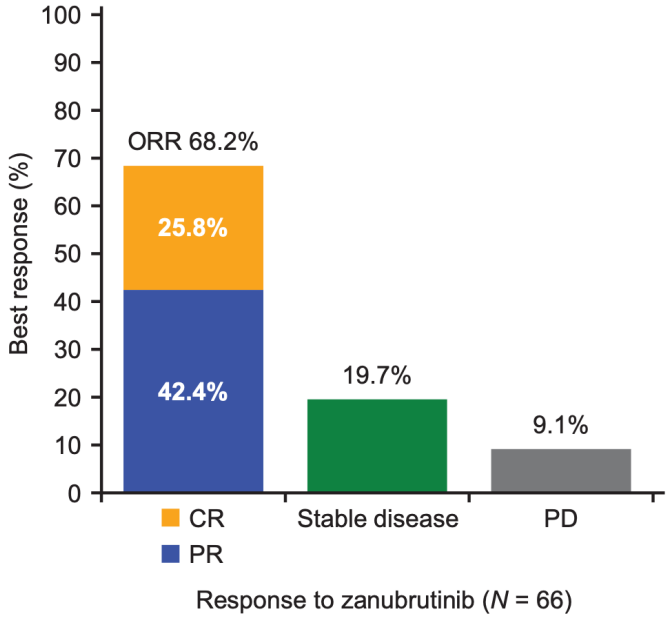
PFS mediana:

- ✓ 13.8 mesi EMZL
- ✓ 19.4 mesi SMZL
- ✓ 8.3 mesi NMZL

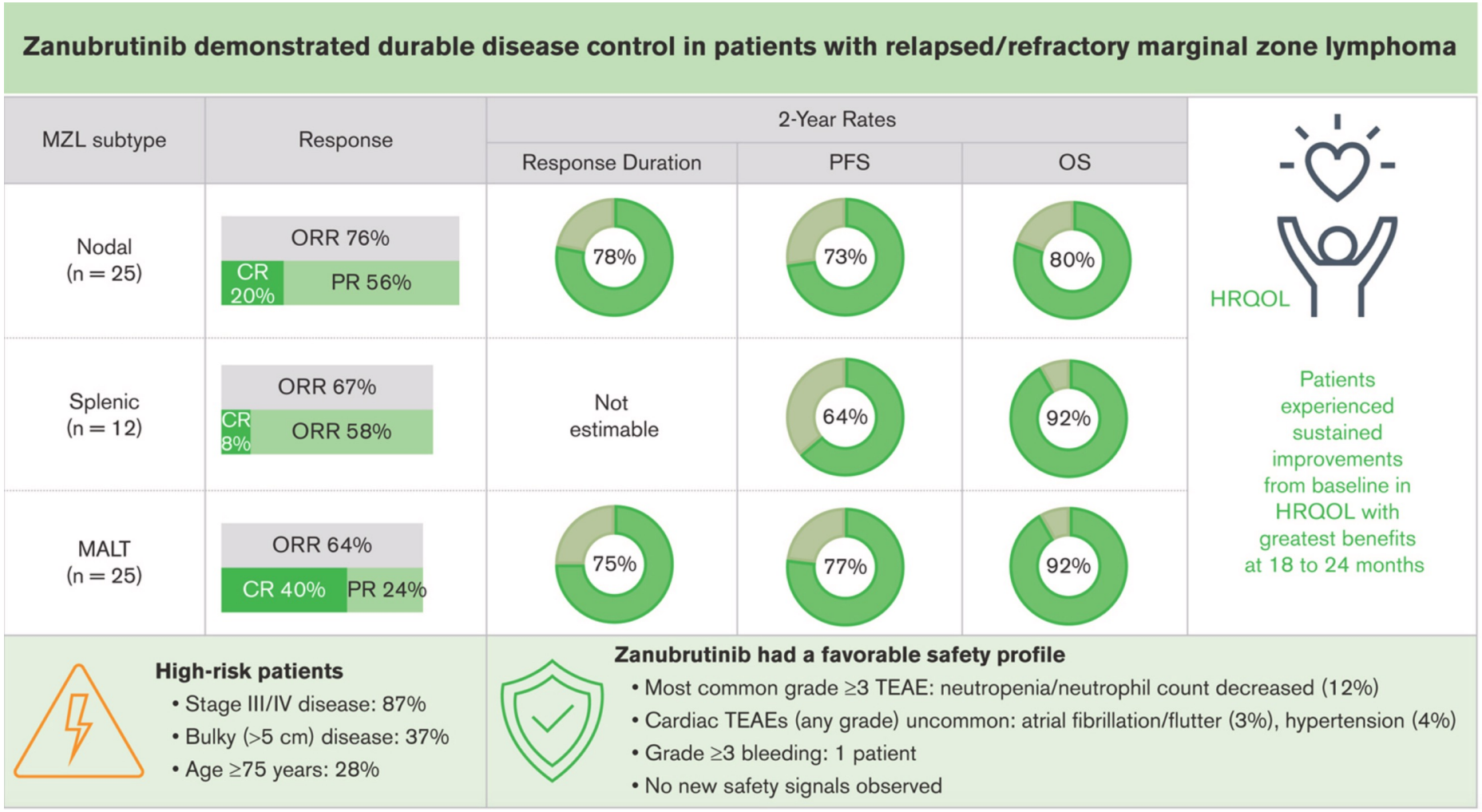
Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Noy A. et al Blood 2017

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

The MAGNOLIA Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inhibitor, Demonstrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma



The Magnolia Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inibithor, Demostrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma. Opat S. et Clin Cancer Res 2021



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EFFICACIA

ORR 68.2%

vs

48% Ibrutinib

49% Umbrasilib

54% Parsaclisib

65% R-Lenalidomide

76% Copanlisib

SICUREZZA

Incidenza sospensione per AE 5.9%	No riduzione dose
vs	vs
17% Ibrutinib	10% Ibrutinib
15.4% Umbrasilib	9.6% Umbrasilib
14.6% R-Lenalidomide	26% R-Lenalidomide

The Magnolia Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inibithor, Demostrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma. Opat S. et Clin Cancer Res 2021

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

The MAGNOLIA Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inhibitor, Demonstrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma

BIOMARKER SUBSTUDY

- Mutazione di geni associati a NF-kB pathway (MYD88 e NTFAIP3) sembrano migliorare PFS
- Mutazioni acquisite di BTK e PLC2 precedono progressione di malattia

The Magnolia Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inibithor, Demostrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma. Opat S. et Clin Cancer Res 2021

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BTK Inhibitors: Past, Present, and Future

