CAR-TALKING

News dal mondo CAR-T

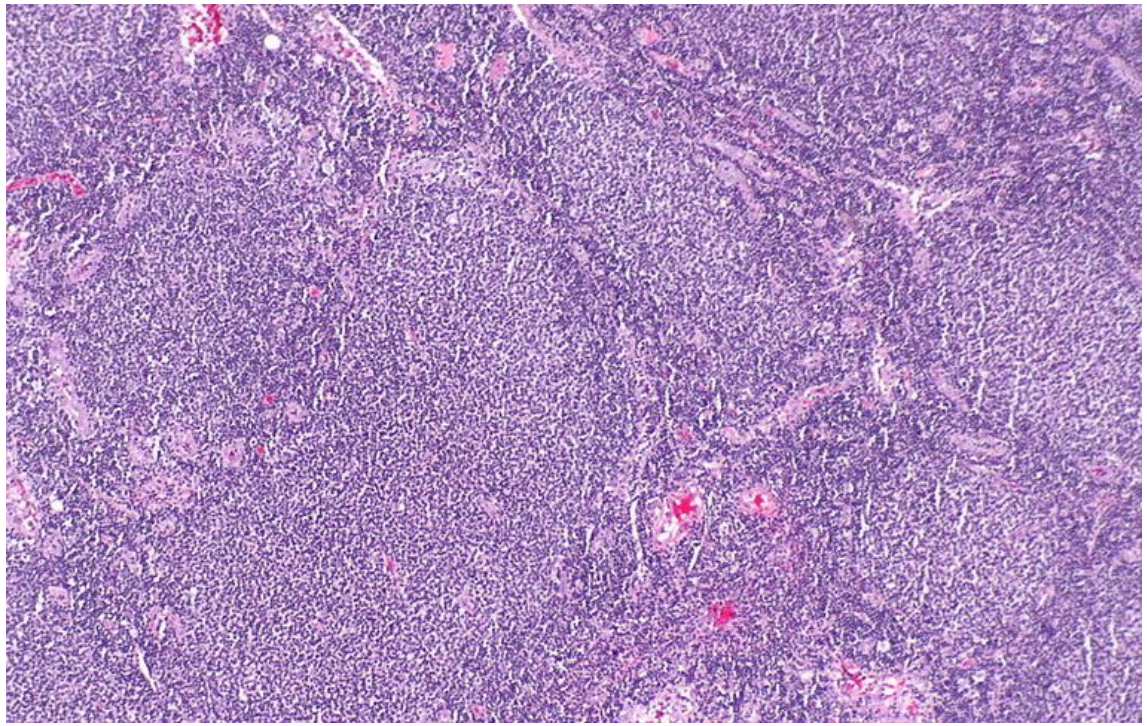
Verona, Hotel Indigo Verona – Grand Hotel Des Arts
28 aprile 2023

Altri approcci terapeutici di salvataggio nel Linfoma Follicolare

Dottor Filippo Gherlinzoni
Direttore Struttura Complessa di Ematologia
Ospedale Ca' Foncello - Treviso

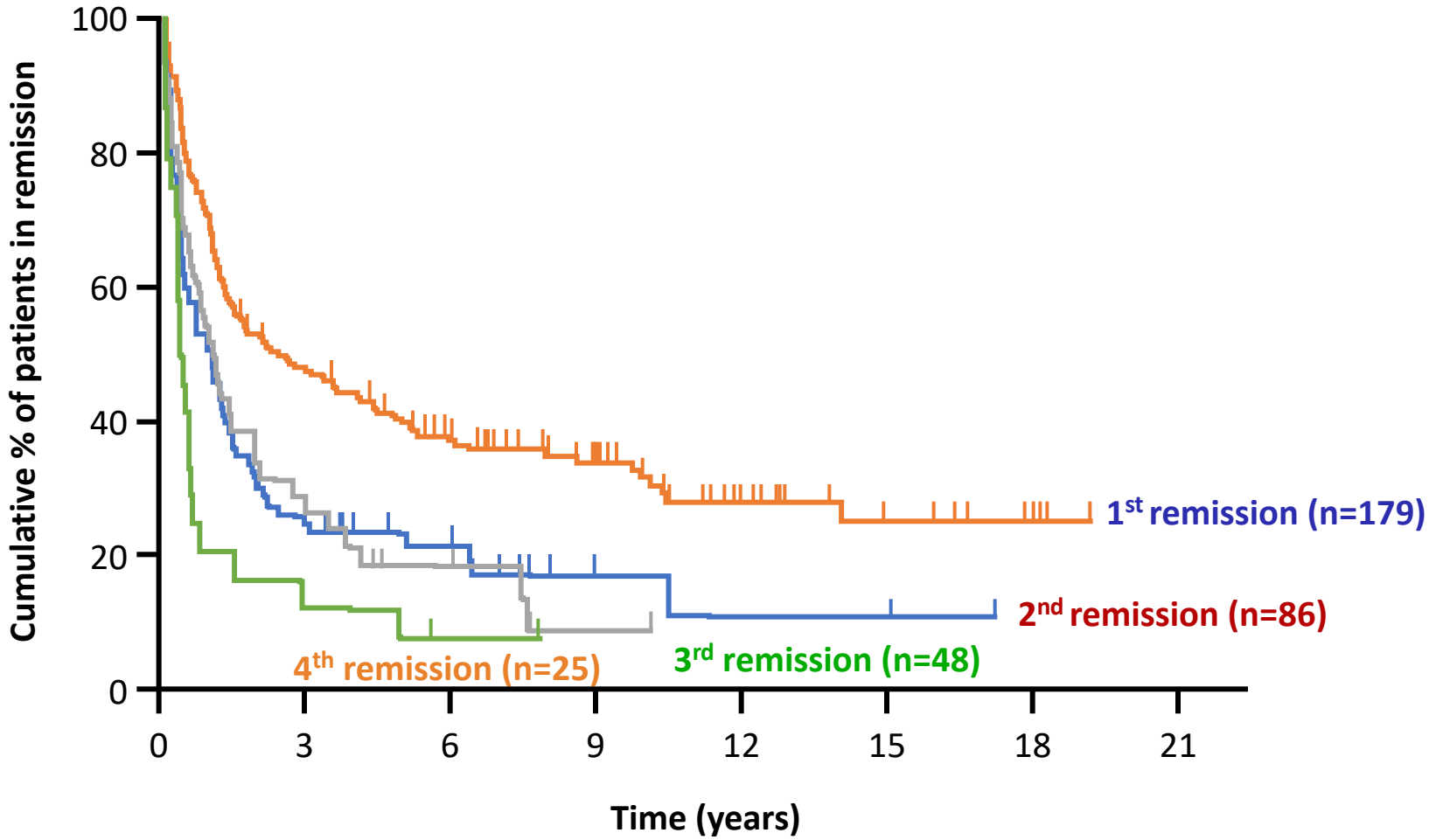
NON SUSSISTE ALCUN CONFLITTO DI INTERESSI

LINFOMA FOLLICOLARE



- «Uncurable disease»
- Outcome clinico caratterizzato da reiterate recidive, con risposte di durata sempre più breve all'aumentare delle linee di terapia.
- Trasformazione in un linfoma ad istologia aggressiva e a prognosi sfavorevole (20% dei pazienti ad un follow-up medio di 8.9 anni nel PRIMA study). Incidenza 2.5-3%/anno

Need for better treatments beyond second line as response duration and survival are short



Pre-rituximab era: most common first-line treatments were single agent chemotherapy, combination chemotherapy, and radiotherapy. Most common treatments for first remission were: chlorambucil (65%), CHOP (10%) and radiotherapy (9%)

Johnson PW, *et al. J Clin Oncol* 1995; 13:140–147.

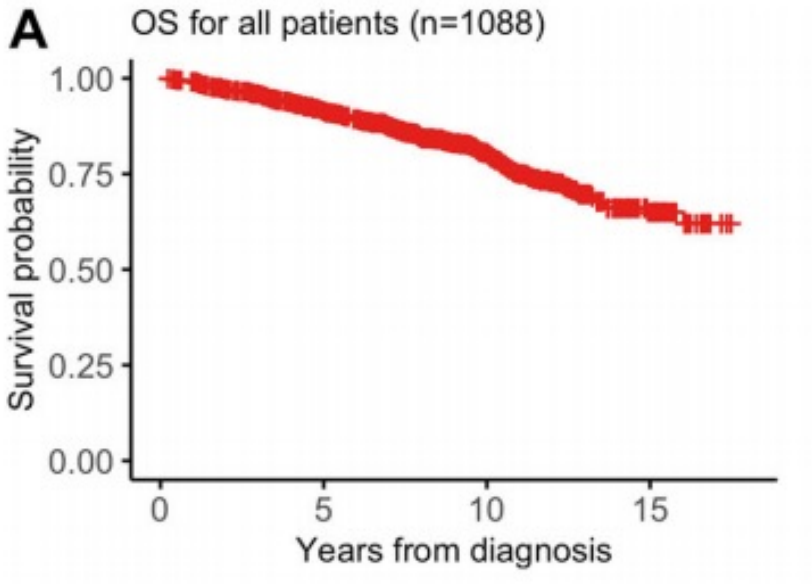
Follicular lymphoma in the modern era: survival, treatment outcomes, and identification of high-risk subgroups

