POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

COORDINATORI
Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO
Paolo Corradini
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Programma Scientifico

GIOVEDÌ 2 FEBBRAIO 2023

13.30 Registrazione dei partecipanti	
13.40 Benvenuto	A.M. CARELLA P. CORRADINI P.L. ZINZANI
13.50 Introduzione alla lettura	P. CORRADINI
14.00 Vexas syndrome	N.S. YOUNG
1° SESSIONE - LINFOMA I	**P.L. ZINZANI**
14.30 Stato dell'arte	P.L. ZINZANI
14.40 Linfoma di Hodgkin	C. RUSCONI
15.00 Linfoma mantellare	C. VISCO
15.20 Linfomi di derivazione T linfocitaria	A. PINTO
15.40 Discussione	
2° SESSIONE - LINFOMA II	**M. MARTELLI**
15.55 Stato dell'arte	M. MARTELLI
16.05 Linfomi indolenti	M. LADETTO
16.25 Linfomi aggressivi di derivazione B linfocitaria	A.J.M. FERRERI
16.45 Terapie di salvataggio con anticorpi monoclonali	L. RIGACCI
17.05 Discussione	

Linfomi Indolenti

Prof. Marco Ladetto, MD

AO SS Antonio e Biagio e Cesare Arrigo, Alessandria
Università degli Studi del Piemonte Orientale

DISCLOSURE INFORMATION

Marco Ladetto

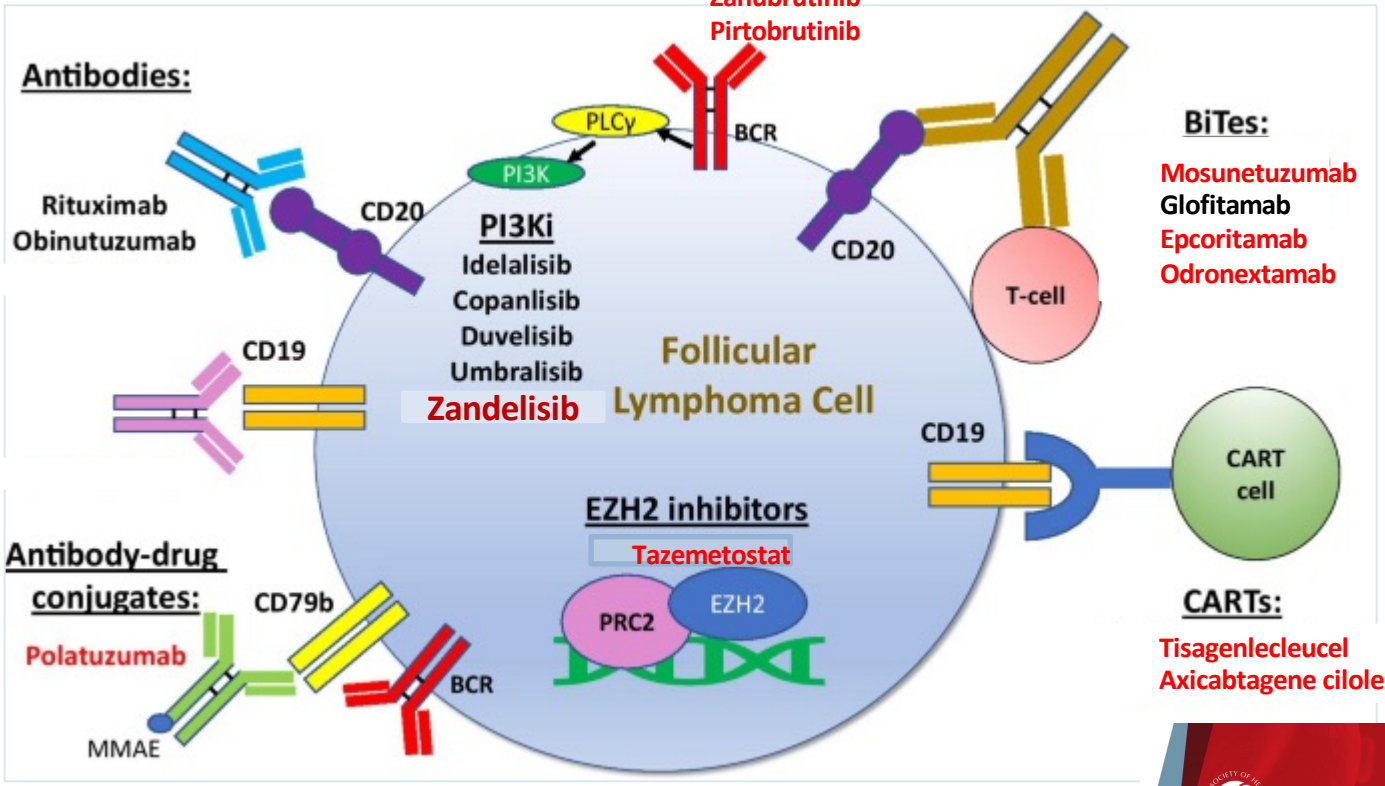
I declare in the last five years the following relationships in terms of consultancy, participation to advisory boards, invitation scientific meetings, institutional research support and contracts with: AbbVie, Acerta, Amgen, ADC Therapeutics, BeiGene, Celgene/BMS, Eusapharma, GSKI, Gentili, Gilead/Kite, Lilly, Novartis, Incyte J&J, Jazz, Regeneron, Roche, Sandoz.

Non-financial interests:
PI or strategic investigator in studies supported by: Celgene, J&J, BeiGene, ADC Therapeutics

Leadership roles:
Vice-President/President elect of Fondazione italiana linfomi (FIL)
Member of the EHA Guideline Committee
Member of the ESMO Guidelines Committee up to Dec 2018
Member of the ESMO Educational Committee
Vice President Associazione italiana leucemie (Alessandria section)

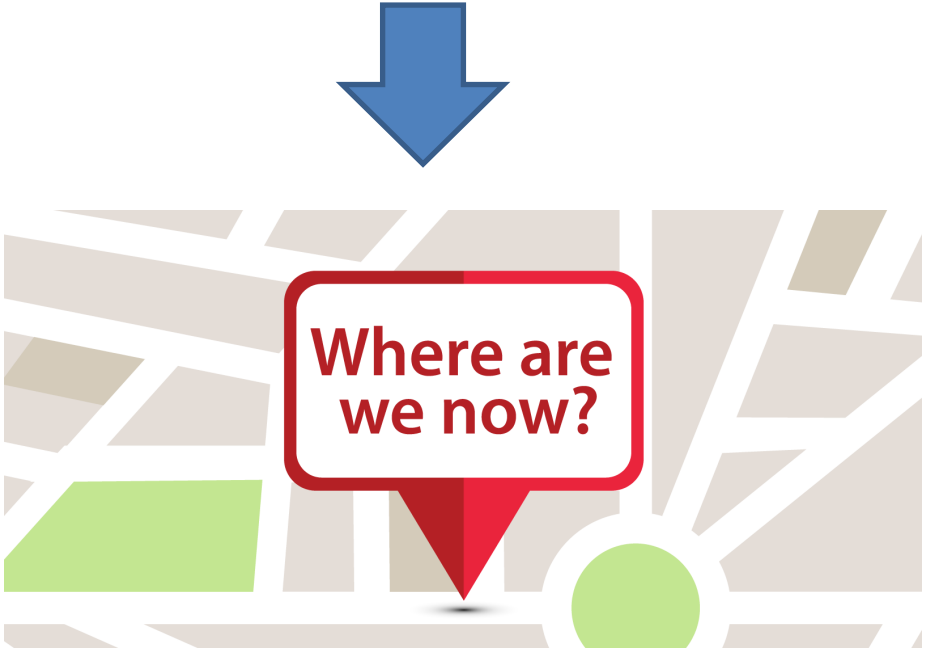
INTRODUCTION

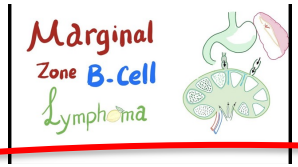
- FL, MZL and WM are forms of indolent non-Hodgkin lymphoma (iNHL) in which malignant tumors slowly grow but can become more aggressive over time. FL is largely the most common
- Therapeutic choices often difficult due to the prolonged natural history and lack of large studies in some settings
- The therapeutic paradigm is shifting from immunochemotherapy to biologicals and T-cell engaging treatments.
- ASH 2022 provided additional evidence on some established combinations (such as R2) as well as insight on novel drugs and combinations



Hanel, W., Epperla, N. Evolving therapeutic landscape in follicular lymphoma: *a look at emerging and investigational therapies*. *J Hematol Oncol* **14**, 104 (2021).

These therapies will likely reshape the treatment approach for patients with iNHL in the coming years.