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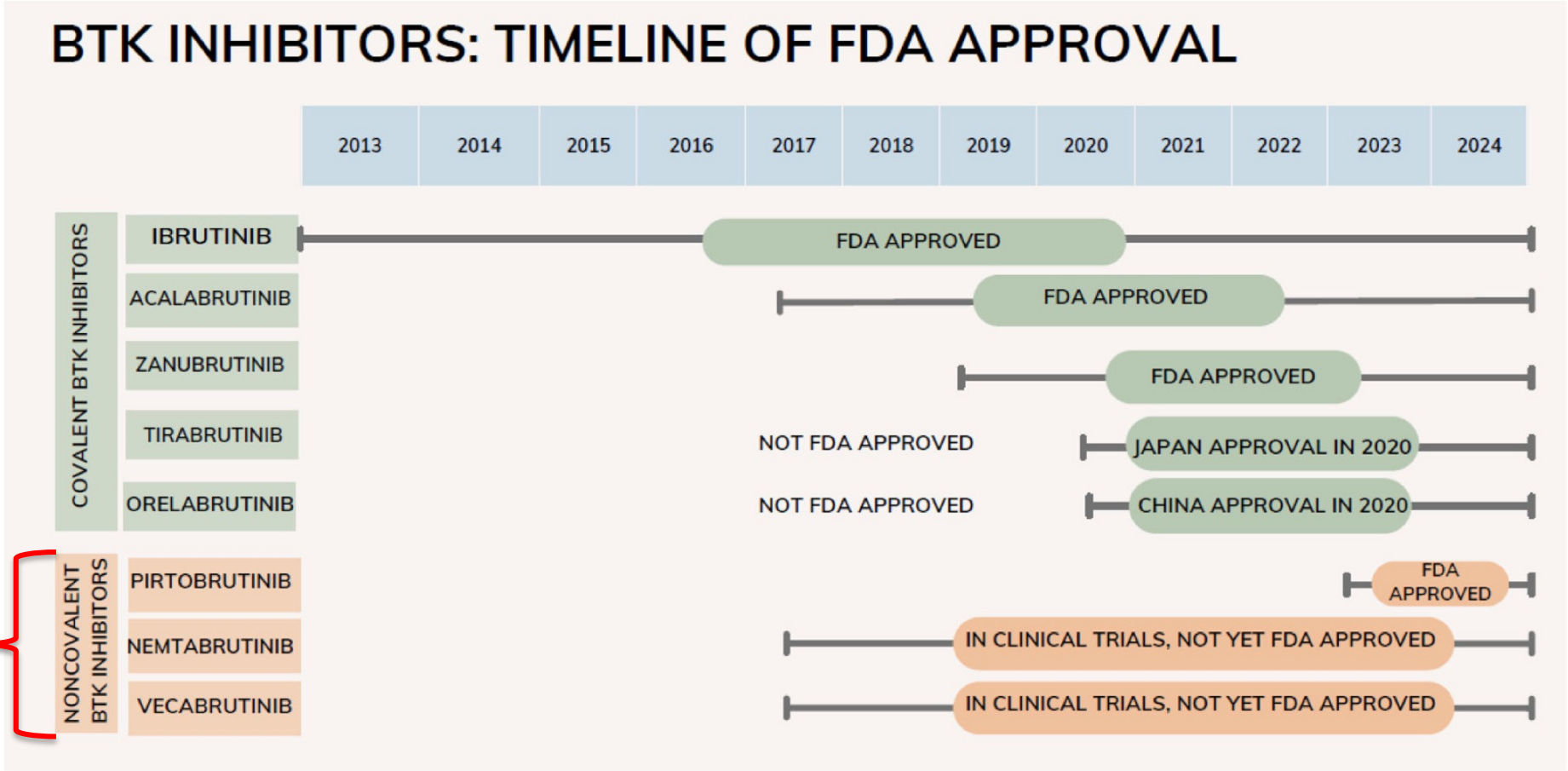
[1]Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine, Miami, FL, USA

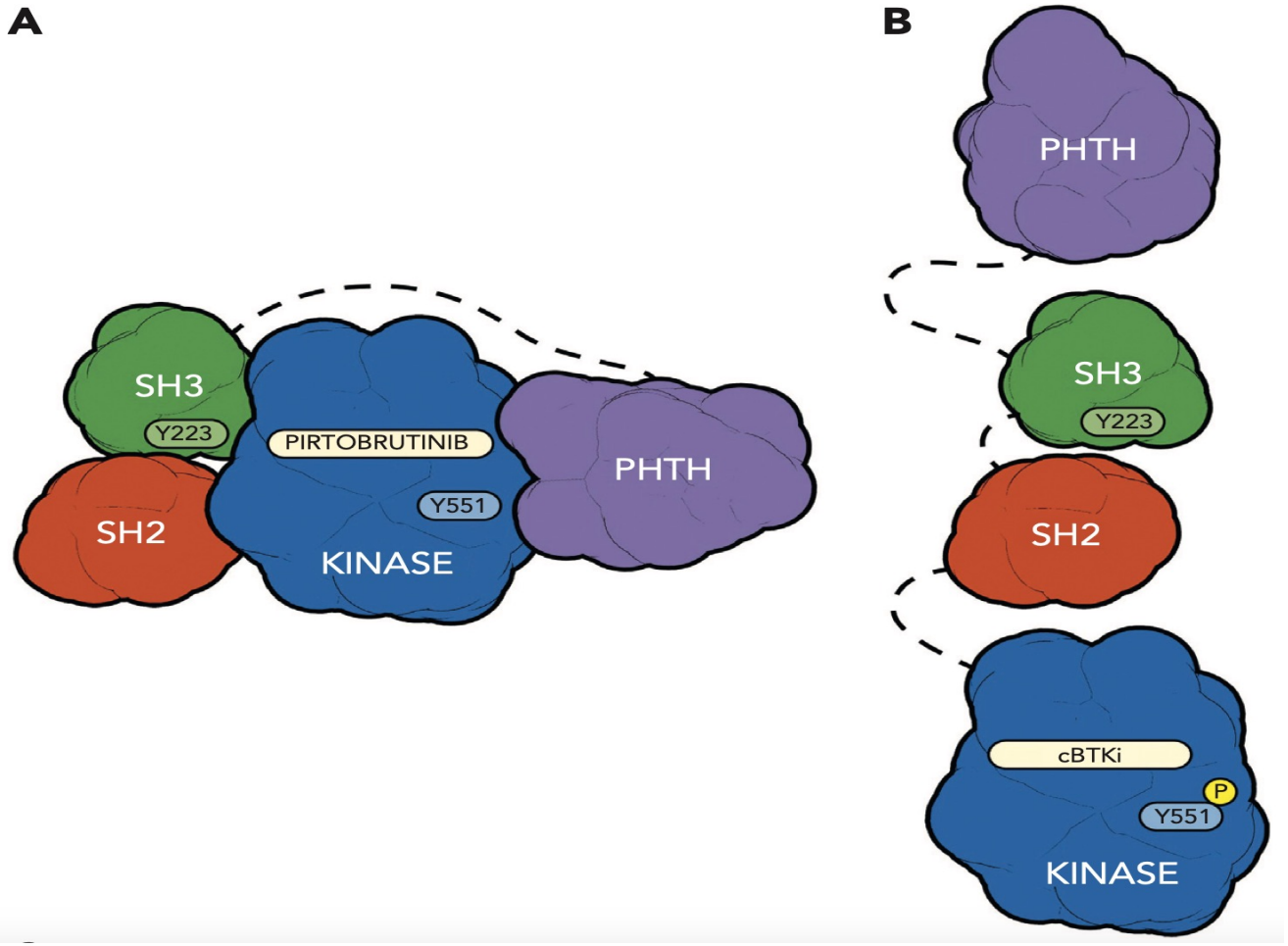
BTK is an Attractive Target Prone to Resistance