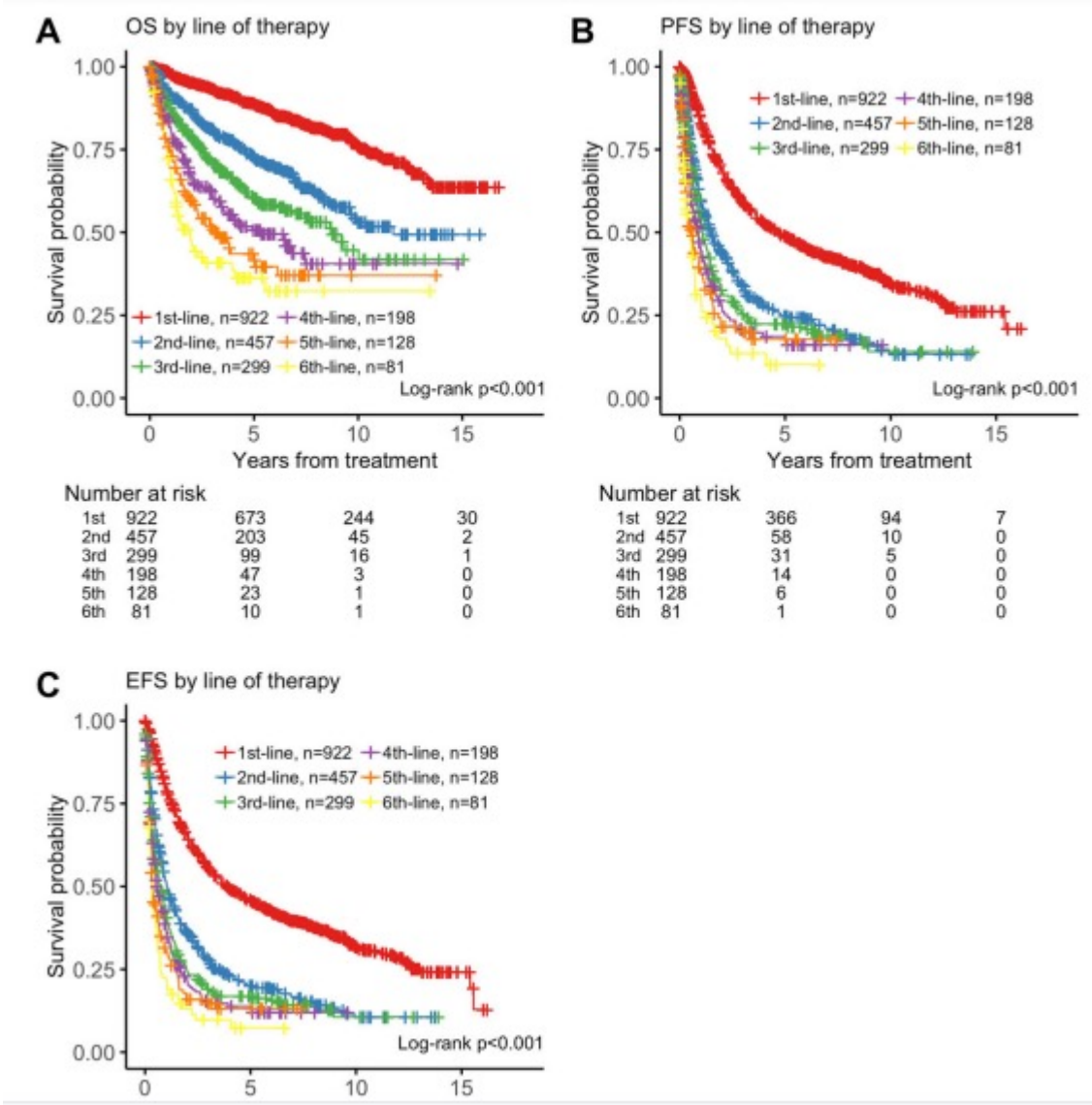
Connie L. Batlevi[1], Fushen Sha[1], Anna Alperovich[1], Ai Ni[2,3], Katy Smith[1,4], Zhitao Ying[1,5], Jacob D. Soumerai[1,6], Philip C. Caron[1], Lorenzo Falchi[1], Audrey Hamilton[1], Paul A. Hamlin[1], Steven M. Horwitz[1], Erel Joffe[1], Anita Kumar[1], Matthew J. Matasar[1], Alison J. Moskowitz[1], Craig H. Moskowitz[1,7], Ariela Noy[1], Colette Owens[1], Lia M. Palomba[1], David Straus[1], Gottfried von Keudell[1], Andrew D. Zelenetz[1], Venkatraman E. Seshan[2] and Anas Younes[1]

Abstract

Patients with follicular lymphoma (FL) frequently require multiple treatments during their disease course; however, survival based on lines of treatment remains poorly described in the post-rituximab era. Also, the Follicular Lymphoma International Prognostic Index (FLIPI) score was developed to predict survival at diagnosis, yet it remains unknown whether increase in FLIPI score following an initial observation period is associated with less-favorable outcomes. To address these knowledge gaps, we retrospectively studied 1088 patients with FL grade 1–3A managed between 1998 and 2009 at our institution. Median overall survival (OS) and progression-free survival (PFS) after first-line treatment were not reached and 4.73 years, respectively. Following successive lines of treatment, years of median OS and PFS were, respectively: after second-line, 11.7 and 1.5; third-line, 8.8 and 1.1; fourth-line, 5.3 and 0.9; fifth-line, 3.1 and 0.6; sixth-line, 1.9 and 0.5. In initially observed, subsequently treated patients, FLIPI score increase after observation was associated with inferior survival following first-line treatment. The reduced survival we observed after second-line and later therapy supports the development of new treatments for relapsed patients and benchmarks historical targets for clinical endpoints. This study also highlights the utility of changes in FLIPI score at diagnosis and after observation in identifying patients likely to have worse outcomes.

Blood Cancer Journal 2020





	1st-line ($n = 922$)	2nd-line ($n = 457$)	3rd-line ($n = 299$)	4th-line ($n = 198$)	5th-line ($n = 128$)	6th-line ($n = 81$)
OS	NR (NR-NR)	11.67 (9.67–NR)	8.75 (6.84–NR)	5.34 (3.51–NR)	3.13 (2.22–6.13)	1.93 (1.25–5.52)
PFS	4.73 (3.93–5.71)	1.51 (1.22–1.92)	1.07 (0.93–1.39)	0.90 (0.59–1.10)	0.55 (0.33–0.92)	0.48 (0.28–0.71)
EFS	3.91 (3.39–4.79)	1.04 (0.89–1.31)	0.73 (0.57–0.94)	0.56 (0.48–0.84)	0.35 (0.29–0.62)	0.30 (0.26–0.50)

Batlevi, Blood Cancer Journal 2020

Clinical outcomes in patients relapsed/refractory after ≥2 prior lines of therapy for follicular lymphoma: a systematic literature review and meta-analysis

Steve Kanters[1*], Graeme Ball[2], Brad Kahl[3], Adriana Wiesinger[4], Eve H. Limbrick-Oldfield[1], Akshay Sudhindra[5], Julia Thornton Snider[5] and Anik R. Patel[5]

Abstract

Background Patients with follicular lymphoma (FL) can have high response rates to early lines of treatment. However, among FL patients relapsed/refractory (r/r) after ≥2 prior lines of therapy (LOT), remission tends to be shorter and there is limited treatment guidance. This study sought to evaluate the clinical outcomes for r/r FL after ≥2 prior LOT identified through systematic literature review.

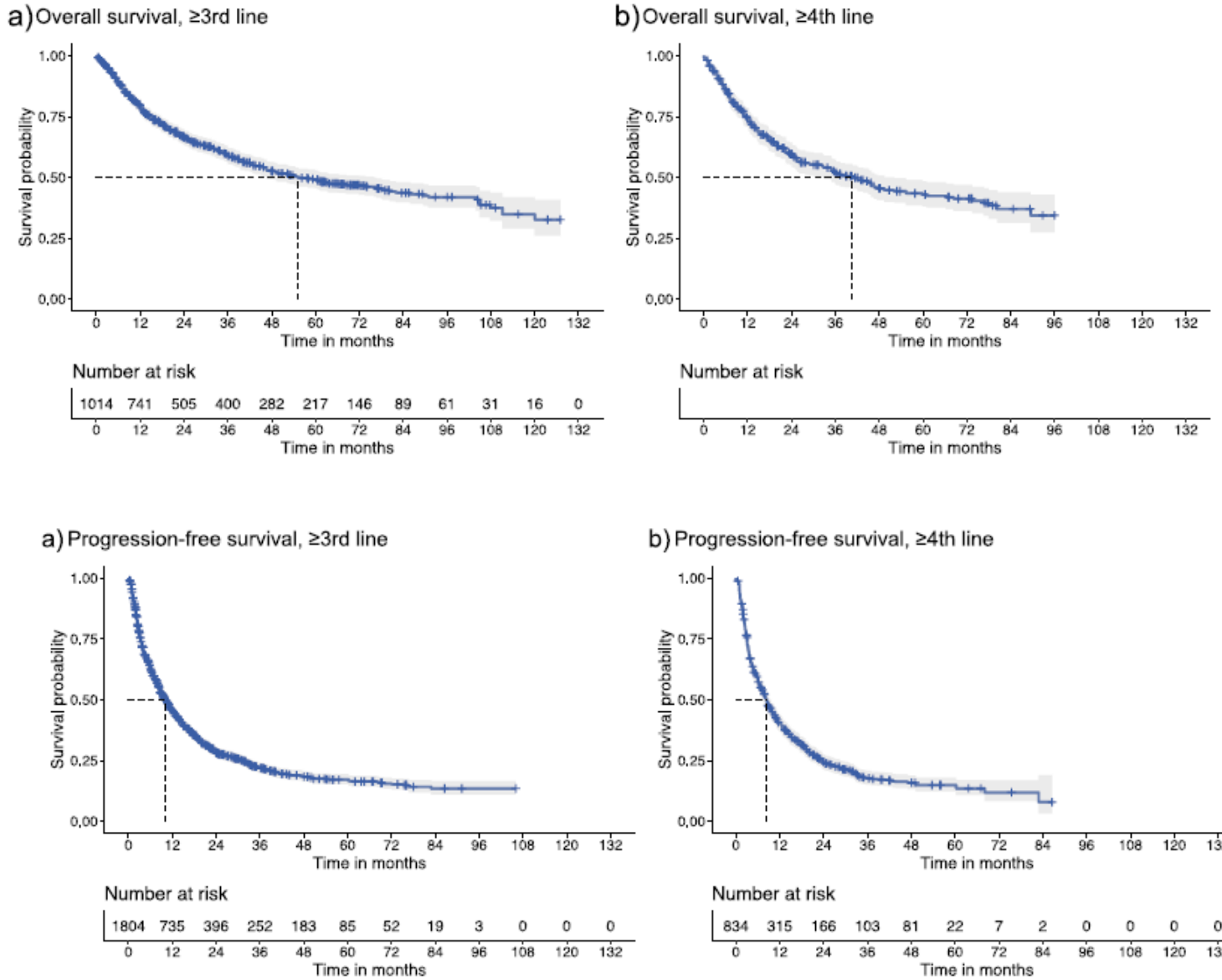
Methods Eligible studies included comparative or non-comparative interventional or observational studies of systemic therapies among adults with FL r/r after ≥2 prior LOT published prior to 31st May 2021. Prior LOT must have included an anti-CD20 monoclonal antibody and an alkylating agent, in combination or separately. Overall response rate (ORR) and complete response (CR) were estimated using inverse-variance weighting with Freeman-Tukey double-arcsine transformations. Kaplan-Meier (KM) curves for progression-free survival (PFS) and overall survival (OS) estimated by reconstructing digitized curves using the Guyot algorithm, and survival analyses were conducted, stratified by ≥2 prior LOT and ≥3 prior LOT groups (as defined in the source material). Restricting the analyses to the observational cohorts was investigated as a sensitivity analysis.

Results The analysis-set included 20 studies published between 2014 and 2021. Studies were primarily US and/or European based, with the few exceptions using treatments approved in US/Europe. The estimated ORR was 58.47% (95% confidence interval [CI]: 51.13–65.62) and proportion of patients with CR was 19.63% (95% CI: 15.02–24.68). The median OS among those ≥2 prior LOT was 56.57 months (95% CI: 47.8–68.78) and median PFS was 9.78 months (95% CI: 9.01–10.63). The 24-month OS decreased from 66.50% in the ≥2 prior LOT group to 59.51% in the ≥3 prior LOT group, with a similar trend in PFS at 24-month (28.42% vs 24.13%).