	1st Line	R/R	1st Line	R/R	1st Line	R/R
MOLECULES		R2		R2		PIRTOBRUTINIB
		ZANDELISIB-ZANUBRUTINIB		ZANUBRUTINIB		
		TAZEMETOSTAT-R2				
MONOCLONAL ANTIBODIES	EPCORITAMAB-R2	MOSUNETUZUMAB				
		ODRONEXTAMAB				
		POLATUZUMAB VEDOTIN-ObinoLen				
CAR-T		TISAGENELECLEUCEL		TISAGENELECLEUCEL		
		AXICELCICLOLEUCEL		AXICELCICLOLEUCEL		

New therapies in development

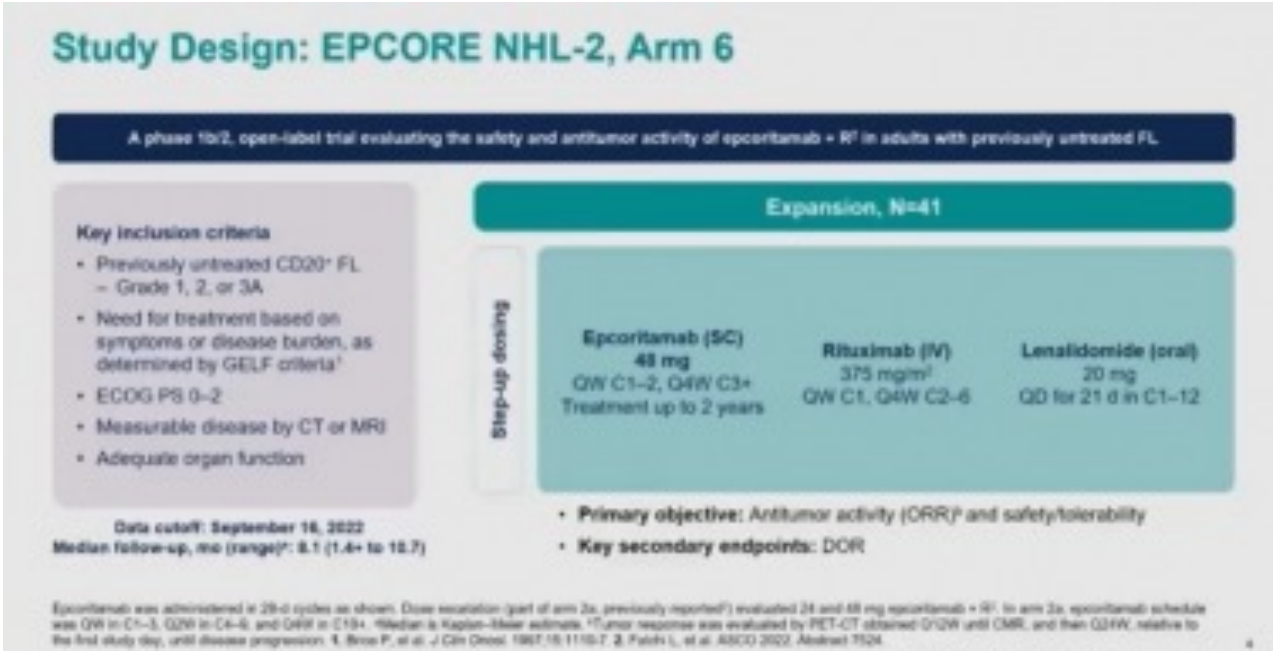
Updated results

Subcutaneous Epcoritamab in Combination with Rituximab + Lenalidomide (R2) for First-Line Treatment of Follicular Lymphoma: Initial Results from Phase 1/2 Trial

Lorenzo Falchi[1], Lori A. Leslie, David Belada, Katerina Kopeckova, Fritz Offner, Joshua Brody,Miguel Canales,Alejandro Martí,García-Sancho,Marcel Nijland, P-O Andersson, Farrukh T. Awan,Jacob Haaber Christensen,Kristina Drott,Mats Hellström, Catharina Lewerin,Mayur Narkhede,Sylvia Snauwaert, Björn E Wahlin, Ali Rana, Aqeel Abbas,Liwei Wang,Minh Dinh,Joost S.P. Vermaat,Pau Abrisqueta

1.Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY

Blood (2022) 140 (Supplement 1): 1471–1473.



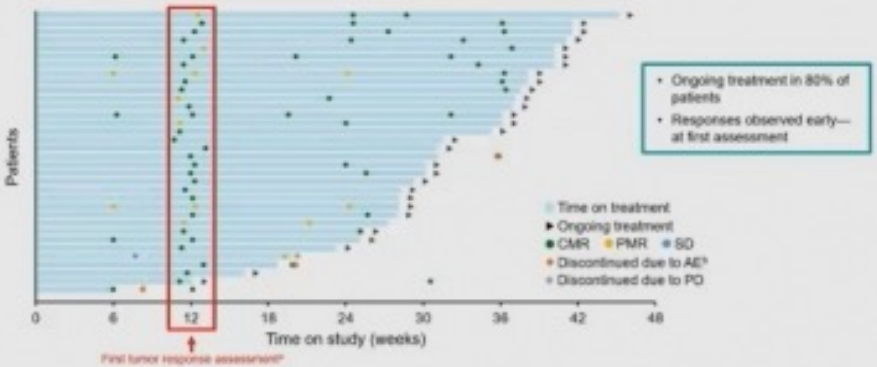
- Median age was 57 y (range, 39–78)
- Median time from initial diagnosis to first dose of epcoritamab was 12 wk (range, 2–352)
- The majority (85%) had grade 2 or 3A FL
- 39% and 51% had stage III and IV disease

High Rates of Overall and Complete Metabolic Response

Best Overall Response[a]	Total Efficacy Evaluable n=36
Overall response	**94%**
CMR	86%
PMR	8%
Progressive disease	3%

Median follow-up, mo (range): 8.1 (1.4+ to 10.7). [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and patients who died within 80 d of first dose. One patient died within 80 d of first dose without assessment (COVID-19).

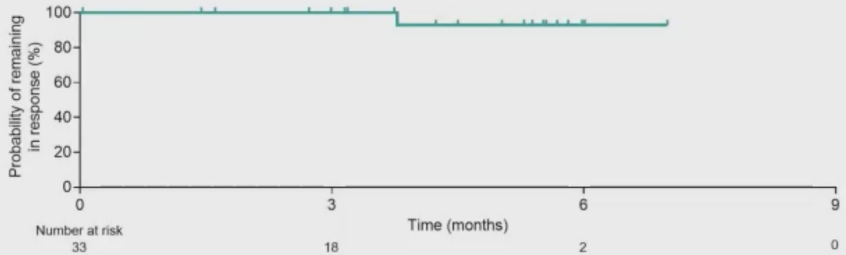
Depth and Duration of Response



Median follow-up, mo (range): 8.1 (1.4+ to 10.7). Per protocol, patients continued to receive xcons if they discontinued treatment for reasons other than PD. [a]Most patients had first assessment at week 12, per protocol; some were assessed at week 8 based on investigator's discretion. [b]Two patients discontinued treatment due to COVID-19; 1 discontinued treatment due to pneumonitis.

Epcor + R² in 1L FL

Duration of Response



Median duration of response not reached (95% CI, NR–NR)

Median follow-up, mo (range): 8.1 (1.4+ to 10.7). Kaplan–Meier estimated probability of remaining in response.

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ASH 2022

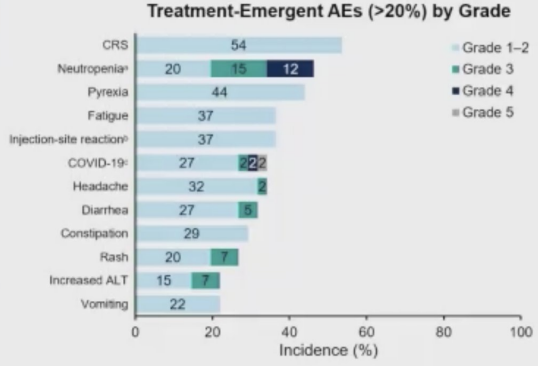
- efficacy-evaluable patients =29
- ORR 90% (26/29) with 69% (20/29) of complete metabolic response (CMR)

Safety Profile

Patients, n (%)	Total N=41
Grade ≥3 TEAE	30 (73)
Related to epcoritamab	14 (34)
Fatal TEAE	2 (5)[a]
Epcoritamab dose delay due to TEAE	22 (54)
Related to epcoritamab	7 (17)
Epcoritamab discontinuation due to TEAE	4 (10)
Related to epcoritamab	3 (7)[b]

[a]COVID-19 pneumonia and septic shock (n=1 each) unrelated to epcoritamab. [b]COVID-19 pneumonia, pneumonitis, and toxic skin eruption (n=1 each).

- No clinical tumor lysis syndrome was observed
- One patient (2%) experienced ICANS (grade 1), which resolved in 2 days



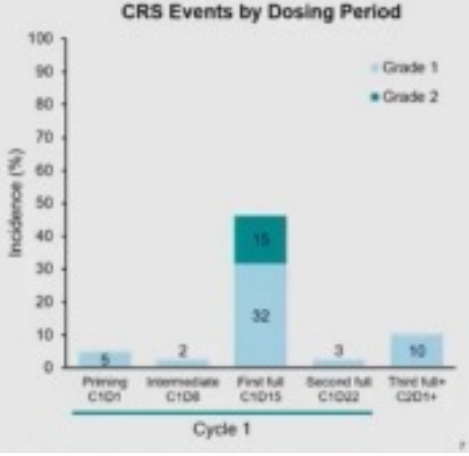
[a]Combined term includes neutropenia and neutrophil count decreased. [b]Combined term includes injection-site reaction, erythema, rash, and hypersensitivity. [c]Combined term includes COVID-19, COVID-19 pneumonia, and post-acute COVID-19 pneumonia.