BTK inhibitors: Past, Present and Future. Cool A. R. et al Trend Pharmacol Sci 2025



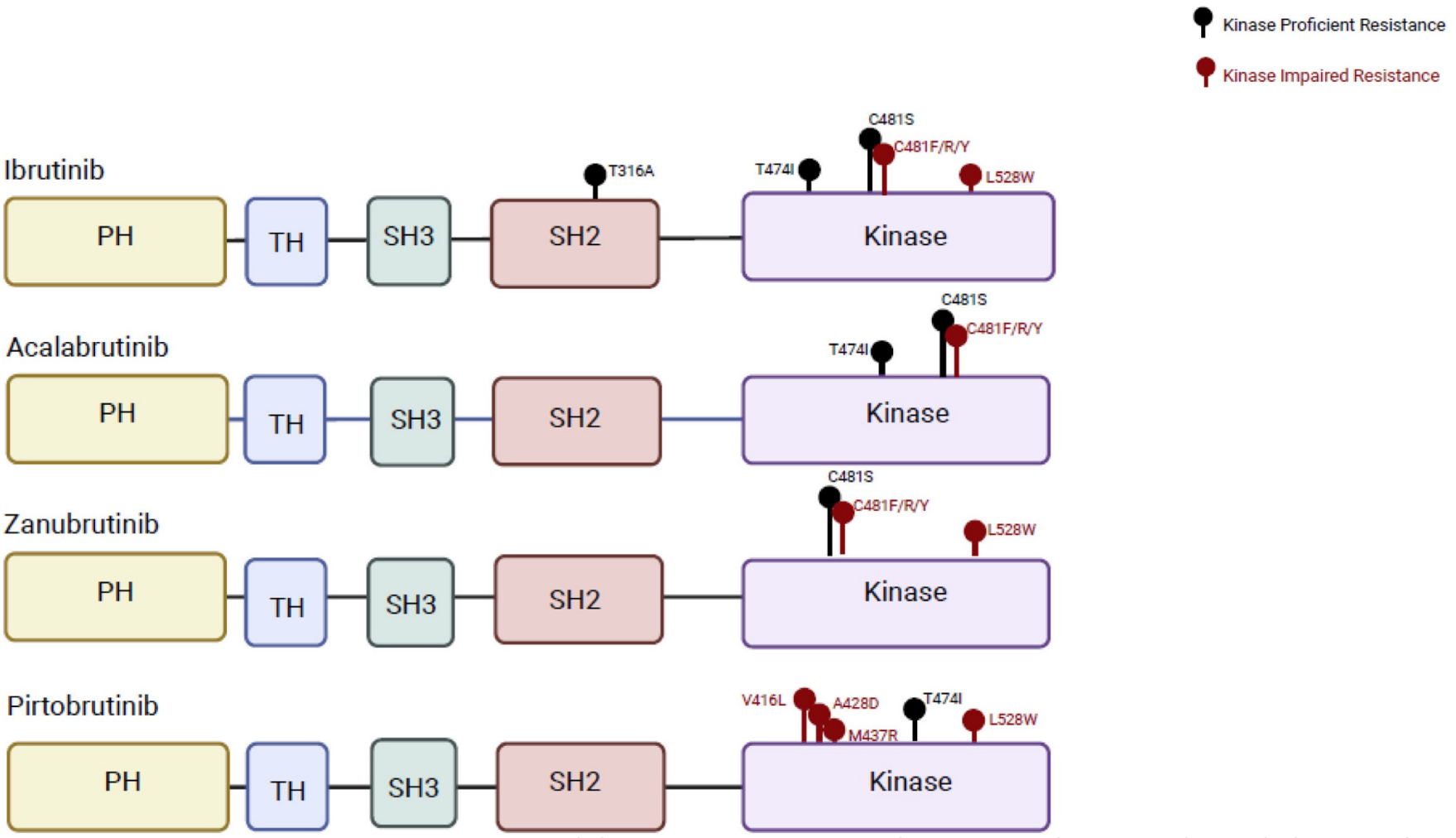
BTK inhibitors: Past, Present and Future. Cool A. R. et al Trend Pharmacol Sci 2025