Conclusions This study found that few r/r FL patients with ≥2 prior LOT achieve CR, and despite some benefit, approximately 1/3 of treated patients die within 24 months. The shorter median PFS with increasing prior LOT suggest treatment durability is suboptimal in later LOT. These findings indicate that patients are underserved by treatments currently available in the US and Europe.

Keywords Relapsed/refractory follicular lymphoma, Clinical outcomes, Systematic literature review, Meta-analysis

Kanters S, BMC Cancer, 2023



Kanters S, BMC Cancer, 2023

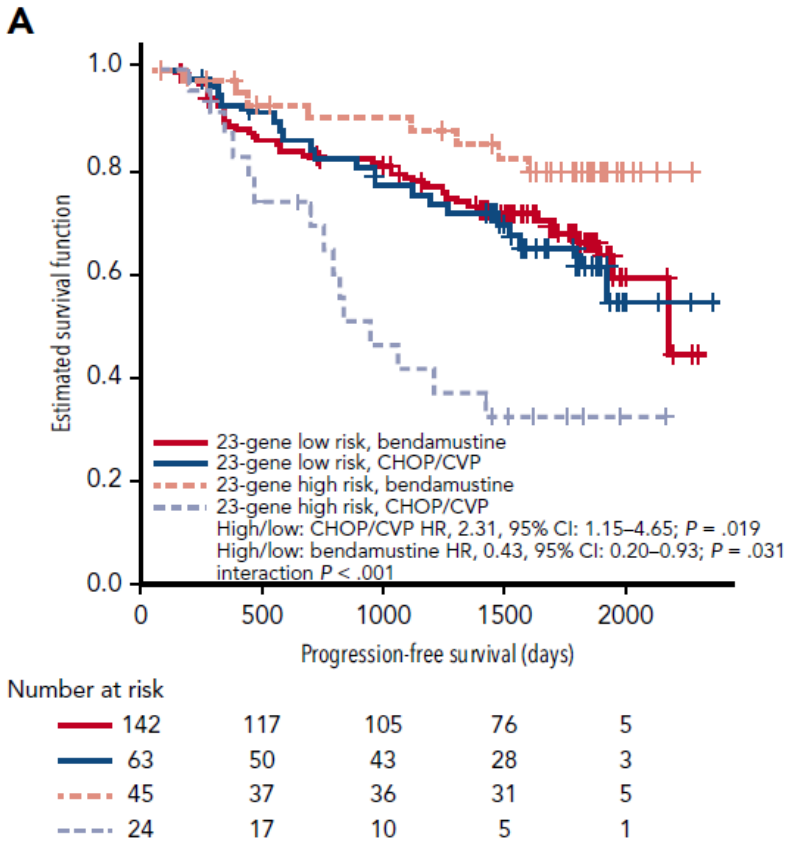
CLINICAL AND BIOLOGICAL RISK MODELS

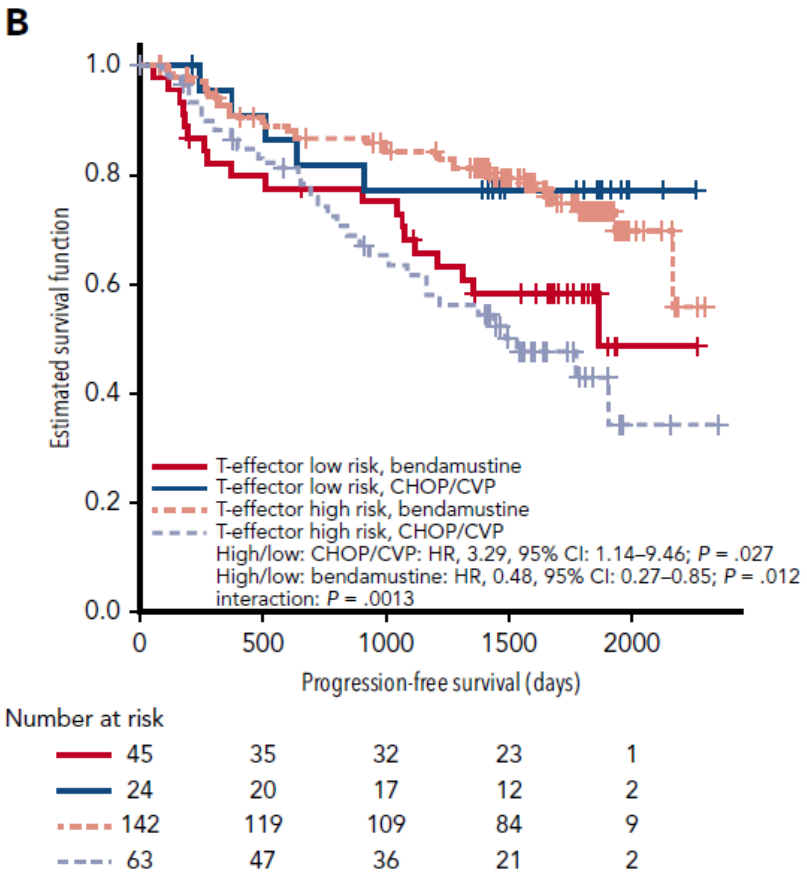
Score	Clinical factors	Biologic factors	Treatment	Associated outcome	References
FLIPI	Nodal sites, LDH, age, stage, hemoglobin	–	Pre-rituximab	OS	43
FLIPI-2	Age, B2-microglobulin, bone marrow involvement, hemoglobin, bulky adenopathy	–	Post-rituximab	PFS	44
M7-FLIPI	FLIPI score plus performance status	EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP and CARD11	R-CHOP or R-CVP	Failure free survival	28
PRIMA-23	–	23 gene signature reflecting FL and TME	Mostly R-CHOP or R-CVP	PFS	48
ICA13	–	CXCR4, AICDA, BACH2, PAU2AF, DCAF12, E2F5, ORAI2, PRDM15, RASSF6, TAGAP, TCF4, and USP44	Mostly R-CHOP or R-CVP	PFS	48
6 gene T effector signature	–	*CD8A, EOMES, GZMA, GZMB, IFNγ, PRF1*	Mostly R-CHOP	PFS	50
Immune response signature	–	Gene expression signature of TME	Previously untreated, pre-rituximab	OS	32

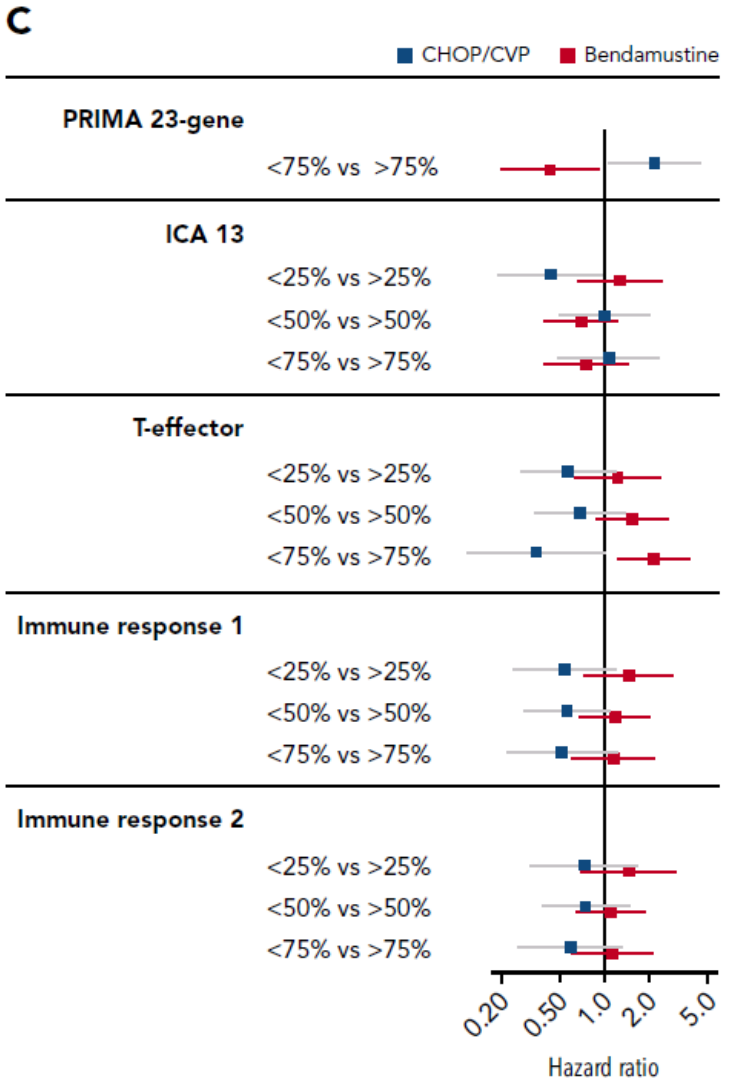
Gordon MJ, Blood Reviews, 2023

Treatment dependence of prognostic gene expression signatures in de novo follicular lymphoma

Christopher R. Bolen,[1] Federico Mattiello,[2] Michael Herold,[3] Wolfgang Hiddemann,[4] Sarah Huet,[5-7] Wolfram Klapper,[8] Robert Marcus,[9] Farheen Mir,[10] Gilles Salles,[5,11] Oliver Weigert,[12-14] Tina Nielsen,[2] Mikkel Z. Oestergaard,[15] and Jeffrey M. Venstrom[16]







Bolen CR, Blood 2021

Fattori prognostici nel FL

Complessità nella capacità di sviluppare modelli prognostici in termini di OS e di PFS che prendano in considerazione aspetti clinici, caratteristiche genomiche della popolazione tumorale e del microambiente linfonodale, e soprattutto il tipo di trattamento.

Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study

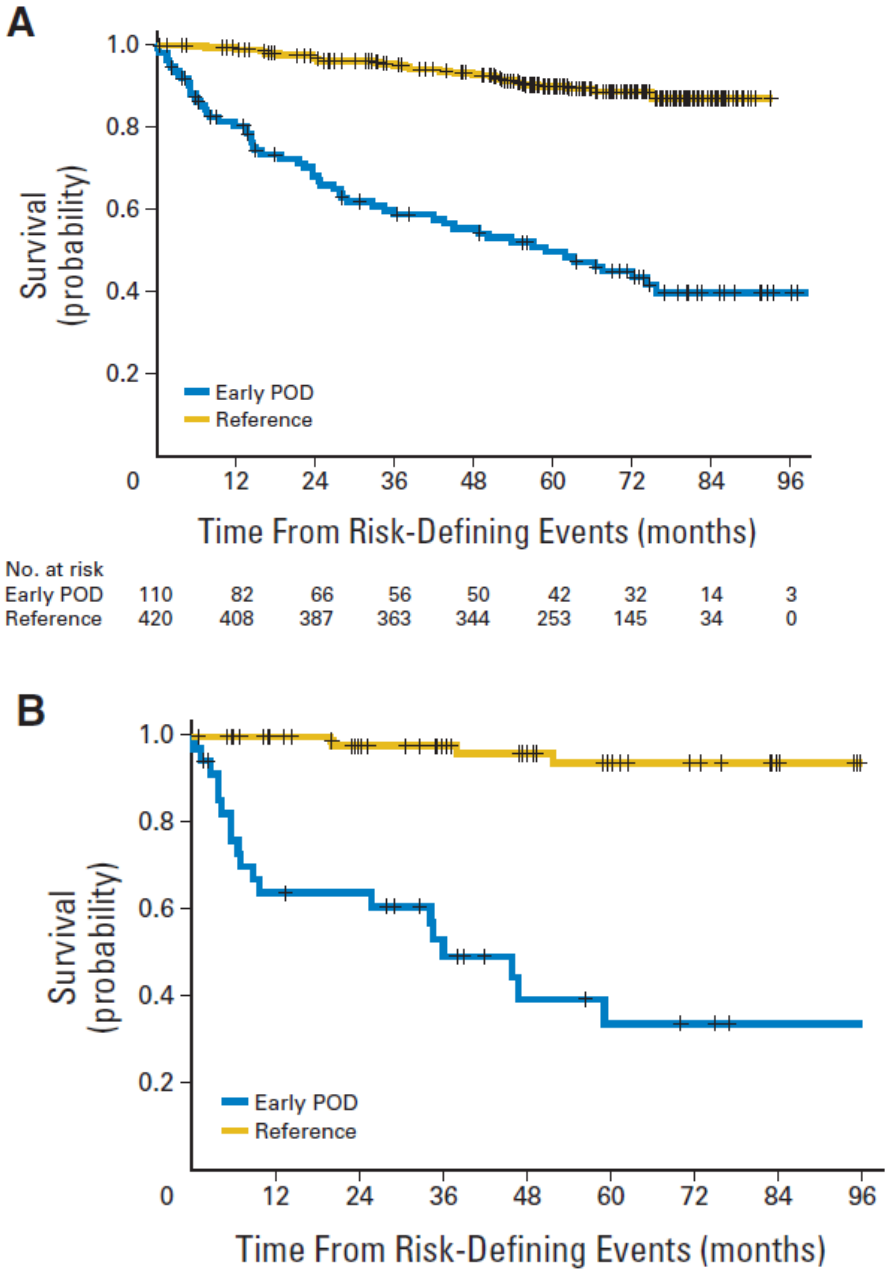
Carla Casulo, Michelle Byrtek, Keith L. Dawson, Xiaolei Zhou, Charles M. Farber, Christopher R. Flowers, John D. Hainsworth, Matthew J. Maurer, James R. Cerhan, Brian K. Link, Andrew D. Zelenetz, and Jonathan W. Friedberg

Purpose
Twenty percent of patients with follicular lymphoma (FL) experience progression of disease (POD) within 2 years of initial chemoimmunotherapy. We analyzed data from the National LymphoCare Study to identify whether prognostic FL factors are associated with early POD and whether patients with early POD are at high risk for death.

Patients and Methods
In total, 588 patients with stage 2 to 4 FL received first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Two groups were defined: patients with early POD 2 years or less after diagnosis and those without POD within 2 years, the reference group. An independent validation set, 147 patients with FL who received first-line R-CHOP, was analyzed for reproducibility.

Results
Of 588 patients, 19% (n = 110) had early POD, 71% (n = 420) were in the reference group, 8% (n = 46) were lost to follow-up, and 2% (n = 12) died without POD less than 2 years after diagnosis. Five-year overall survival was lower in the early-POD group than in the reference group (50% *v* 90%). This trend was maintained after we adjusted for FL International Prognostic Index (hazard ratio, 6.44; 95% CI, 4.33 to 9.58). Results were similar for the validation set (FL International Prognostic Index–adjusted hazard ratio, 19.8).

Conclusion
In patients with FL who received first-line R-CHOP, POD within 2 years after diagnosis was associated with poor outcomes and should be further validated as a standard end point of chemoimmunotherapy trials of untreated FL. This high-risk FL population warrants further study in directed prospective clinical trials.

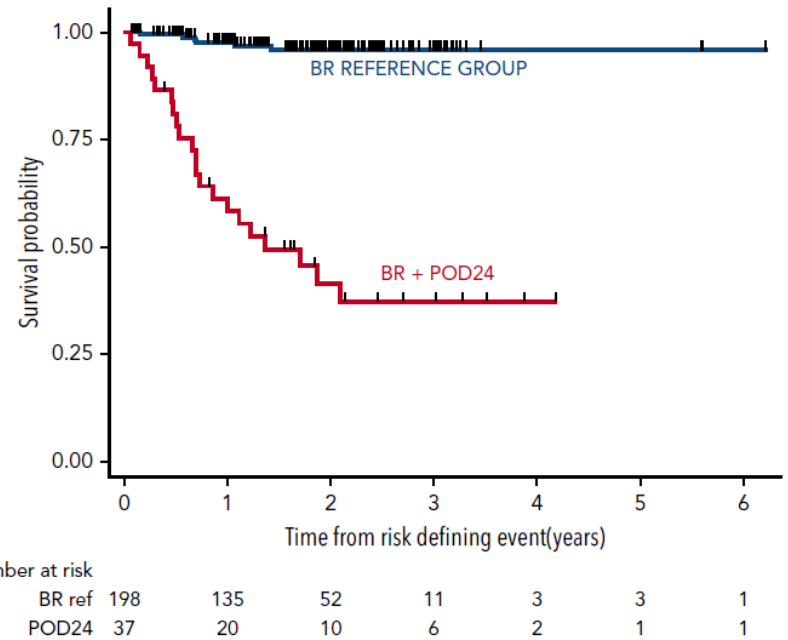


Casulo C, JCO 2015

Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma

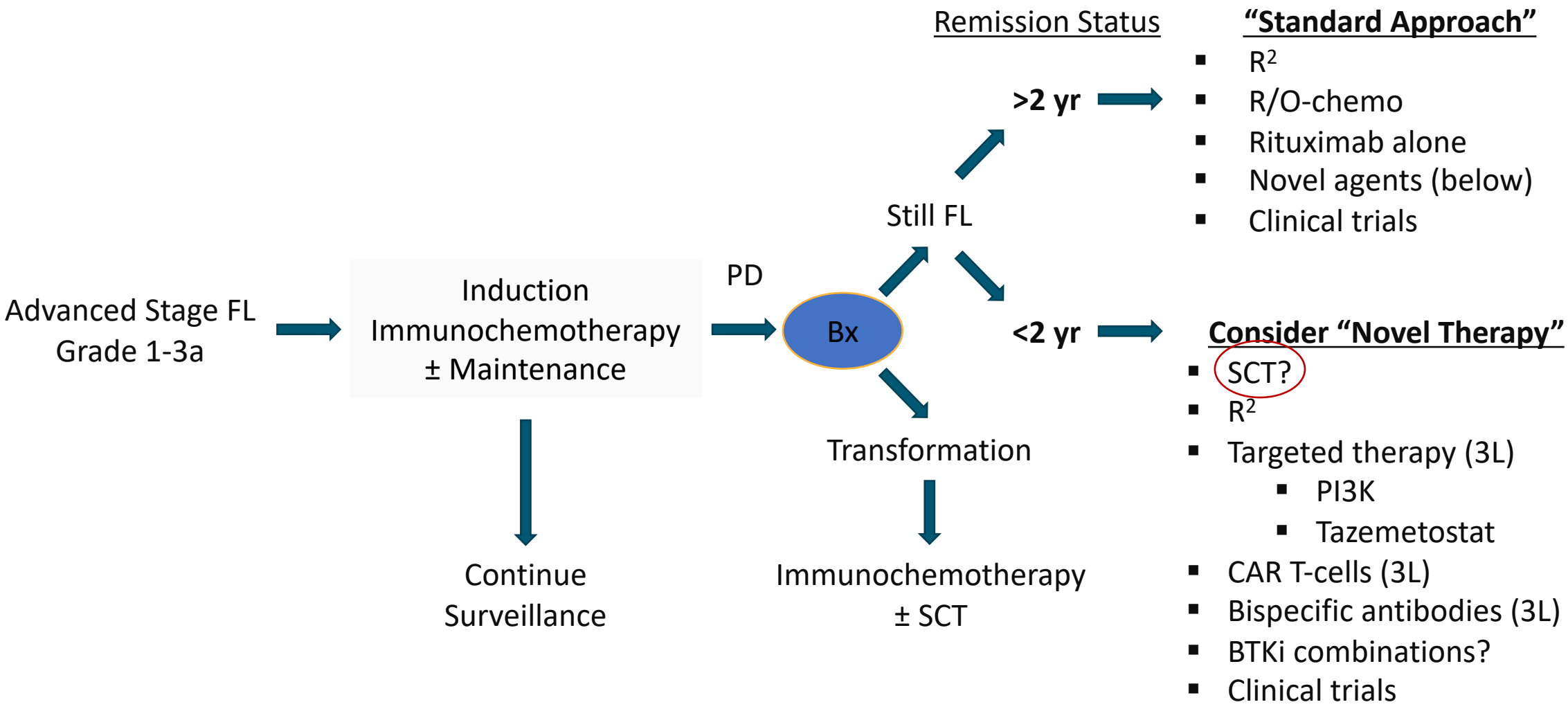
Ciara L. Freeman,[1,2] Robert Kridel,[3] Alden A. Moccia,[4] Kerry J. Savage,[1,2] Diego R. Villa,[1,2] David W. Scott,[1,2] Alina S. Gerrie,[1,2] David Ferguson,[5] Fergus Cafferty,[5] Graham W. Slack,[1,2,6] Pedro Farinha,[1,2,6] Brian Skinnider,[1,2,6] Joseph M. Connors,[1,2] and Laurie H. Sehn[1,2]