CRS Events

	Total, N=41
CRS, n (%)[a]	22 (54)
Grade 1	16 (39)
Grade 2	6 (15)
Median time to onset after first full dose, d (range)	3 (1–6)
CRS resolution, n (%)	22 (100)
Median time to resolution, d (range)[b]	4 (1–10)
Treated with tocilizumab, n (%)	4 (10)
Leading to treatment discontinuation, n (%)	**0**

[a]Graded by Lee et al 2019 criteria. [b]Median is Kaplan-Meier estimate based on longest CRS duration in patients with CRS.

- No grade ≥3 events
- All CRS events resolved
- Timing was predictable, with most cases occurring after the first full dose



- All patients experienced treatment-emergent AE (TEAE)
- Most CRS events occurred after the first full dose of epcoritamab, all resolved (median time to resolution, 4 d; tocilizumab given to 5 patients), and none led to treatment discontinuation.
- 1 ICANS and no clinical tumor lysis syndrome.
- One fatal TEAE (COVID-19 pneumonia, not related to epcoritamab).

Five-Year Results and Overall Survival Update from the Phase 3 Randomized Study Augment: Lenalidomide Plus Rituximab (R2) Vs Rituximab Plus Placebo in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

john P. Leonard[1], Marek Trneny,Fritz Offner,Jiri Mayer,Huilai Zhang,Grzegorz S. Nowakowski,Phillip Scheinberg,Argyrios Gkasiamis,Joanna Mikita-Geoffroy,Everton Rowe, John G. Gribben

1.Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY

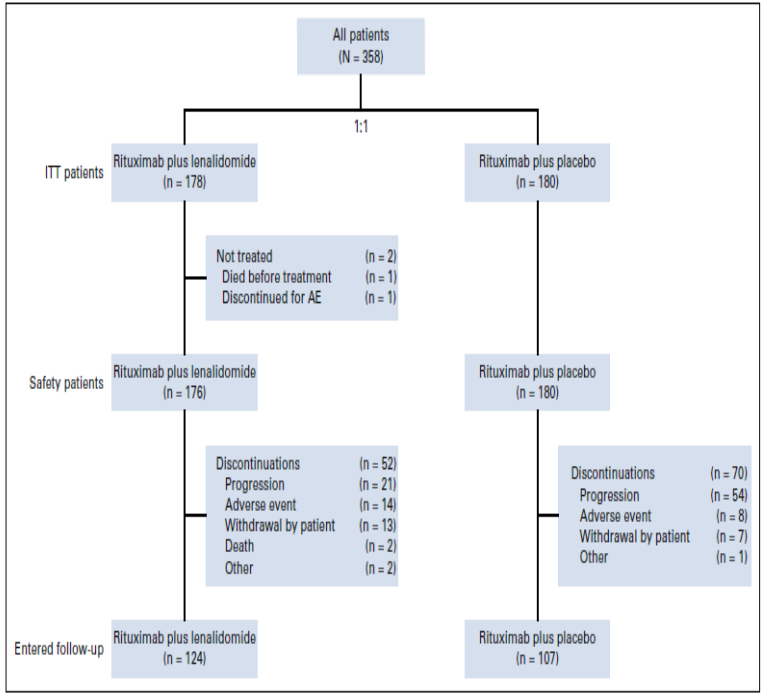
Blood (2022) 140 (Supplement 1): 561–563.

original report

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

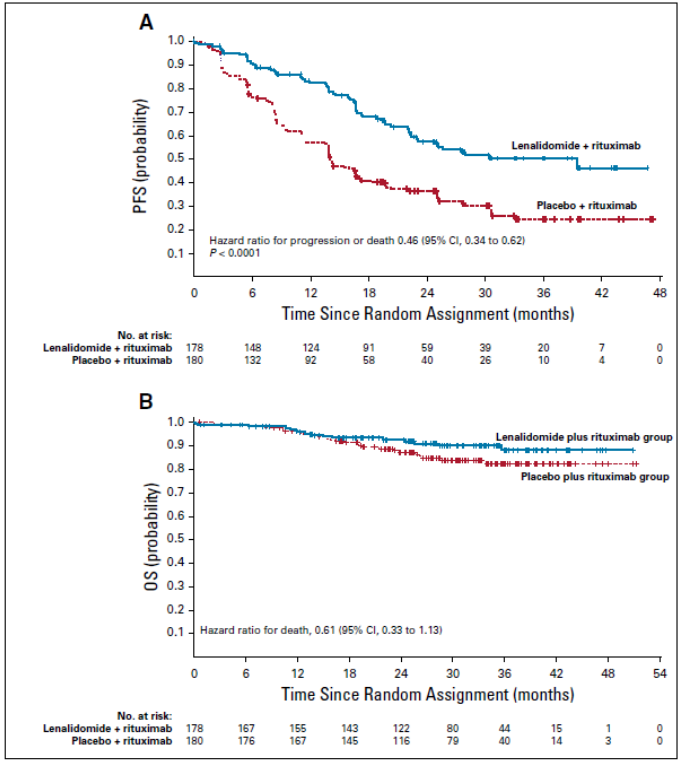
John P. Leonard, MD[1]; Marek Trneny, MD[2]; Koji Izutsu, MD[3]; Nathan H. Fowler, MD[4]; Xiaonan Hong, MD[5]; Jun Zhu, PhD[6]; Huilai Zhang, MD[7]; Fritz Offner, MD, PhD[8]; Adriana Scheliga, MD[9]; Grzegorz S. Nowakowski, MD[10]; Antonio Pinto, MD[11]; Francesca Re, MD[12]; Laura Maria Fogliatto, MD, PhD[13]; Phillip Scheinberg, MD[14]; Ian W. Flinn, MD, PhD[15]; Claudia Moreira, MD[16]; José Cabeçadas, MD[17]; David Liu, MD, PhD[18]; Stacey Kalambakas, MD[18]; Pierre Fustier, PhD[19]; Chengqing Wu, PhD[18]; and John G. Gribben, MD, DSc[20]; for the AUGMENT Trial Investigators

J Clin Oncol 37:1188-1199. © 2019



➢ **Median follow-up : 28.3 months**

FIRSTREPORT™



Baseline characteristics

Characteristic	R² (n = 178)	R-placebo (n = 180)	Total (N = 358)
Median age (range), years	64 (26-86)	62 (35-88)	63 (26-88)
Male, n (%)	75 (42)	97 (54)	172 (48)
ECOG PS (0/1/2), %	65/34/1	71/28/1	68/31/1
Positive bone marrow involvement, n (%)	33 (19)	31 (17)	64 (18)
Biopsy not performed	72 (40)	69 (38)	141 (39)
Ann Arbor stage (I-II/III-IV), %	23/77	31/69	27/73
Bulky disease, n (%)	45 (25)	49 (27)	94 (26)
Histology (FL/MZL), %	83/17	82/18	82/18
FLIPI score (0-1/2/3-5), %	29/31/39	37/32/30	33/32/34

Table adapted by permission of Wolters Kluwer from Leonard JP, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol 2019;37:1188-1199. https://ascopubs.org/doi/full/10.1200/JCO.19.00810.

- Baseline characteristics were generally similar between treatment arms

FLIPI, Follicular Lymphoma International Prognostic Index; PS, performance status.

Leonard JP, et al. ASH 2021 [Abstract 150].

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Patient disposition (ITT population)

Disposition, n (%)	R² (n = 178)	R-placebo (n = 180)	Total (N = 358)
Patients treated, n	176	180	356
Completed treatment[a]	124 (70)	110 (61)	234 (66)
Discontinued treatment[a,b]	52 (30)	70 (39)	122 (34)
Discontinued study[c,d]	65 (37)	77 (43)	142 (40)
Withdrew consent	33 (19)	22 (12)	55 (15)
Death	27 (15)	47 (26)	74 (21)
Lost to follow-up	4 (2)	7 (4)	11 (3)
AEs	0	0	0
Other	1 (1)	1 (1)	2 (1)

- At the final data cutoff (January 26, 2022), median (range) follow-up was 65.9 (0.1-95.2) months

[a]Percentages were calculated using the safety population (R², n = 176; R-placebo, n = 180). [b]Included any patient who discontinued treatment within 12 cycles but remained on the study during the follow-up phase. [c]Percentages were calculated using the ITT population (R², n = 178; R-placebo, n = 180). [d]One patient in the R² arm was missing information on study completion.

AE, adverse event; ITT, intent-to-treat.

Leonard JP, et al. ASH 2021 [Abstract 150].