BTK inhibitors non covalenti



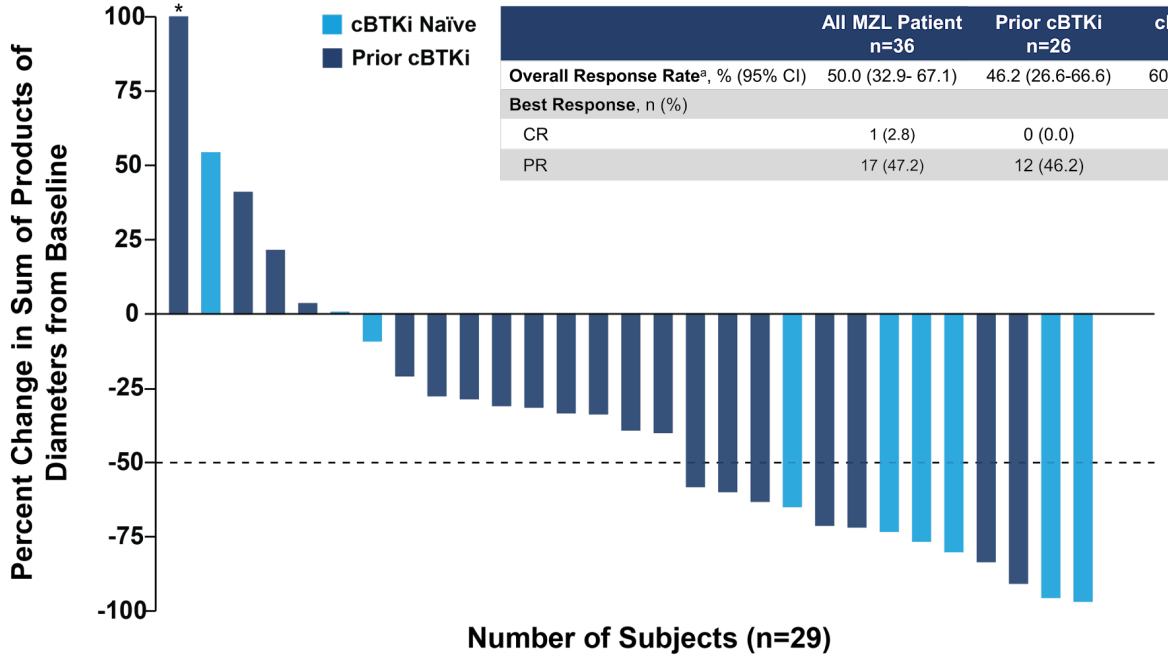
BTK inhibitors covalenti

Preclinical characterization of pirtobrutinib, a highly selective, noncovalent (reversible) BTK inhibitor. Gomez E. B. et al Blood 2023



BTK inhibitors: Past, Present and Future. Cool A. R. et al Trend Pharmacol Sci 2025

Pirtobrutinib, a Highly Selective, Non-covalent (Reversible) BTK Inhibitor in Relapsed / Refractory Marginal Zone Lymphoma: Results from Phase 1/2 BRUIN Study



	All MZL Patient n=36	Prior cBTKi n=26	cBTKi Naïve n=10
Overall Response Rate[a], % (95% CI)	50.0 (32.9- 67.1)	46.2 (26.6-66.6)	60.0 (26.2-87.8)
Best Response, n (%)			
CR	1 (2.8)	0 (0.0)	1 (10.0)
PR	17 (47.2)	12 (46.2)	5 (50.0)

- Median time-to-response was 1.9 months (range, 1.6-19.3)

Review

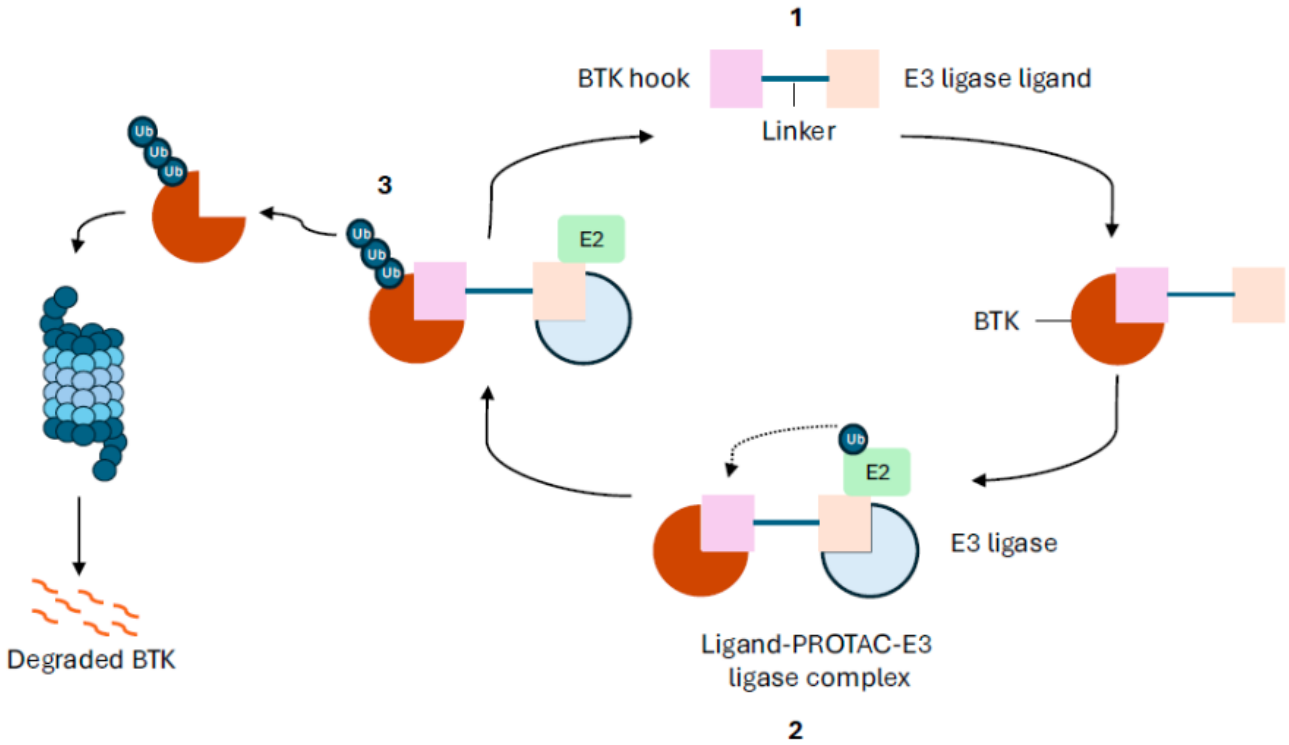
BTK Is the Target That Keeps on Giving: A Review of BTK-Degrader Drug Development, Clinical Data, and Future Directions in CLL

BTK Mutations Leading to Covalent BTKi Resistance	BTK Mutation Enriched by Exposure to Specific cBTKi	Pirtobrutinib Sensitive?	BTK Mutations Leading to Pirtobrutinib Resistance	BTK Degrader Sensitive?
C481S [22]	Ibrutinib/zanubrutinib/ acalabrutinib	Yes [13]	L528W [20,23]	Yes
L528W [24]	Zanubrutinib	No [20]	T474I [20,23]	Yes
T474I [25]	Acalabrutinib	No [20]	A428D [20,23]	?BGB-16673 resistant [26]
			M437R [20,23]	Yes
			V416L [23]	Yes
			C481F [23]	Yes
			C481R [20]	Yes

BTKi, Bruton tyrosine kinase inhibitor; cBTKi, covalent BTK inhibitor; ?, query.