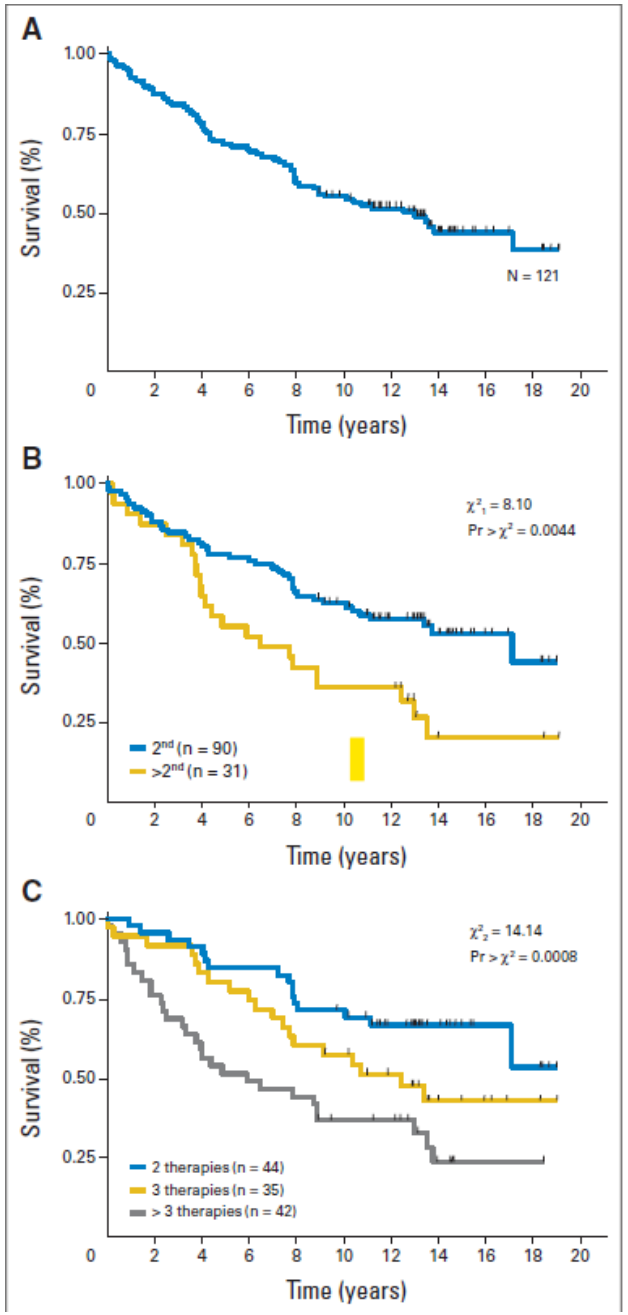
Despite widespread use of bendamustine and rituximab (BR) as frontline therapy for advanced-stage follicular lymphoma (FL), little is known about the risk of early progression or incidence of histological transformation. We performed a retrospective analysis of a population-based cohort of 296 patients with advanced-stage FL treated with frontline BR and maintenance rituximab. As previously demonstrated, outcomes with this regimen are excellent, with 2-year event-free survival estimated at 85% (95% confidence interval [95% CI], 80-89) and 2-year overall survival 92% (95% CI, 88-95). Progression of disease within 24 months (POD24) occurred in 13% of patients and was associated with a significantly inferior outcome with 2-year overall survival of 38% (95% CI, 20-55). The only significant risk factor for POD24 at baseline was elevated lactate dehydrogenase ($P < .001$). Importantly, the majority of POD24 patients (76%) had transformed disease. Compared with a historical cohort treated with rituximab, cyclophosphamide, vincristine, and prednisone, event-free survival has improved and the risk of POD24 has decreased, but a higher proportion of patients with POD24 harbor transformation. The overall incidence of transformation appears unchanged. The presence of occult or early transformation is the main driver of POD24 in FL patients treated with frontline BR. Identification of biomarkers and improved management strategies for transformation will be crucial to improving outcomes. (*Blood*. 2019;134(9):761-764)



- Se il POD-24 rappresenti un surrogato per la trasformazione istologica o se denoti uno specifico pattern biologico di resistenza alla chemio/immunoterapia standard o sia entrambe le cose, configura uno dei maggiori bisogni clinici insoddisfatti nel linfoma follicolare.
- Non abbiamo ancora sufficienti certezze per una terapia risk-adapted (ad esempio, MRD → FOLL12)

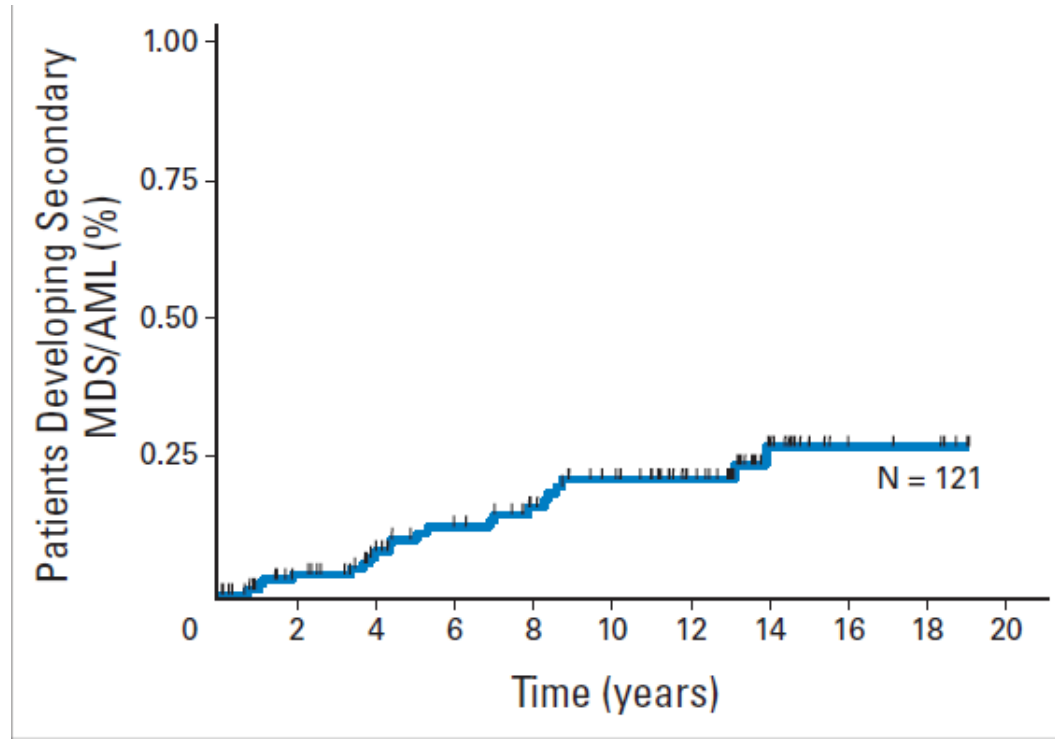
Treatment of Follicular Lymphoma





Myeloablative Therapy With Autologous Bone Marrow Transplantation for Follicular Lymphoma at the Time of Second or Subsequent Remission: Long-Term Follow-Up

Ama Z.S. Rohatiner, Lee Nadler, Andrew J. Davies, John Apostolidis, Donna Neuberg, Janet Matthews, John G. Gribben, Peter M. Mauch, T. Andrew Lister, and Arnold S. Freedman

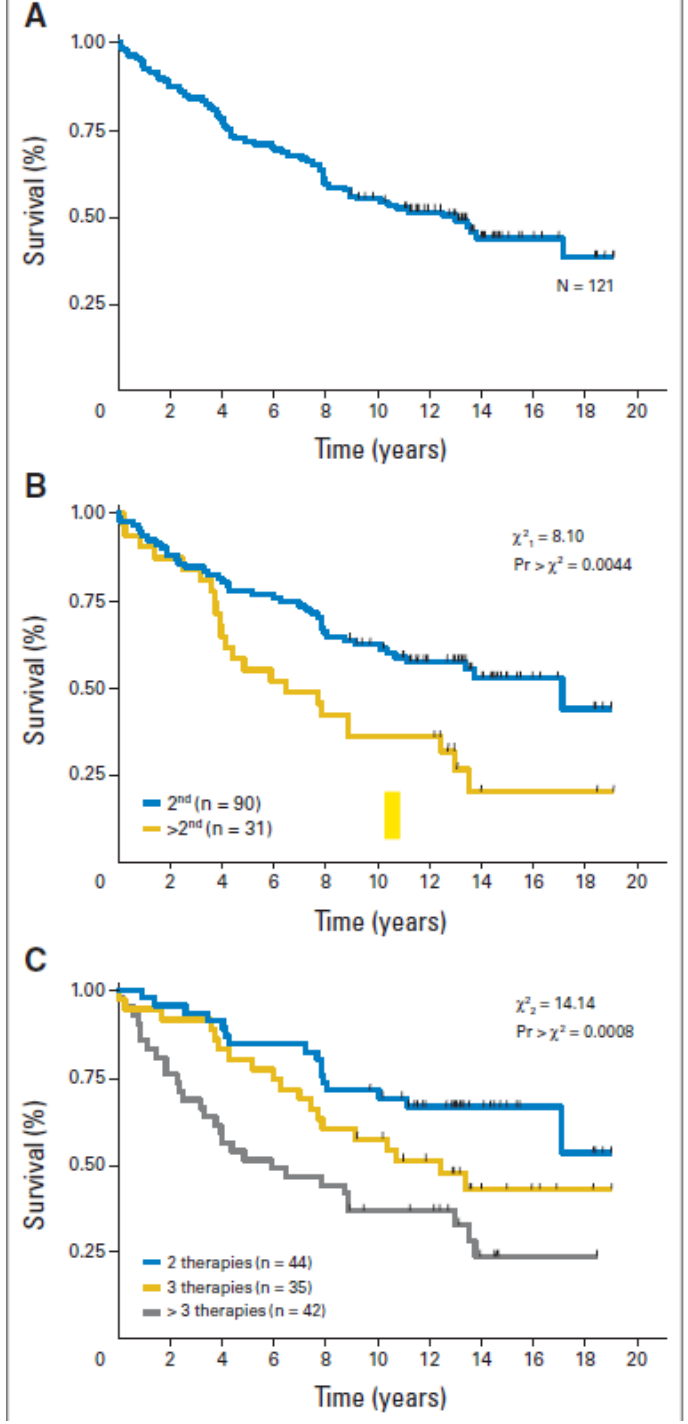


JCO,2007

Table 2. Causes of Death

Cause of Death	No. of Patients	Additional Information
Recurrent lymphoma	37	
Other causes	27	
Treatment related	4	Hemorrhage, fungal infection, nonengraftment, and veno-occlusive disease
Treatment-related AML/MDS	15	Nine patients in remission
Other malignancy	4	Three patients in remission of lymphoma
Other causes	2	Cardiac and suicide; both patients in remission
Unknown	2	Patients were in remission at time of last follow-up
Total	64	

Abbreviations: MDS, myelodysplastic syndrome; AML, acute myeloblastic leukemia.