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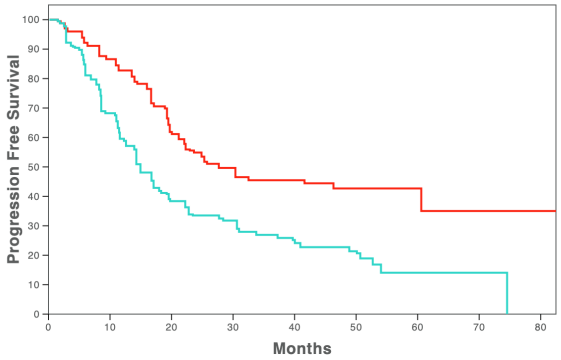
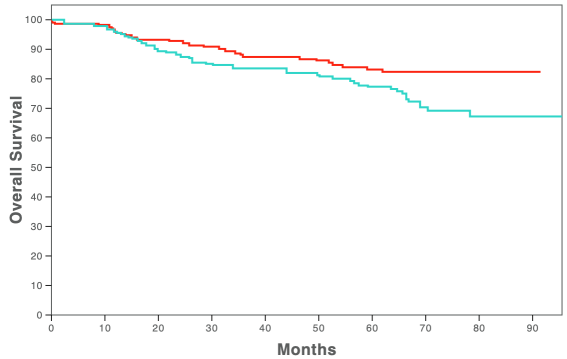
- 358 pts were randomized (n = 178 R2; n = 180 control)
- Baseline characteristics were similar in both groups.



Curves	N	Median (95% CI)
Lenalidomide + Rituximab	178	27.6 (22-60.5)
Rituximab + Placebo	180	14.3 (12.4-17.7)

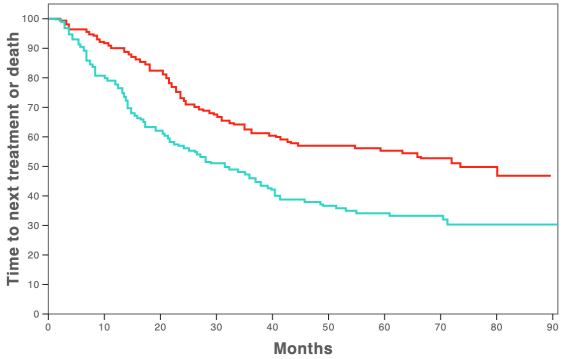
	HR (95% CI)
Lenalidomide + Rituximab vs Rituximab + Placebo	0.5 (0.38 - 0.66)



Curves	N
Lenalidomide + Rituximab	178
Rituximab + Placebo	180

	HR (95% CI)	P-value
Lenalidomide + Rituximab vs Rituximab + Placebo	0.59 (0.37 - 0.95)	0.0285

- median follow-up of 65.9 m
- Median OS was not reached for either group, there was an improvement in OS for R2



Curves	N	Median (95% CI)
Lenalidomide + Rituximab	178	73.1 (43-0)
Rituximab + Placebo	180	31.8 (22.2-39.4)

	HR (95% CI)
Lenalidomide + Rituximab vs Rituximab + Placebo	0.53 (0.39 - 0.71)

- SPMs occurred in 13 (7%) R2-treated and 21 (12%) control pts
- 9 pts died of SPM (n = 3 R2, n = 6 R-placebo)
- The incidence rate of SPMs per 100 y was 1.62 (95% CI, 0.94-2.78) in the R2 group vs 2.66 (95% CI, 1.73-4.07) in the control group.
- Fewer histological transformations occurred in the R2 arm than in the control group (n = 10 vs n = 15, respectively)

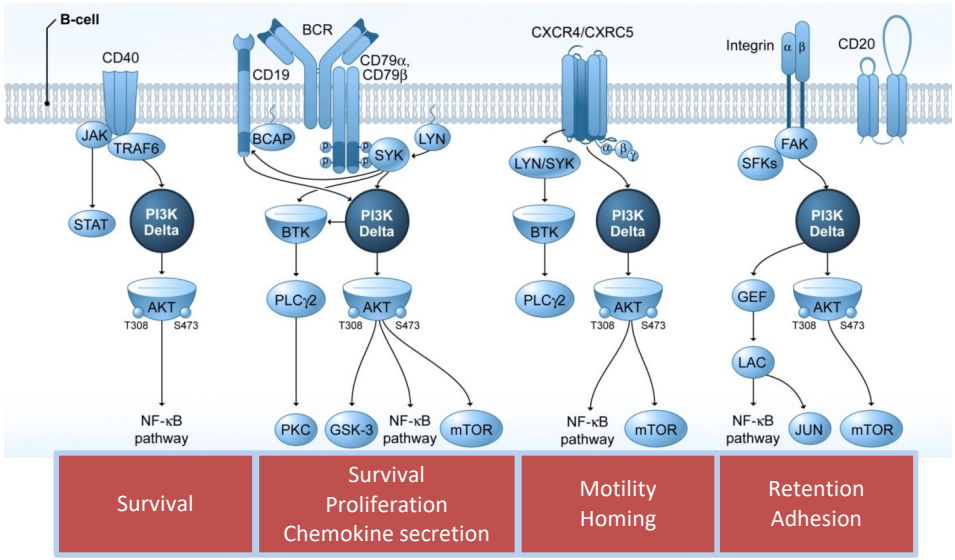
Safety and Efficacy of the PI3Kδ Inhibitor Zandelisib in Combination with the BTK Inhibitor Zanubrutinib in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) or Mantle Cell Lymphoma (MCL)

Jacob D. Soumerai, MD1, Catherine S. Diefenbach, MD, Felipe Samaniego, MD, Abhijeet Kumar, Michaela L. Tsai, Adam S. Asch, MD, Deepa Jagadeesh, MD, Vaishalee P. Kenkre, MD, Izidore S. Lossos, MD, Huda Salman, MD, PhD, Farrukh T. Awan, M.D., Lu Miao, Richard G. Ghalie, MD and Andrew D. Zelenetz, MD, PhD

1. *Center for Lymphoma, Massachusetts General Hospital, Boston, MA*

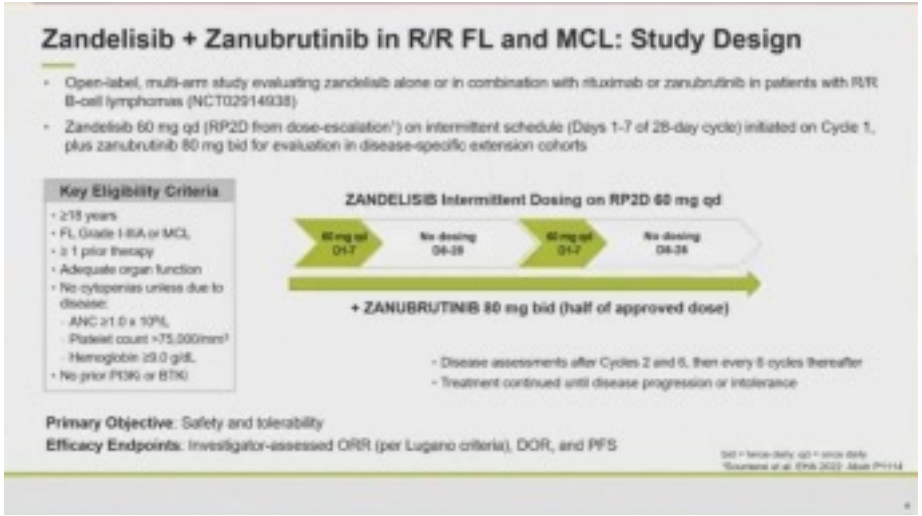
Blood (2022) 140 (Supplement 1): 189–191.

PI3K inhibition impacts multiple critical pathways in B-cell malignancies



BCAP: B-cell adaptor for PI3K; BCR: B-cell receptor; BTK: Bruton's tyrosine kinase;
GEF: guanine nucleotide exchange factor; mTOR: mammalian target of rapamycin;
PI3K: phosphatidylinositol-3-kinase; PKC: protein kinase C; SFK: Src family kinase; SYK: spleen tyrosine kinase

Coutre SE, *et al. Leuk Lymphoma* 2015; 56:2779–2786.