BTK Is the Target That Keeps on Giving: A Review of BTK-Degrader Drug Development, Clinical Data, anf Future Direction in CLL. Salvaris R. T. et al Cancer 2025

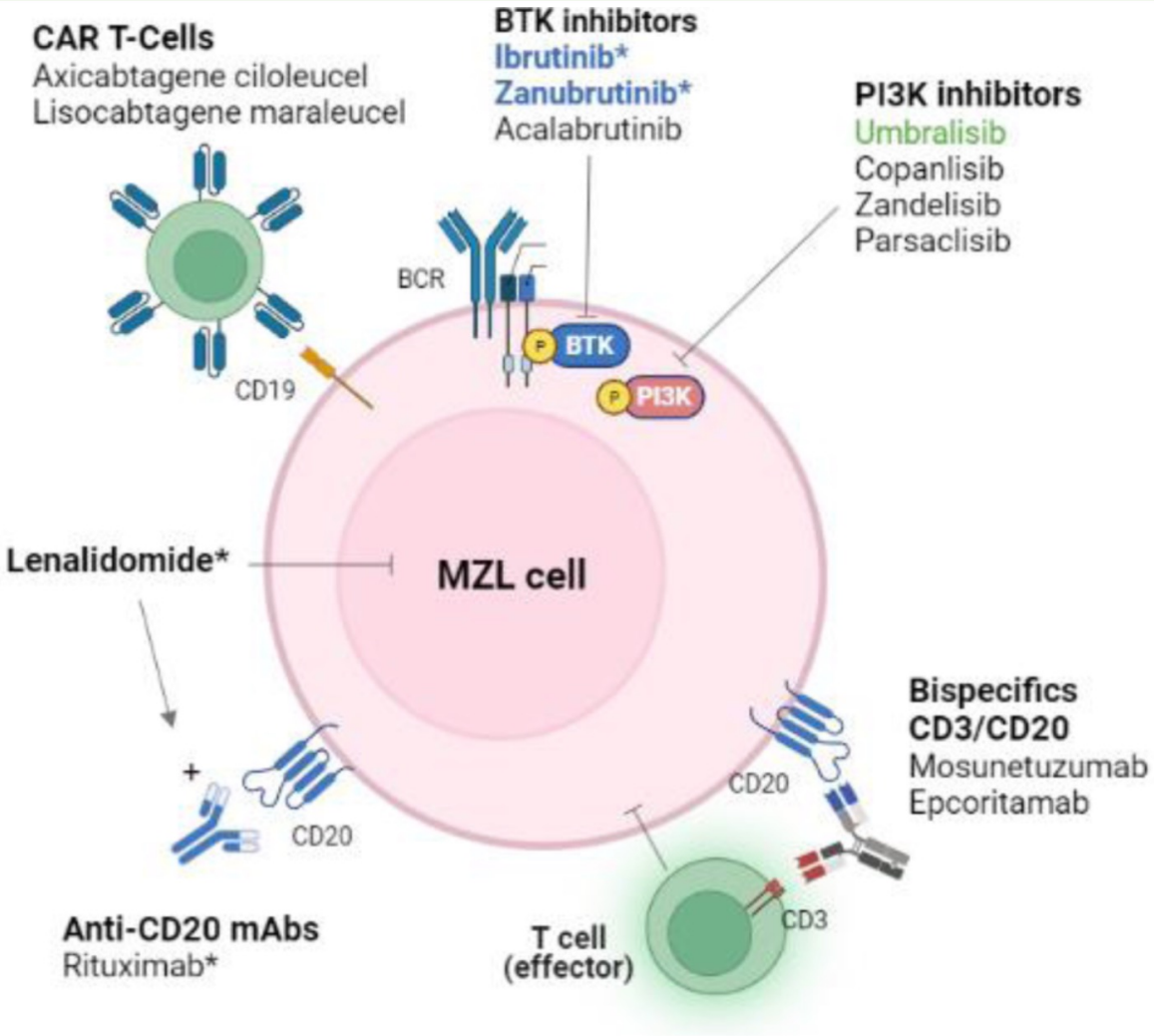
BTK degrader



BTK Is the Target That Keeps on Giving: A Review of BTK-Degrader Drug Development, Clinical Data, anf Future Direction in CLL. Salvaris R. T. et al Cancer 2025

Compound	Trial	CLL/SLL pts, n	CLL Features	Regimen	Prior Therapies (Range)	Efficacy (CLL) n (%)	Toxicity n (%)			FU Months (Range)	Notes
							Adverse Event	All	G ≥ 3		
BGB-16673 [46]	CaDAnCe-101 (NCT05006716)	49	IGHVu 82% TP53 mut or 17p—63% Complex karyotype 47% Known BTK mutation 32%	QD Oral Continuous Dose levels 50–600 mg	Median 4 (2–10) cBTKi: 92% BCL2i: 86% ncBTKi: 24% 22%	ORR 38/49 (78%) ORR at 200 mg dose = (15/16) 94% CR 2/49 (4%) (both at 200 mg) Responses in high risk and patient with BTK mutations	Fatigue Contusion Anemia Diarrhea Neutropenia No AF, No G ≥ 3 hypertension	17 (35%) 14 (29%) 11 (22%) 13 (27%) 11 (22%)	1 (2%) - 1 (2%) 1 (2%) 10 (20%)	Median 7.9 (0.3–23.1)	Other eligible B-cell histologies: MZL, FL, MCL, WM, DLBCL, RT N = 1 dose limiting toxicity; grade 3 rash—resolved to grade 1 and patient continued on treatment without recurrence. Median time to first response = 2.8 months range (2.6–8.3) 40/49 (82%) remain on treatment
NX-5948 [47]	NX-5948-301 (NCT05131022)	34	Known BTK mutation 42% TP53 mutation 48.4% PCLG2 mutation 17%	QD Oral Continuous Dose levels 50–600 mg	Median 4 (2–14) cBTKi/ncBTKi + BCL2i: 88%	ORR 30/34 (76.4%) CR 0/30 (0%)	Contusion Platelet decreased Neutropenia No AF	15 (44.1%) 8 (23.5%) 6 (17.6%)	- 1 (2.9%) 5 (14.7%)	Median 4.7 (0.7–17.0)	Pre-clinical data—can cross blood-brain-barrier → patients with CNS involvement eligible (n = 6 NHL) n = 1 Grade 5 pulmonary embolism, not treatment related 10/16 = response evaluable
NX-2127 [43]	NX-2127-001 (NCT04830137)	29	BTK and BCL2 mutations in some patients	QD Oral Continuous Dose levels 100–300 mg	Median 4 (2–10) cBTKI and/or ncBTKi 100% BCL2i 76%	ORR 9/24 (37.5) CR 0/24 (0%) SD 11/24 (46%)	Fatigue Neutropenia Hypertension Anemia Atrial arrythmia	23 (49%) 20 (43%) 17 (36%) Unk 3 (6%)	- 18 (38%) 7 (15%) 6 (13%) 3 (6%)	Median 9.5 (0.1–24.3)	iMID-like activity 24/29 = response evaluable
AC676 [48]	AC676-001 NCT05780034	NA	NA	QD Oral Continuous Dose levels planned 50–600 mg	NA	NA	NA	NA	NA	NA	NA