ASCT vs No ASCT for Early Progressing FL

Study	Casulo et al[1]	Manna et al[2]	Jurunovic et al[3]
Patient cohorts	NLCS and CIBMTR	Calgary	GLSG
Patient population	Failure to achieve at least a PR or early relapse ≤ 2 yrs on frontline rituximab-based CIT	Early relapse ≤ 2 yrs following frontline CIT	Progressive, relapsed, or refractory disease ≤ 2 yrs on systemic frontline therapy*
N	349 ▪ ASCT cohort: 175 ▪ Non-ASCT cohort: 174	84 ▪ ASCT cohort: 50 ▪ Non-ASCT cohort: 34	113 ▪ ASCT cohort: 52 ▪ Non-ASCT cohort: 46†
5-Yr PFS, %	Not reported	Not reported	▪ ASCT cohort: 51% ▪ Non-ASCT cohort: 19% ▪ *P* < .0001
5-Yr OS, %	▪ ASCT cohort: 67% ▪ Non-ASCT cohort: 60% ▪ *P* = .16	▪ ASCT cohort: 85% ▪ Non-ASCT cohort: 58% ▪ *P* = .001	▪ ASCT cohort: 77% ▪ Non-ASCT cohort: 59% ▪ *P* = .031

*At ≤ 65 yrs of age. †Excludes patients with cytoreduction failure.

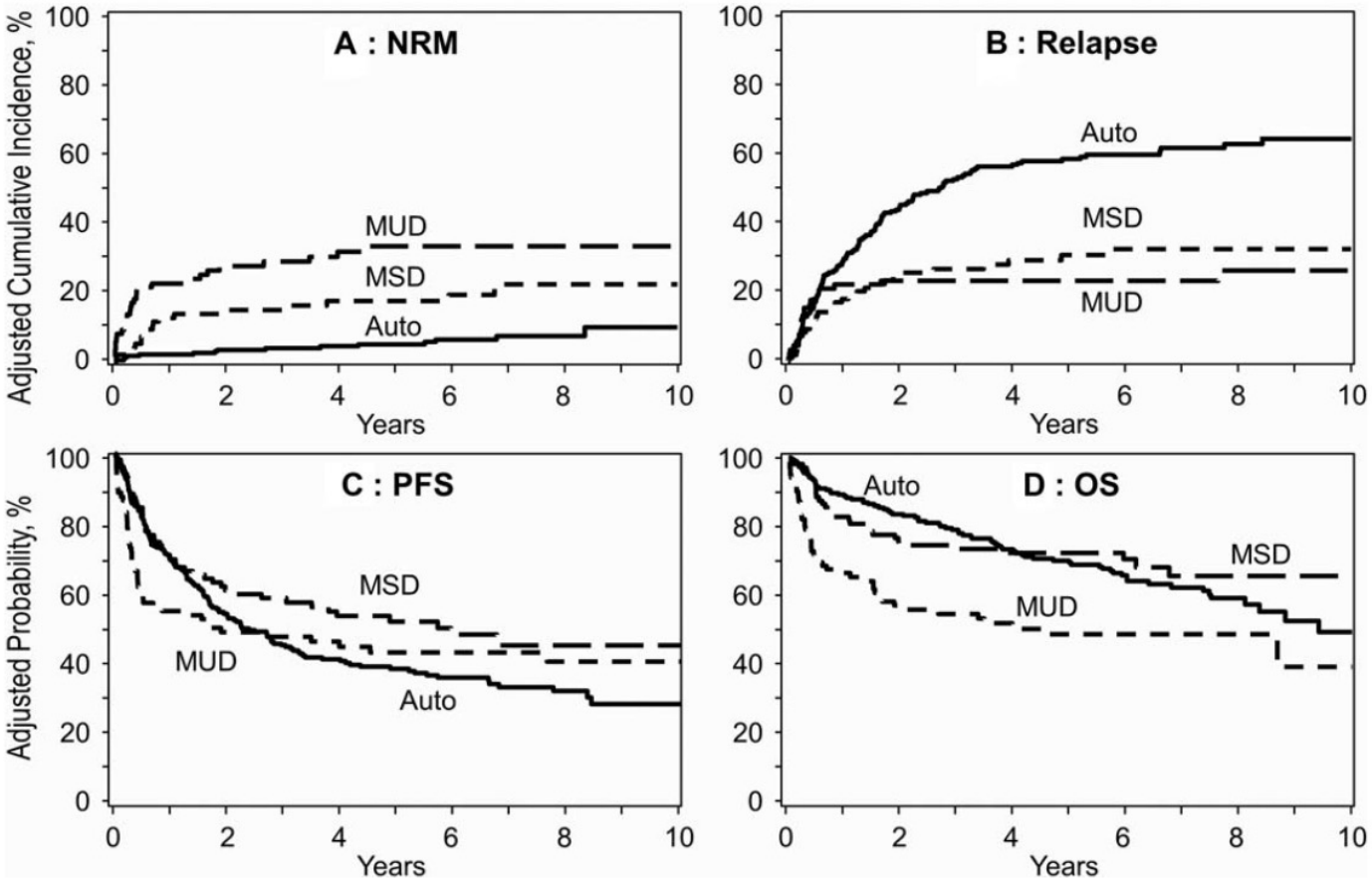
1. Casulo. Biol Blood Marrow Transplant. 2018;24:1163. 2. Manna. Leuk Lymphoma. 2019;60:133. 3. Jurinovic. Biol Blood Marrow Transplant. 2018;24:1172.

Autologous Transplantation Versus Allogeneic Transplantation in Patients With Follicular Lymphoma Experiencing Early Treatment Failure

Smith SM, Cancer 2018

Sonali M. Smith[1]; James Godfrey[2]; Kwang Woo Ahn[3,4]; Alyssa DiGilio[3]; Sairah Ahmed[5]; Vaibhav Agrawal[6]; Veronika Bachanova[7]; Ulrike Bacher[8,9]; Asad Bashey[10]; Javier Bolaños-Meade[11]; Mitchell Cairo[12]; Andy Chen[13]; Saurabh Chhabra[14]; Edward Copelan[15]; Parastoo B. Dahi[16]; Mahmoud Aljurf[17]; Umar Farooq[18]; Siddhartha Ganguly[19]; Mark Hertzberg[20]; Leona Holmberg[21]; David Inwards[22]; Abraham S. Kanate[23]; Reem Karmali[24]; Vaishalee P. Kenkre[25]; Mohamed A. Kharfan-Dabaja[26]; Andreas Klein[27]; Hillard M. Lazarus[28]; Matthew Mei[29]; Alberto Mussetti[30]; Taiga Nishihori[26]; Praveen Ramakrishnan Geethakumari[31]; Ayman Saad[32]; Bipin N. Savani[33]; Harry C. Schouten[34]; Nirav Shah[14]; Alvaro Urbano-Ispizua[35,36,37]; Ravi Vij[38]; Julie Vose[39]; Anna Sureda[40]; and Mehdi Hamadani, MD[3]

BACKGROUND: Early treatment failure (ETF) in follicular lymphoma (FL), defined as relapse or progression within 2 years of frontline chemoimmunotherapy, is a newly recognized marker of poor survival and identifies a high-risk group of patients with an expected 5-year overall survival (OS) rate of approximately 50%. Transplantation is an established option for relapsed FL, but its efficacy in this specific ETF FL population has not been previously evaluated. **METHODS:** This study compared autologous hematopoietic stem cell transplantation (auto-HCT) with either matched sibling donor (MSD) or matched unrelated donor (MUD) allogeneic hematopoietic cell transplantation (allo-HCT) as the first transplantation approach for patients with ETF FL (age $\geq$ 18 years) undergoing auto-HCT or allo-HCT between 2002 and 2014. The primary endpoint was OS. The secondary endpoints were progression-free survival, relapse, and nonrelapse mortality (NRM). **RESULTS:** Four hundred forty FL patients had ETF (auto-HCT, 240; MSD hematopoietic stem cell transplantation [HCT], 105; and MUD HCT, 95). With a median follow-up of 69 to 73 months, the adjusted probability of 5-year OS was significantly higher after auto-HCT (70%) or MSD HCT (73%) versus MUD HCT (49%; $P = .0008$). The 5-year adjusted probability of NRM was significantly lower for auto-HCT (5%) versus MSD (17%) or MUD HCT (33%; $P < .0001$). The 5-year adjusted probability of disease relapse was lower with MSD (31%) or MUD HCT (23%) versus auto-HCT (58%; $P < .0001$). **CONCLUSIONS:** Patients with high-risk FL, as defined by ETF, undergoing auto-HCT for FL have low NRM and a promising 5-year OS rate (70%). MSD HCT has lower relapse rates than auto-HCT but similar OS. *Cancer* **2018;124:2541-51.** © *2018 American Cancer Society.*



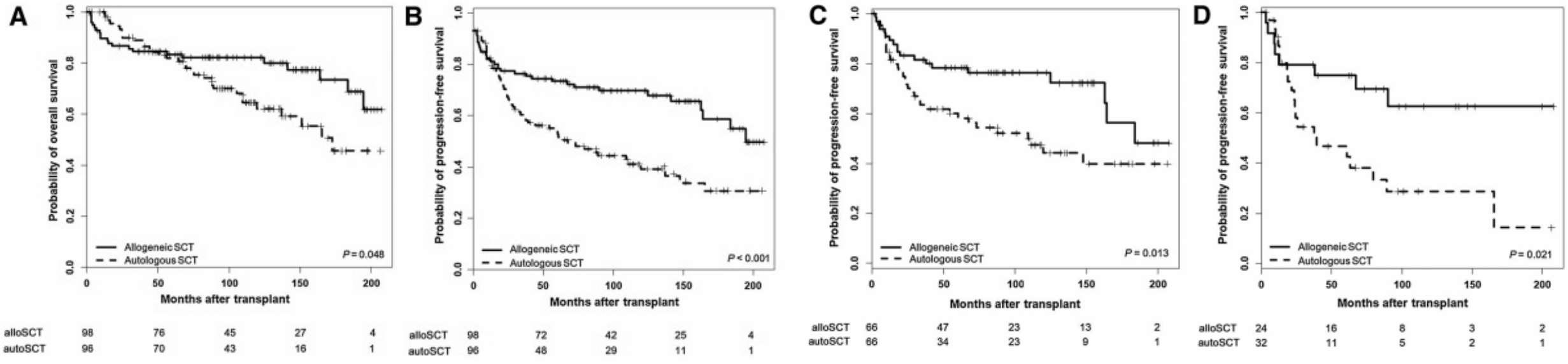
Cause of Death	No. of Deaths		
	Auto-HCT	MSD	MUD
Total	81	33	48
Infection	1 (1)	6 (18)	6 (13)
Idiopathic pneumonia syndrome	1 (1)	0	1 (2)
Acute respiratory distress syndrome	1 (1)	1 (3)	1 (2)
Graft-versus-host disease	0	5 (15)	10 (21)
Primary disease	67 (83)	14 (42)	20 (42)
Organ failure	1 (1)	2 (6)	7 (15)
New malignancy	2 (2)	1 (3)	1 (2)
Other[a]	2 (2)	2 (6)	0
Unknown	6 (7)	2 (6)	2 (4)

Smith SM, Cancer 2018

Nine-Year Follow-up of Patients with Relapsed Follicular Lymphoma after Nonmyeloablative Allogeneic Stem Cell Transplant and Autologous Transplant

Issa F. Khouri[1], Denái R. Milton[2], Alison M. Gulbis[3], Elias J. Jabbour[4], Loretta Nastoupil[5], Celina Ledesma[1], Paolo Anderlini[1], Qaiser Bashir[1], May Daher[1], Jin S. Im[1], Swaminathan P. Iyer[5], David Marin[1], Rohtesh S. Mehta[1], Amanda L. Olson[1], Uday R. Popat[1], Muzaffar Qazilbash[1], Neeraj Saini[1], Felipe Samaniego[5], Gabriela Rondon[1], L. Jeffrey Medeiros[6], and Richard E. Champlin[1]

Figure 2.
Kaplan–Meier survival curves of OS (**A**) and PFS (**B**) after allogeneic and autoSCT for patients with relapsed follicular lymphoma. **C,** Matched analysis of OS curves after allogeneic and autoSCT in these patients. **D,** Survival curves of PFS after allogeneic and autoSCT for patients >60 years old.