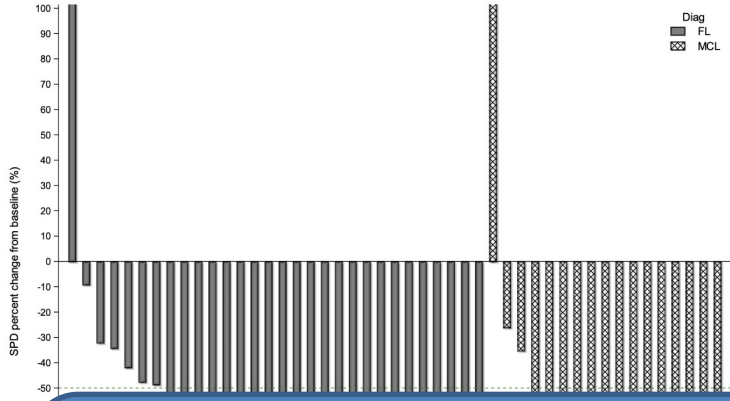
- 50 pts were treated
- 31 with FL and 19 with MCL
- Median age of 67 years (range 40-83)
- Median number of prior therapies was 2 (range 1-5)
- 15 pts (30%) were refractory to last therapy
- 14 pts (28%) had a lesion ≥5 cm
- 22 of 31 FL pts (71%) had POD24

Table 1: Response Rates by Histology

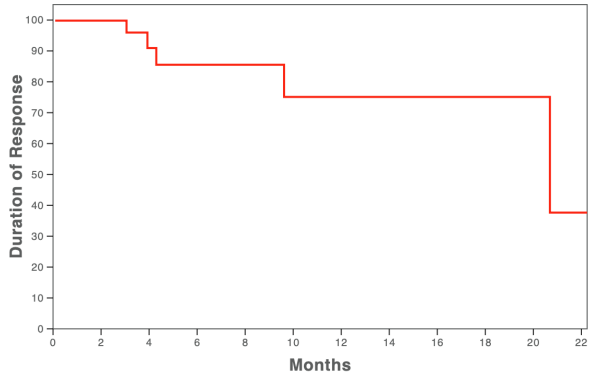
	FL (N = 31)	MCL (N = 19)
ORR, n (%, 95% CI) *	24/30 (80%, 61.4-92.3)	13/17 (76%, 50.1-93.2)
CRR, n (%, 95% CI) *	6/30 (20%, 7.8-38.6)	6/17 (35%, 14.2-61.7)

*3 pts were not evaluable for response: 1 FL pt discontinued in cycle 1 due to a DRESS syndrome and 2 ongoing MCL pts have not yet reached the end of cycle 2 disease assessment

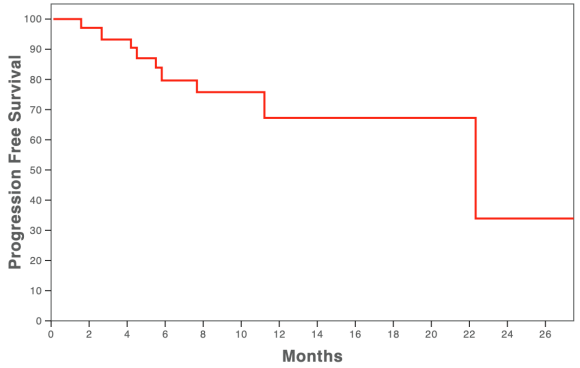
Figure 1: Maximum Change in SPD from Baseline



- Zandelisib plus zanubrutinib was well tolerated with no increase in the rate or severity of class-related AEs compared to either agent alone.
- Few pts (4%) have discontinued due to an AE.



Curves	N	Median (95% CI)
Zanubrutinib	26	20.6 (9.6-0)



Curves	N	Median (95% CI)
Zanubrutinib	31	22.4 (11.4-0)

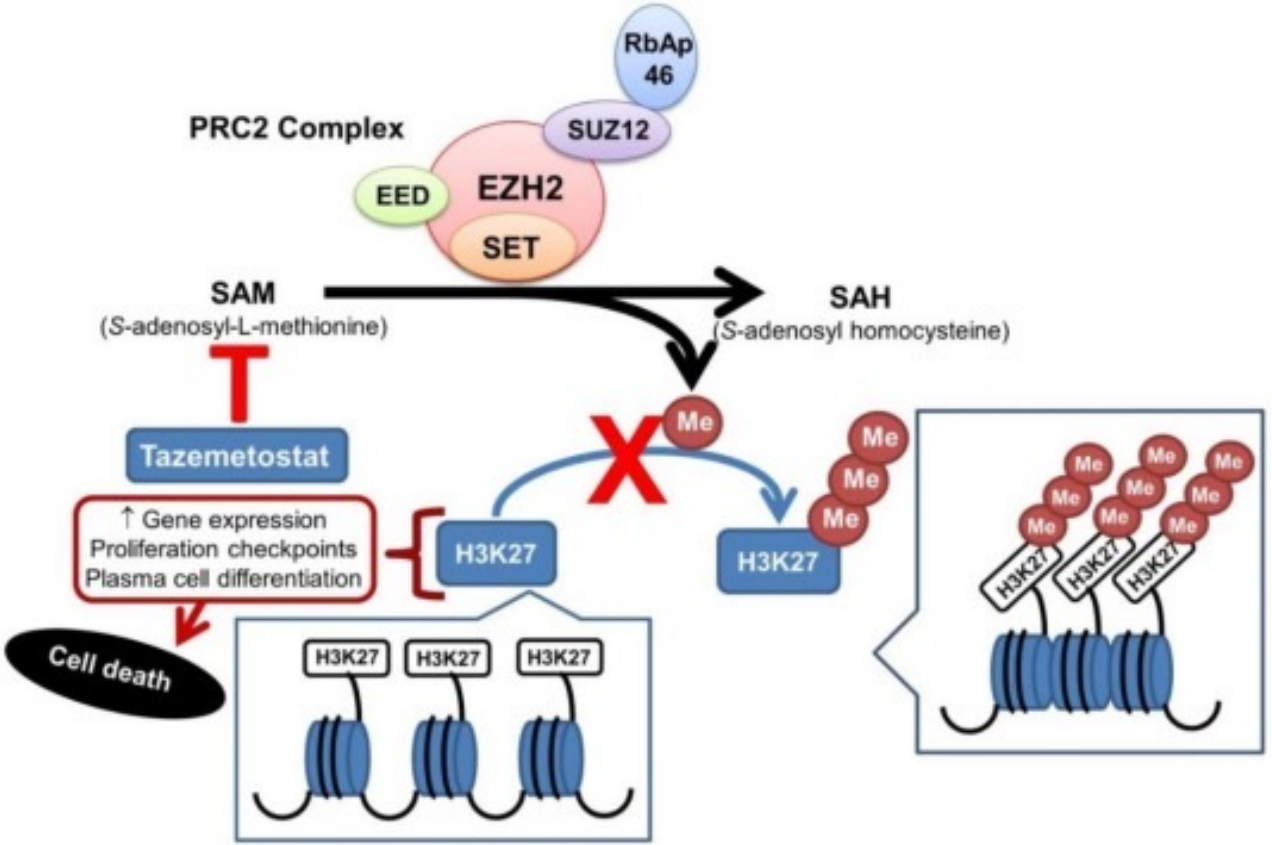
Tazemetostat in Combination with Lenalidomide and Rituximab in Patients with Relapsed/Refractory Follicular Lymphoma: Phase 1b Results of Symphony-1

Connie Lee Batlevi[1],Gilles Salles,Steven I. Park,Tycel J. Phillips,Jennifer E. Amengual,David Andorsky,Philip Campbell,Pamela McKay, John P. Leonard,Manu Sondhi,Yingxue Chen,Pamela L. Slatcher,Richard Lin,Attila Szanto,Sara Abbadi,Franck Morschhauser

1. *Lymphoma Service, Cellular Therapy Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, NEW YORK, NY*

Blood (2022) 140 (Supplement 1): 2296–2298

EZH2 inhibition



Christian MichaelHedrich. Chapter 21 - Pharmacoepigenetics of Systemic Lupus Erythematosus. Pharmacoepigenetics. Volume 10 in Translational Epigenetics. 2019, Pages 597-608

Results – patient characteristics and baseline demographics

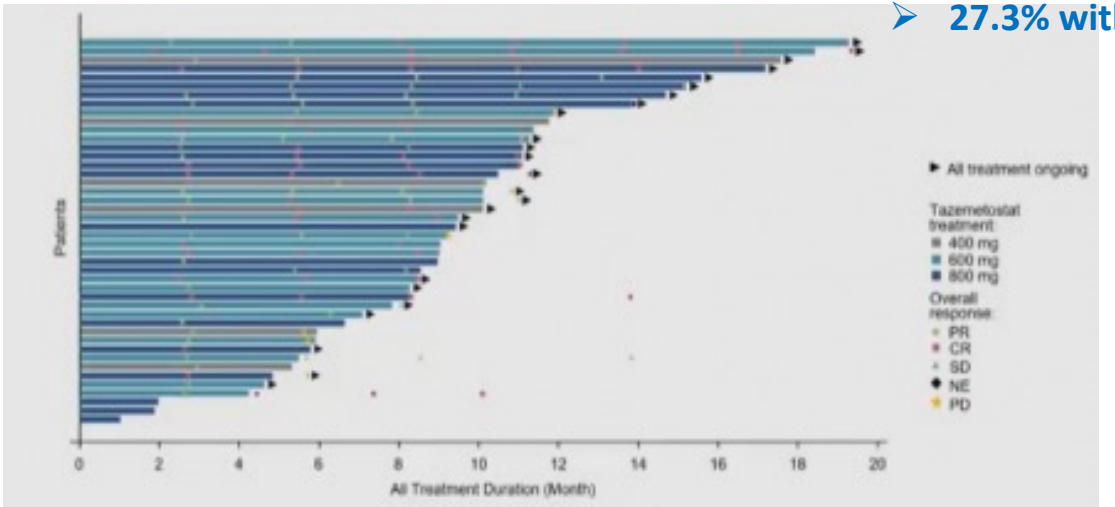
As of June 14, 2022, 44 patients were enrolled and receiving TAZ + R² (400 [n=6], 600 [n=19], or 800 mg [n=19])