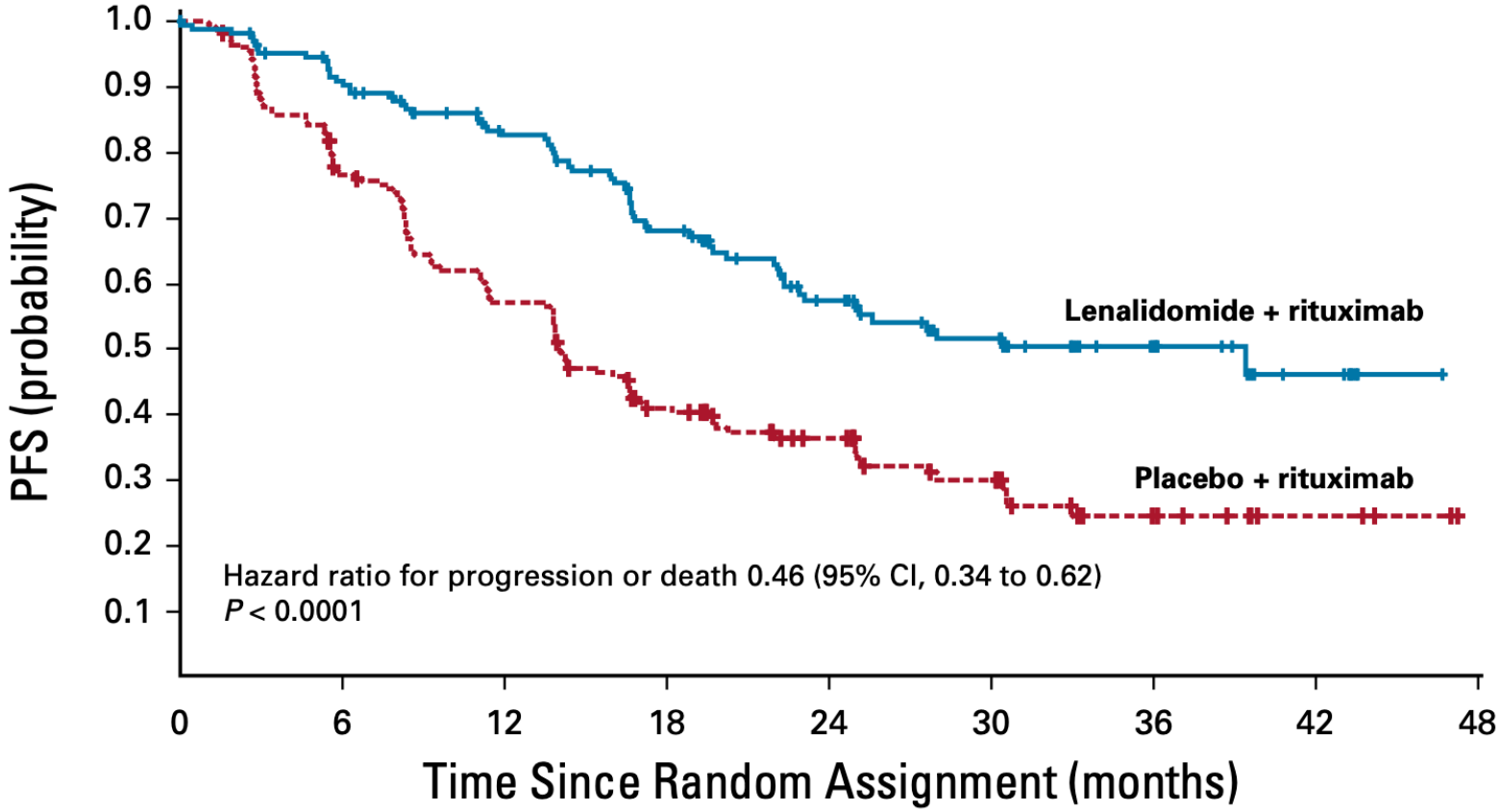
BTK Is the Target That Keeps on Giving: A Review of BTK-Degrader Drug Development, Clinical Data, anf Future Direction in CLL. Salvaris R. T. et al Cancer 2025


CAR T-Cells
Axicabtagene ciloleucel
Lisocabtagene maraleucel
BTK inhibitors
Ibrutinib*
Zanubrutinib*
Acalabrutinib
PI3K inhibitors
Umbralisib
Copanlisib
Zandelisib
Parsaclisib
BCR
BTK
PI3K
CD19
Lenalidomide*
MZL cell
+
CD20
CD20
Bispecifics
CD3/CD20
Mosunetuzumab
Epcoritamab
CD3
Anti-CD20 mAbs
Rituximab*
T cell
(effector)

AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma

Histology			
FL grade	147 (83)	148 (82)	295 (82)
1 or 2	125 (70)	123 (68)	248 (69)
3a	22 (12)	25 (14)	47 (13)
MZL	31 (17)	32 (18)	63 (18)
Extranodal MZL of mucosa-associated lymphoid tissue	14 (8)	16 (9)	30 (8)
Nodal	8 (4)	10 (6)	18 (5)
Splenic	9 (5)	6 (3)	15 (4)

AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. Leonard J. P. et al JCO 2019