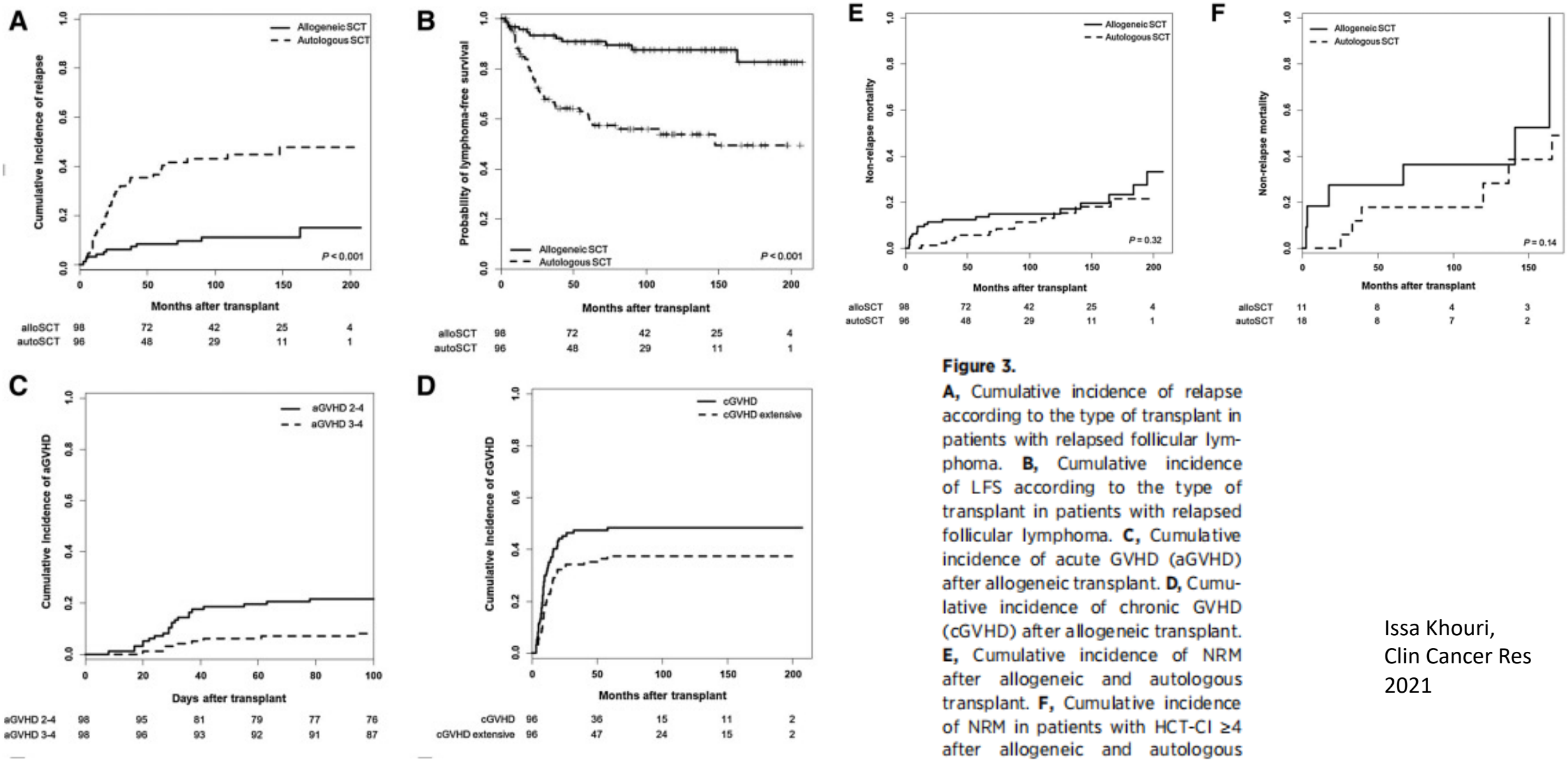


Figure 3.

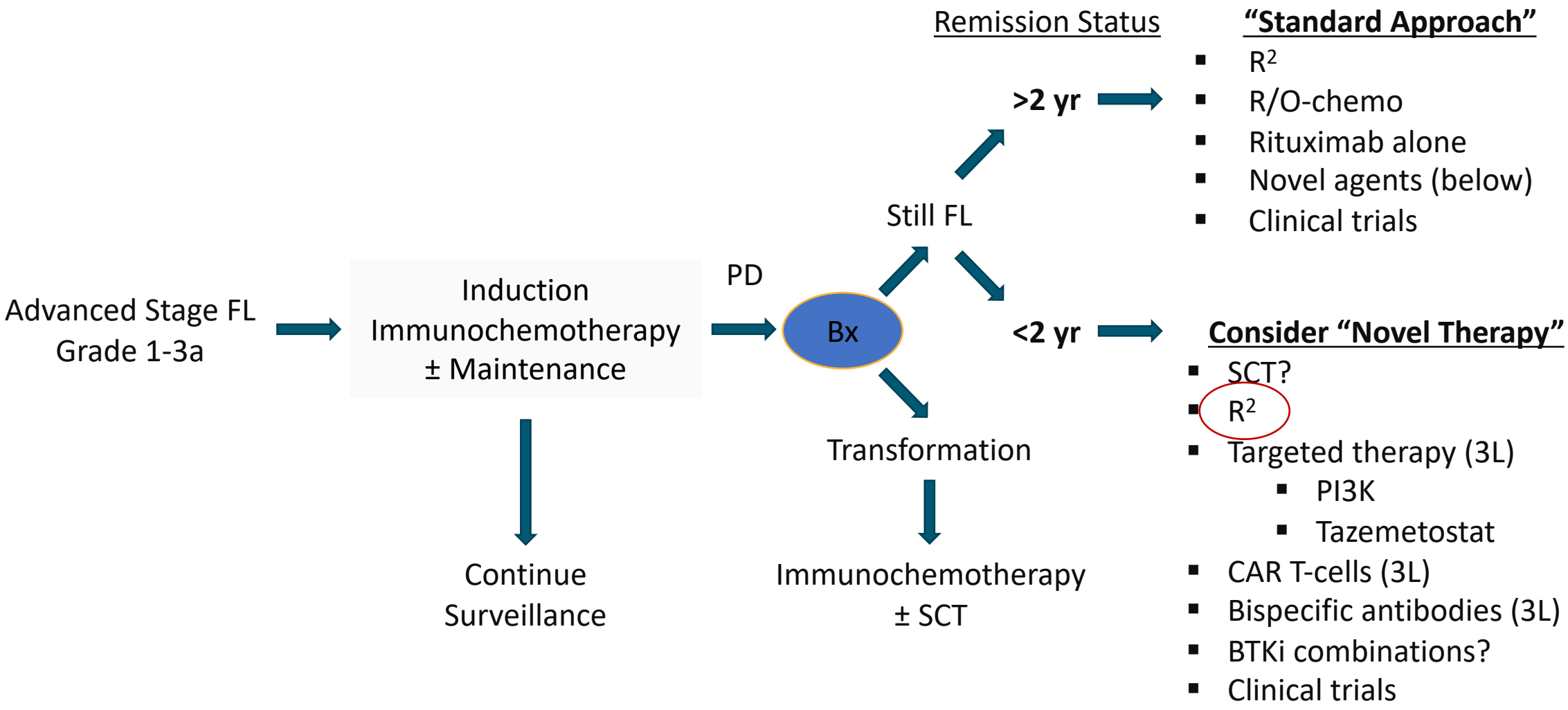
A, Cumulative incidence of relapse according to the type of transplant in patients with relapsed follicular lymphoma. **B,** Cumulative incidence of LFS according to the type of transplant in patients with relapsed follicular lymphoma. **C,** Cumulative incidence of acute GVHD (aGVHD) after allogeneic transplant. **D,** Cumulative incidence of chronic GVHD (cGVHD) after allogeneic transplant. **E,** Cumulative incidence of NRM after allogeneic and autologous transplant. **F,** Cumulative incidence of NRM in patients with HCT-CI ≥4 after allogeneic and autologous transplant.

Issa Khouri,
Clin Cancer Res
2021

Trapianto autologo o allogenico in ricaduta nel linfoma follicolare

La disponibilità di nuovi agenti terapeutici offre alternative meno invasive e ne ha ridotto e ne sta riducendo i numeri.
Confronto con i CAR-T
Selezione accurata dei pazienti, timing, qualità di vita
A tutt'oggi comunque l'allotrapianto rimane l'unica procedura in grado di indurre la guarigione nei pazienti con linfoma follicolare ricaduto, sulla base del follow-up a lungo termine e della rarità di ricadute tardive.