Parameter	TAZ + R² (N=44)
Age (range), median, years	67 (38–83)
Male, n (%)	26 (59.1)
Age ≥65 years, n (%)	26 (59.1)
ECOG PS, n (%)	
0	33 (75.0)
1	11 (25.0)
Grade at diagnosis, n (%)	
1	11 (25.0)
2	20 (45.5)
3A	12 (27.3)
Unknown/not reported	1 (2.3)
LDH>ULN, n (%)	7 (15.9)
B symptoms, n (%)	6 (13.6)
Transformed from DLBCL to FL	4 (9.1)

Parameter	TAZ + R² (N=44)
Time from last therapy (range), median, months	15.7ª (0.6–193.6)
Prior lines of systemic anticancer therapy,ᵇ n (%)	
1	30 (68.2)
2	7 (15.9)
3	2 (4.5)
4	5 (11.4)
Median (range)	1 (1-4)
Prior classes of treatment, n (%)	
Prior anti-CD20 antibody + chemotherapyᶜ	33 (75)
Prior anti-CD20 antibody as only therapy	11 (25)
Refractory to rituximabᵈ at baseline, n (%)	15 (34.1)
POD24, n (%)	12 (27.3)
MT *EZH2*, n (%)	7/42ᵉ (16.7)
WT *EZH2*, n (%)	35/42ᵉ (83.3)

ᵃData not available for one patient. ᵇFourteen patients received rituximab maintenance, which was not counted as a separate line of treatment. ᶜR/O-bendamustine, R/O-CHOP-based therapy. ᵈNo response to either rituximab monotherapy or rituximab-containing therapy or progressive disease within 6 months of completion of rituximab-containing therapy. ᵉTwo patients had unknown *EZH2* status.

DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; *EZH2*, enhancer of zeste homolog 2; FL, follicular lymphoma; LDH, lactate dehydrogenase; MT, mutant; POD24, progression of disease in 24 months; R², lenalidomide plus rituximab; RIA, rituximab-idelalisib; R/O-CHOP, rituximab-otlertuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TAZ, tazemetostat; ULN, upper limit of normal; WT, wild-type.



- 44 patients were enrolled and receiving TAZ + R2 (400 [n=6], 600 [n=19], and 800 mg [n=19]).
- Median age was 67 years
- 31.8% of patients had received >1 prior therapy
- 35/42 patients (83.3%) had wild-type (WT) EZH2 FL
- 34.1% with rituximab-refractory disease
- 27.3% with POD24 disease

- Of 41 patients evaluable: 21 (51.2%) had a complete response, 19 (46.3%) had a partial response, and 1 (2.4%) had stable disease.

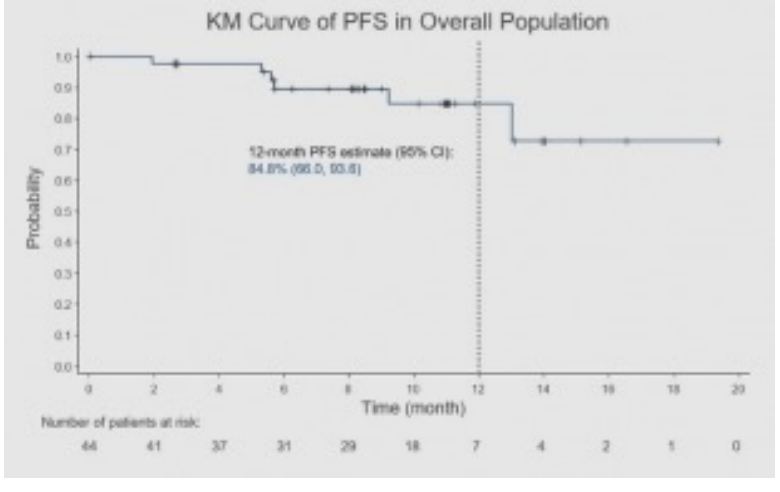
Results – efficacy by mutation status

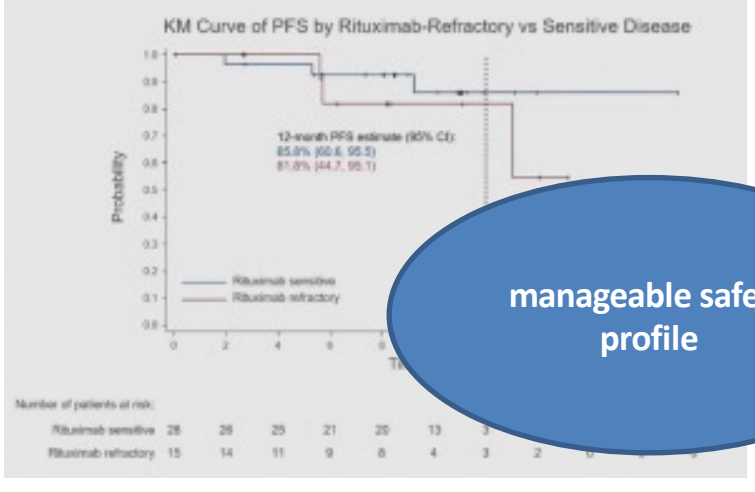
Best Overall Response,* % (n)	WT (n=33)	MT (n=7)
ORR	97.0 (32)	100 (7)
Complete response	45.5 (15)	71.4 (5)
Partial response	51.5 (17)	28.6 (2)
Stable disease	3.0 (1)	0

- ORR was 97.0% in patients with WT *EZH2* (n=32)
- ORR was 100% in patients with MT *EZH2* (n=7)
- mPFS and mDOR were not reached

*EZH2 status for 1 patient with best overall response was unknown.
KM, Kaplan-Meier; mDOR, median duration of response; mPFS, median progression-free survival; MT, mutant; NE, not evaluable; ORR, objective response rate; WT, wild-type.

Durable responses were seen in patients with high-risk disease, including those with rituximab-refractory and POD24 disease.





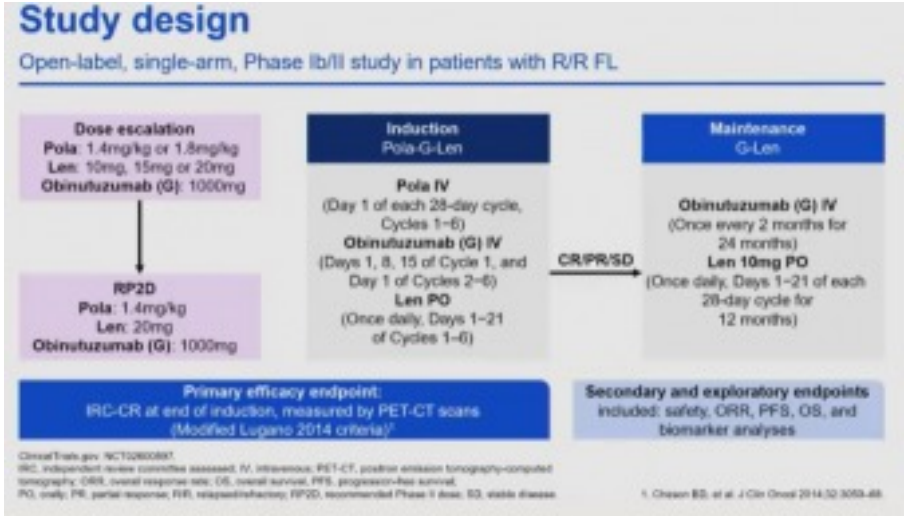
manageable safety profile

A Phase Ib/II Study of Polatuzumab Vedotin Plus Obinutuzumab and Lenalidomide in Patients with Relapsed/Refractory Follicular Lymphoma: Final Analysis and Progression-Free Survival Update

Catherine S. Diefenbach[1],Brad S. Kahl,Lalita Banerjee,Andrew K. McMillan,Fiona Miall,Javier Briones,Raul Cordoba,John M. Burke,Jamie Hirata,Sunil Sharma, Lisa Musick,Pau Abrisqueta Costa

1. *Perlmutter Cancer Center at NYU Langone Health, New York, NY*

Blood (2022) 140 (Supplement 1): 2286–2288.