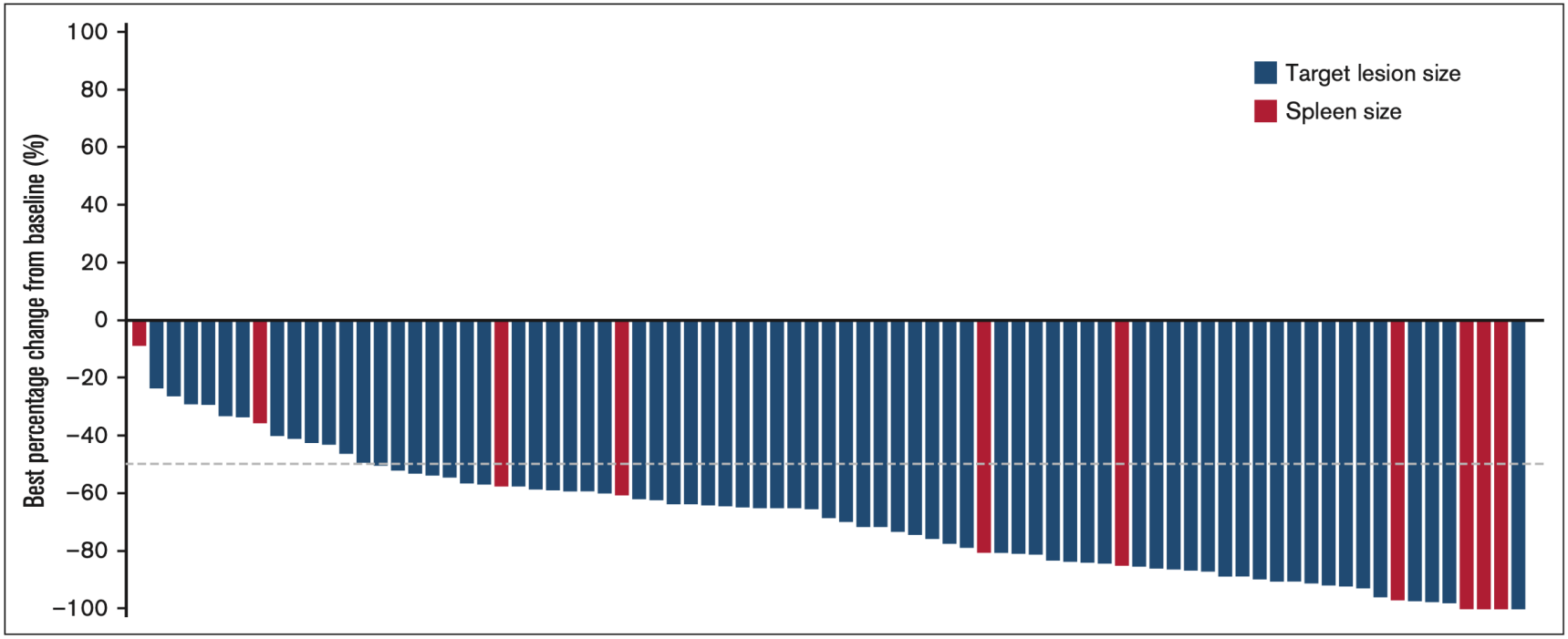
No. at risk:									
Lenalidomide + rituximab	178	148	124	91	59	39	20	7	0
Placebo + rituximab	180	132	92	58	40	26	10	4	0

AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. Leonard J. P. et al JCO 2019

Variable	Lenalidomide + Rituximab (n = 31)	Placebo + Rituximab (n = 32)	HR (95% CI)*	*P**
Best response, as assessed by IRC				
ORR, No. (% [95% CI])	20 (65 [45 to 81])	14 (44 [26 to 62])		.1313
CR, No. (% [95% CI])	9 (29 [14 to 48])	4 (13 [4 to 29])		.1289
PR, No. (%)	11 (35)	10 (31)		
SD, No. (%)	6 (19)	11 (34)		
PD/death, No. (%)	0	4 (13)		
Not done/missing/no evidence of disease at baseline, No. (%)	5 (16)	3 (9)		
Median PFS, as assessed by IRC, months (95% CI)	20.2 (16.0 to NR)	25.2 (11.1 to NR)	1.00 (0.47 to 2.13)	.9984
Median PFS, as assessed by investigator, months (95% CI)	19.2 (13.9 to 30.4)	22.1 (8.7 to NR)	1.04 (0.54 to 2.01)	.8918
Median EFS as assessed by IRC, months (95% CI)	20.2 (14.5 to NR)	25.1 (9.2 to NR)	1.18 (0.60 to 2.29)	.6324
Median DOR, as assessed by IRC, months (95% CI)	17.4 (13.2 to NR)	NR (8.4 to NR)	1.81 (0.56 to 5.84)	.3111
Median TTNLT, months (95% CI)	25.8 (17.7 to NR)	NR (21.6 to NR)	1.58 (0.68 to 3.67)	.3057
OS probability at 2 years, % (95% CI)	82 (61 to 92)	94 (77 to 98)	2.89 (0.56 to 14.92)	
Deaths, No. (%)	5 (16)	2 (6)		

AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. Leonard J. P. et al JCO 2019

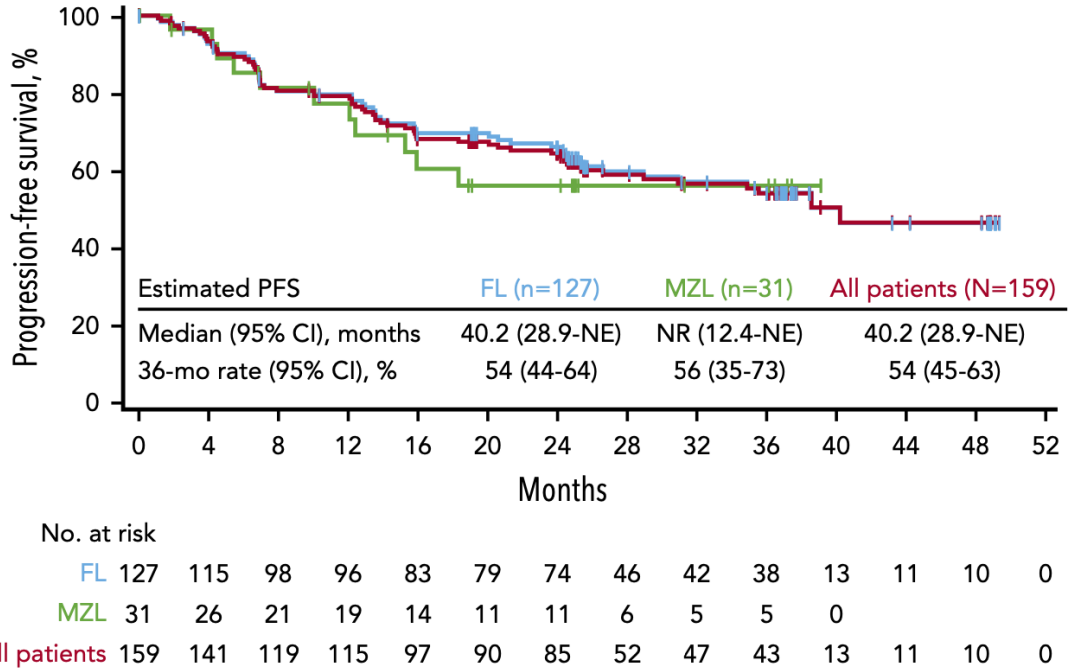
A phase 2 study of the PI3Kδ inhibitor parsaclisib in relapsed and refractory marginal zone lymphoma (CITADEL-204)



A Phase 2 study of the PI3Kδinhinitor parsaclisib in relapsed and refractory marginal zone lymphoma (CITADEL-204). Philips T. J. et al Blood 2024