- Median age, 62 years
- Male 59%
- Ann Arbor Stage III–IV, 88%
- Follicular Lymphoma International Prognostic Index 1 high-risk (≥3), 55%
- Bulky disease (≥7cm), 16%
- Median prior lines of treatment, 3 (range: 1–7); ≥2 prior lines of therapy, 77%
- Refractory to last line of prior regimen, 59% (Refractory to last line of anti-CD20 treatment, 55%)
- POD24 (defined as disease progression within 24 months of initiation of first anti-lymphoma treatment with chemoimmunotherapy), 27%

Efficacy

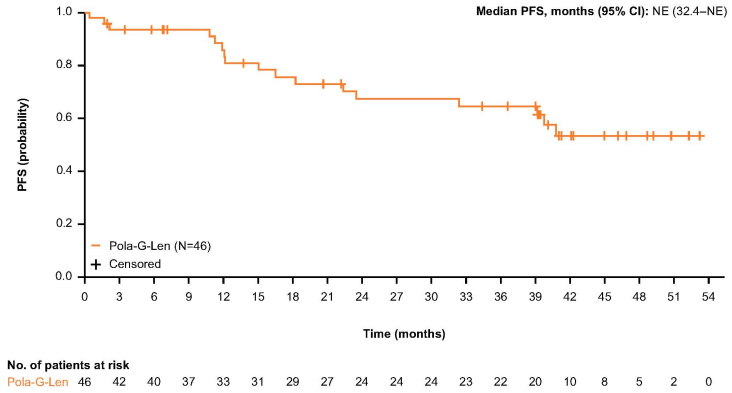
EOI response analysis

EOI response, n (%)	Efficacy-evaluable population (N=46)			
	Modified Lugano 2014[*1]		Lugano 2014	
	INV	IRC	INV	IRC
Objective response	38 (83)	35 (76)	38 (83)	35 (76)
Complete response	28 (61)[†]	28 (61)[†]	34 (74)	33 (72)
Partial response	10 (22)	7 (15)	4 (9)	2 (4)
Stable disease	3 (7)	4 (9)	3 (7)	4 (9)
Disease progression	2 (4)	1 (2)	2 (4)	1 (2)
Missing/not evaluable/not available	3 (7)	6 (13)[‡]	3 (7)	6 (13)[‡]

Clinical cut-off date: March 30, 2022.
[*]Modified Lugano requires a negative bone marrow biopsy to confirm PET-CR and PET-PR; 1CR downgraded to PR due to missing bone marrow biopsy in 6 patients by INV and 5 patients by IRC. [†]Three patients did not have PCR scans completed (missing by INV and IRC). for two patients who experienced early disease progression, scans were not sent to IRC and therefore were classified as missing; one patient had stable disease by INV but was not evaluable by IRC.
EOI, end of induction; INV, investigator assessed.

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

Figure. Investigator-assessed PFS



CI, confidence interval; NE, not estimable; No., number; PFS, progression-free survival; Pola-G-Len, polatuzumab vedotin plus obinutuzumab and lenalidomide

- High CR rates in a heavily pre-treated and refractory population
- median PFS and OS were not reached
- more than half of the patients treated with Pola-G-Len had not experienced disease progression after 4 years

Long-Term Efficacy and Safety of Zanubrutinib in Patients with Relapsed/Refractory (R/R) Marginal Zone Lymphoma (MZL): Final Analysis of the Magnolia (BGB-3111-214) Trial

Stephen Opat[1], Alessandra Tedeschi,Bei Hu,Kim M. Linton,Pamela McKay,Henry Chan,Jie Jin,Mingyuan Sun,Magdalena Sobieraj-Teague,Pier Luigi Zinzani,Peter J. Browett,Xiaoyan Ke,Craig A. Portell,Catherine Thieblemont,Kirit Ardeshna,Fontanet Bijou,Patricia Walker,Eliza Hawkes,Shir-Jing Ho,Keshu Zhou,Zhiyu Liang, Jianfeng Xu,Chris Tankersley,Richard Delarue, Melannie Co, Judith Trotman

1. *Monash Health and Monash University, Clayton, Victoria, Australia*

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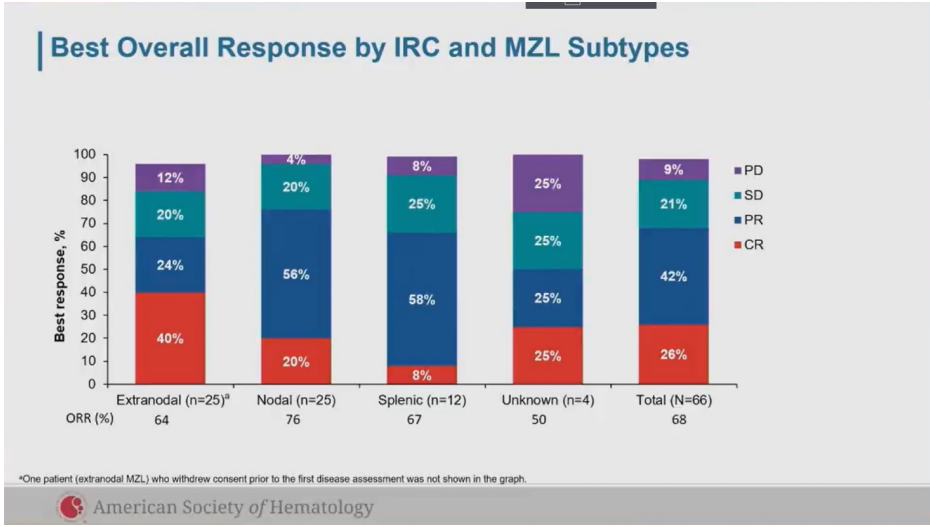
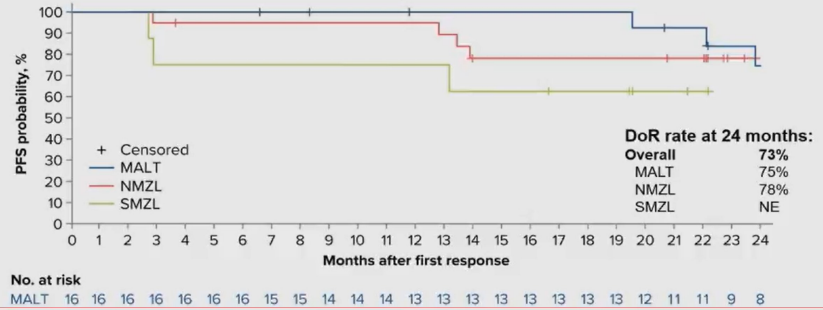
Baseline Characteristics	R/R MZL (N=68)[a]
Male sex, n (%)	36 (52.9)
ECOG PS 0-1, n (%)	63 (92.7)
Bone marrow involvement, n (%)	29 (42.6)
Extranodal sites, n (%)	53 (77.9)
Stage III/IV, n (%)	59 (86.8)

- 68 pts were enrolled
- The median age was 70 years
- MZL subtypes included extranodal (mucosa-associated lymphoid tissue) in 38.2%, nodal in 38.2%, splenic in 17.6%, and unknown in 5.9% of pts.
- Median number of prior therapies was 2 (range 1-6)
- 32.4% of pts had disease refractory to last therapy
- Most (89.7%) pts received prior chemoimmunotherapy
- 7 (10.3%) received rituximab monotherapy as their only prior treatment



DOR by MZL Subtypes by IRC Assessment

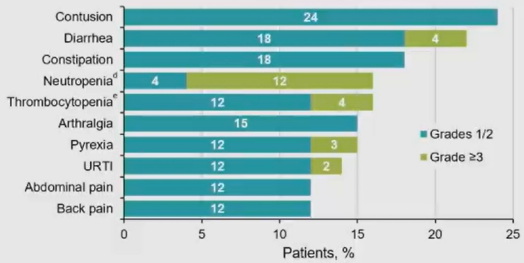


TEAEs in All Patients

Safety Summary

TEAEs, n (%)	N=68
Patients with ≥1 TEAE	68 (100)
Grade ≥3 TEAE	33 (48)
Serious TEAE	30 (44)
Leading to death	5 (7)[a]
Leading to dose interruption	25 (37)[b]
Leading to study drug discontinuation	5 (7)[c]
Leading to dose reduction	0

Most Common TEAEs



[a]Five patients died owing to AEs: COVID-19 pneumonia (n=2); myocardial infarction in a patient with preexisting cardiovascular disease (n=1); acute myeloid leukemia in a patient with prior exposure to an alkylating agent (n=1); septic encephalopathy following radical cystectomy and ileal conduit in a patient with recurrent bladder cancer (in CR at the time of death; [n=1]). [b]Most common AEs leading to dose interruption: COVID-19 pneumonia (n=4), neutropenia (n=3), diarrhea (n=2), lower respiratory tract infection (n=2), pneumonia (n=2), pyrexia (n=2), syncope (n=2), and tonsillitis (n=2). [c]Five patients discontinued owing to AEs: COVID-19 pneumonia (n=2); pyrexia later attributed to disease progression (n=1); myocardial infarction (n=1); septic encephalopathy (n=1). [d]Includes neutropenia and neutrophil count decreased. [e]Includes thrombocytopenia and platelet count decreased
TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

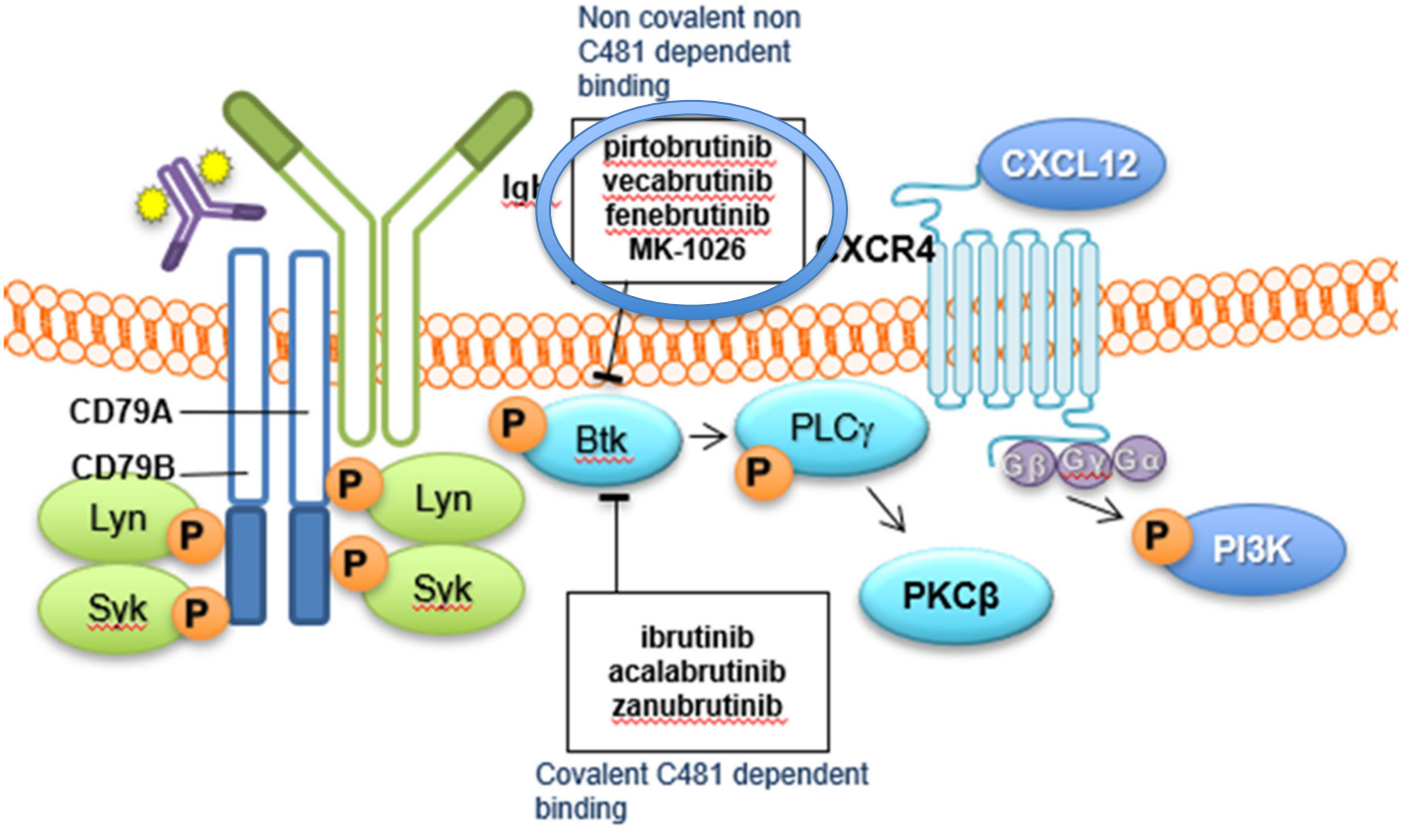
- **High response rates and durable disease control**
- **well tolerated, with no new safety signals**

Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed / Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study

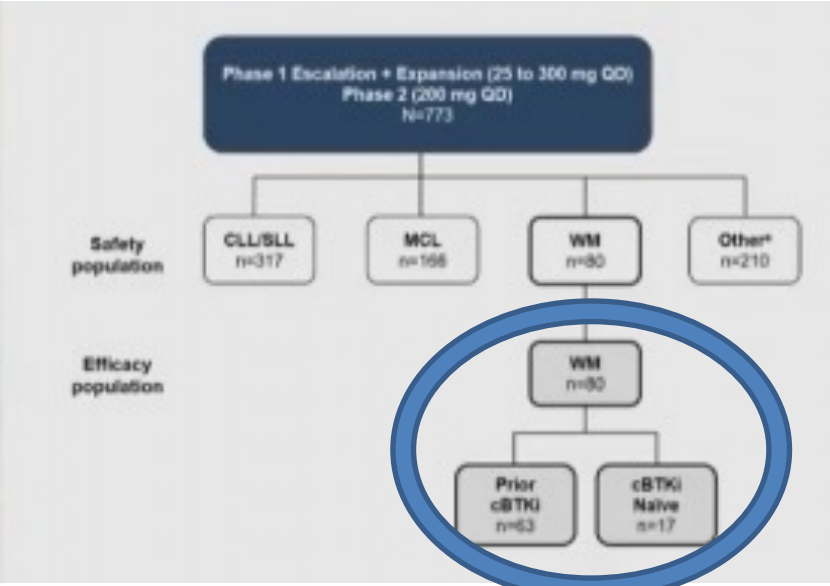
M.Lia Palomba[1], Manish R. Patel,Toby A. Eyr e,Wojciech Jurczak,David John Lewis,Thomas Gastinne,Shuo Ma,Jonathon B. Cohen,Krish Patel,Jennifer R. Brown,Lydia Scarfò,Talha Munir,Ewa Lech-Marańda,Marc Hoffmann,Chaitra S. Ujjani,Bita Fakhri,Michael L. Wang,Koji Izutsu,Hirokazu Nagai,Constantine S. Tam,John F. Seymour,Joanna M. Rhodes,Julie M. Vose,Matthew McKinney,James N. Gerson,Minal A. Barve,Bryone J. Kuss,Youngil Koh,Wei Gao,Amy S. Ruppert, Richard A. Walgren,Donald E. Tsai,Binoj Nair,Katherine Bao,Anthony R. Mato,Chan Y. Cheah

1. *Memorial Sloan Kettering Cancer Center, New York, NY*

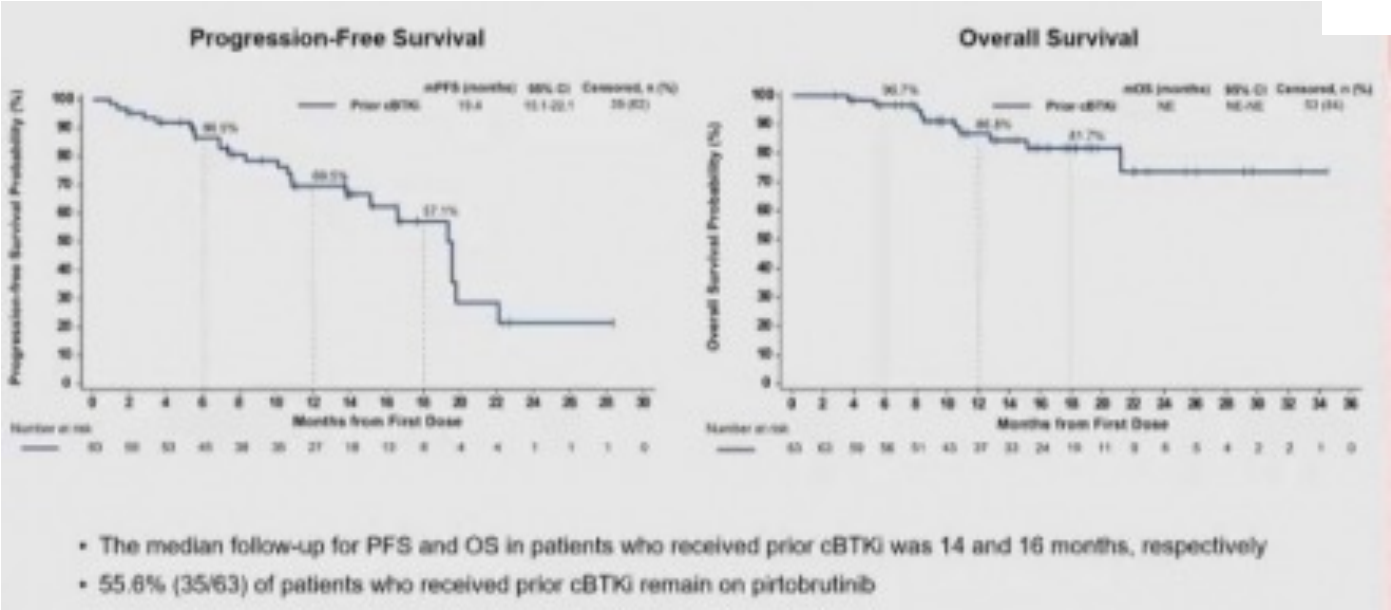
Blood (2022) 140 (Supplement 1): 557–560.



Lewis KL, Cheah CY. Non-Covalent BTK Inhibitors-The New BTKids on the Block for B-Cell Malignancies. J Pers Med. 2021 Aug 3;11(8):764.



- Median age was 68 (range, 42-84) years
- Median number of prior therapies was 3 (range, 1-11).
- 66 (85%) pts had received chemotherapy + anti-CD20 antibody
- 61 (78%) pts had received ≥1 prior BTKi (≥2 BTKi in 13/61, 21%)
- 40 (66%) discontinued prior BTKi therapy due to disease progression
- 50 (64%) pts had received chemotherapy + anti-CD20 antibody + BTKi



- The median follow-up for PFS and OS in patients who received prior cBTKi was 14 and 16 months, respectively
- 55.6% (35/63) of patients who received prior cBTKi remain on pirtobrutinib

➢ **Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity.**

CONCLUSIONS

- ASH 2022 confirmed the strong shift toward chemo-free treatments in indolent lymphoma.
- Several different approaches proved effective, crowding the therapeutic armamentarium especially in R/R disease.
- Apart for efficacy, growing importance will be acquired by:

  - Safety profile
  - Duration of treatment
  - Costs and complexity
  - Patient choice