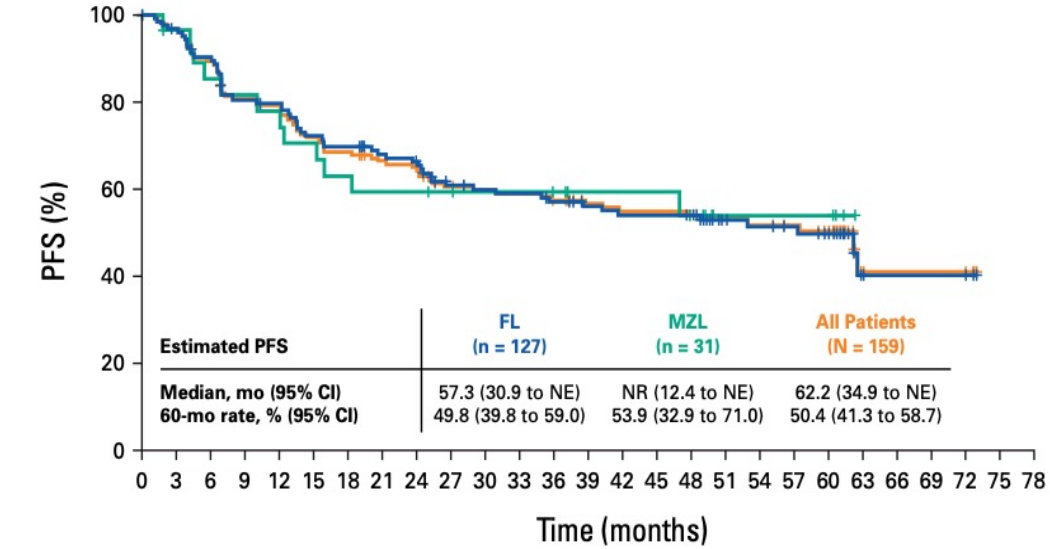
CLINICAL TRIALS AND OBSERVATIONS

Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5)



Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). Neelapu S. S.et al Blood 2024

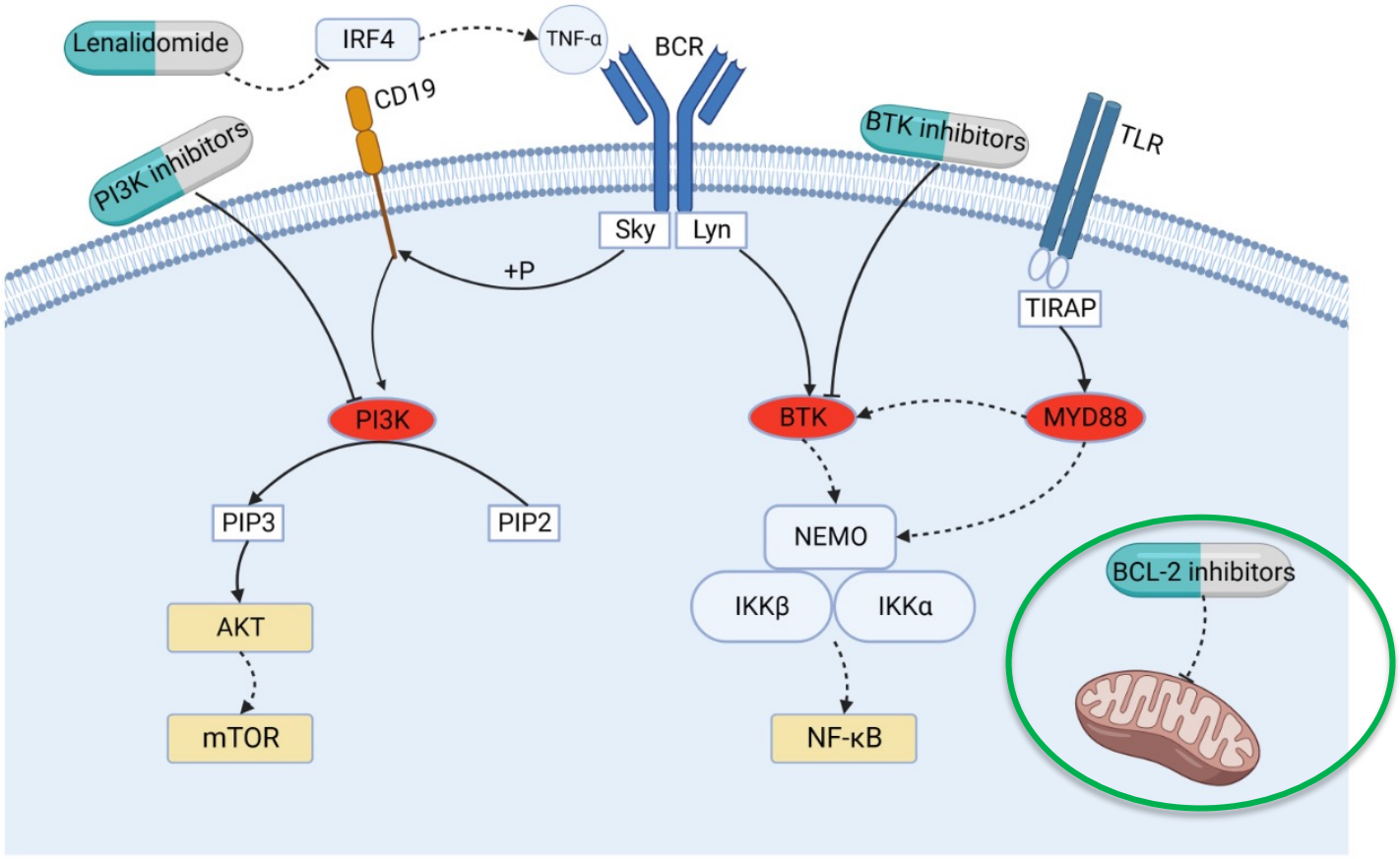
Five-Year Follow-Up Analysis of ZUMA-5: Axicabtagene Ciloleucel in Relapsed/Refractory Indolent Non-Hodgkin Lymphoma



Number at risk:

FL	127	120	111	98	96	87	84	78	75	65	63	62	59	55	53	53	52	36	34	32	29	7	6	6	6	0
MZL	31	26	23	22	21	19	17	16	16	15	14	14	13	11	11	11	9	4	4	4	4	0				
All patients	159	146	134	120	117	106	101	94	91	80	77	76	72	66	64	64	61	40	38	36	33	7	6	6	6	0

Five-year Follow-up Analysis of ZUMA-5: Axicabtagene Ciloleucel in Relapsed/Refractory Indolent Non-Hodgkin Lymphoma. Neelapu S. S.et al JCO 2025



Venetoclax

Sonrotoclax

Advances in the treatment of relapsed/refractory marginal zone lymphoma. Wang H. S.et al Frontiers 2024

Grazie per l'attenzione!