Treatment of Follicular Lymphoma



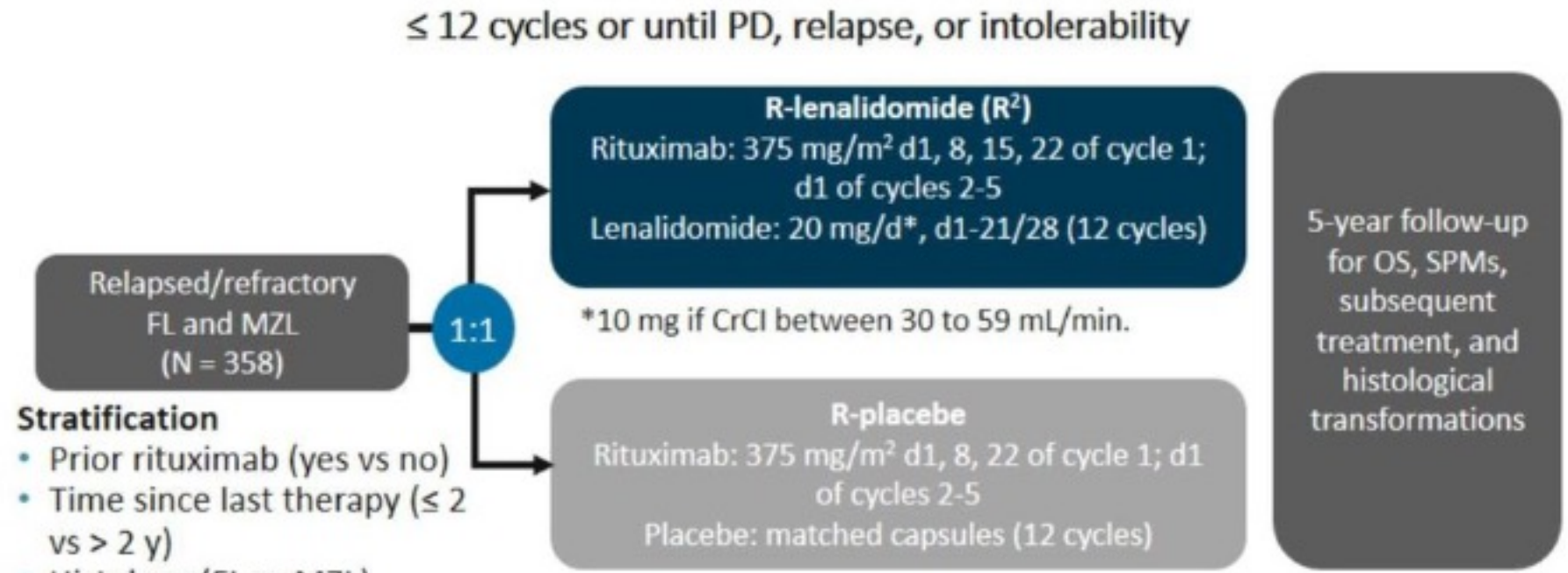
Five-Year Results and Overall Survival Update from the Phase 3 Randomized Study Augment: Lenalidomide Plus Rituximab (R2) Vs Rituximab Plus Placebo in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

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.

AUGMENT: Study Design



Stratification

- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

Key eligibility criteria

- MZL or FL (grades 1-3a) in need of treatment
- ≥ 1 prior chemotherapy, immunotherapy or chemoimmunotherapy
- Not rituximab refractory

- Prophylactic anticoagulation / antiplatelet Rx recommended for at risk patients
- Growth factor use was allowed per ASCO®/ESMO guidelines [1,2]

Primary endpoint: PFS by IRC (2007 IWG criteria w/o PET)

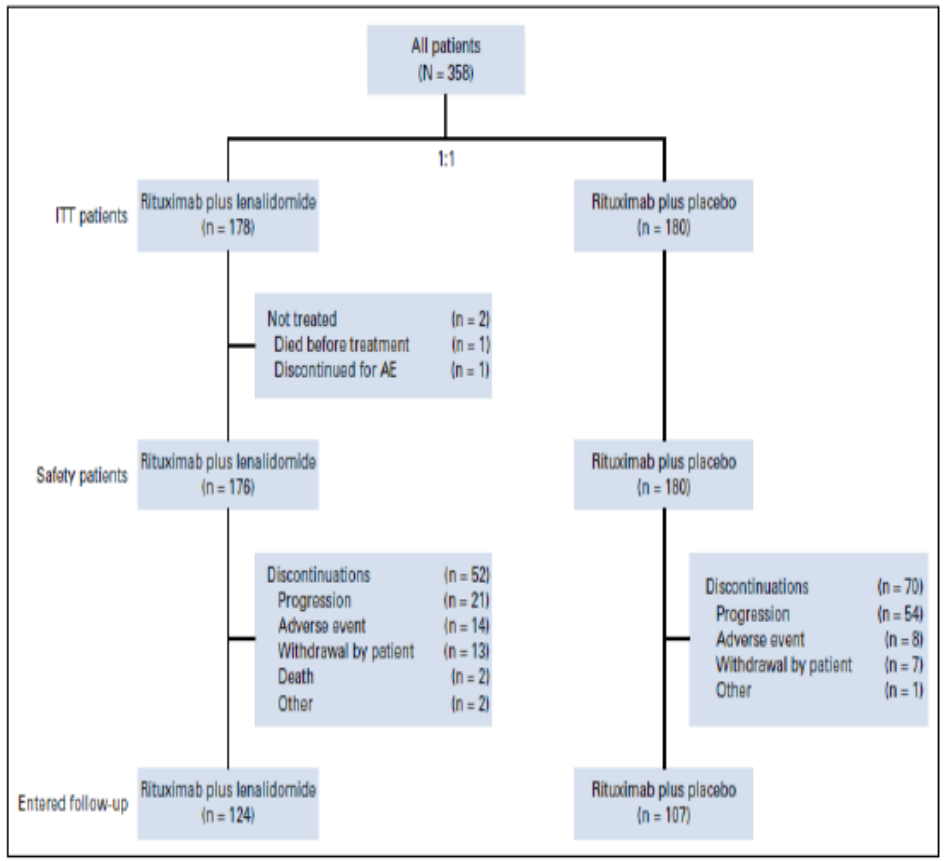
Leonard JP, et al. ASH 2018. Abstract 445.

original report

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

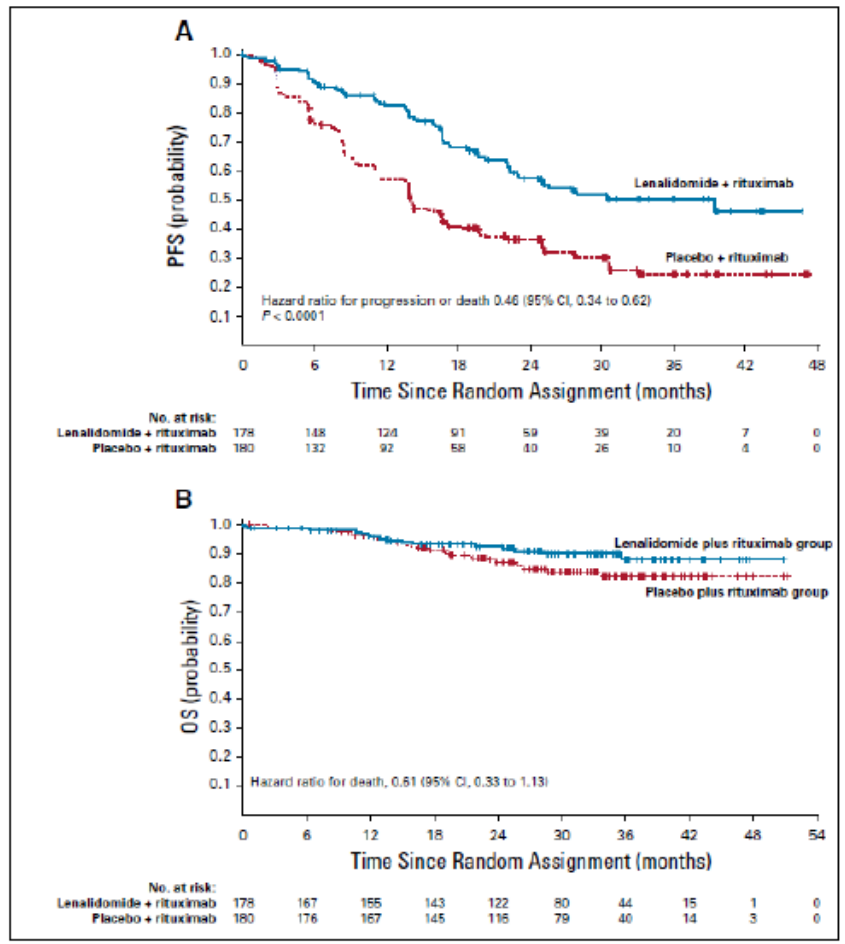
John P. Leonard, MD[1]; Marek Trneny, MD[2]; Koji Izutsu, MD[3]; Nathan H. Fowler, MD[4]; Xiaonan Hong, MD[5]; Jun Zhu, PhD[6]; Huilai Zhang, MD[7]; Fritz Offner, MD, PhD[8]; Adriana Scheliga, MD[9]; Grzegorz S. Nowakowski, MD[10]; Antonio Pinto, MD[11]; Francesca Re, MD[12]; Laura Maria Fogliatto, MD, 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.19.00010.

- Baseline characteristics were generally similar between treatment arms

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

Leonard JP, et al. ASH 2022 [Abstract 150]

5

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

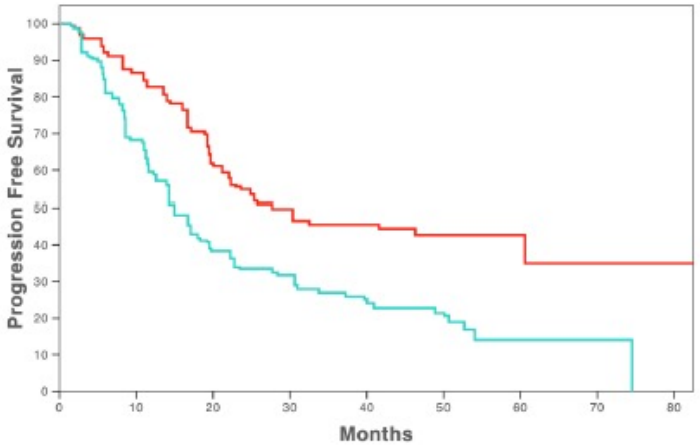
[a]Percentages were calculated using the safety population (R², n = 176; R-placebo, n = 180). [b]Included any patient who discontinued treatment within 12 cycles but remained on the study during the follow-up phase. [c]Percentages were calculated using the ITT population (R², n = 178; R-placebo, n = 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 2022 [Abstract 150]

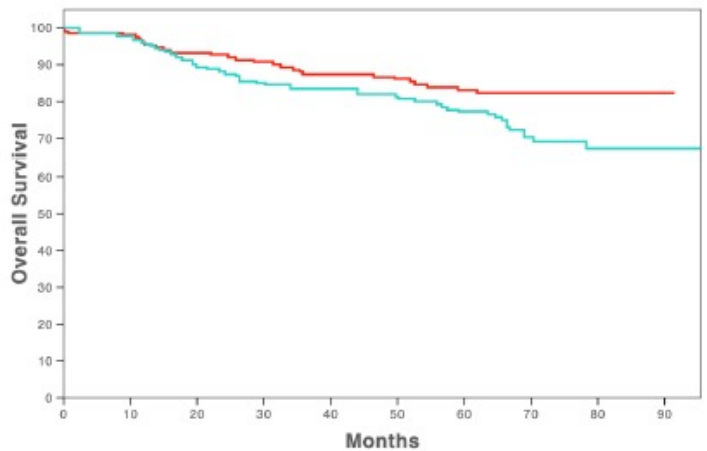
7

- **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)

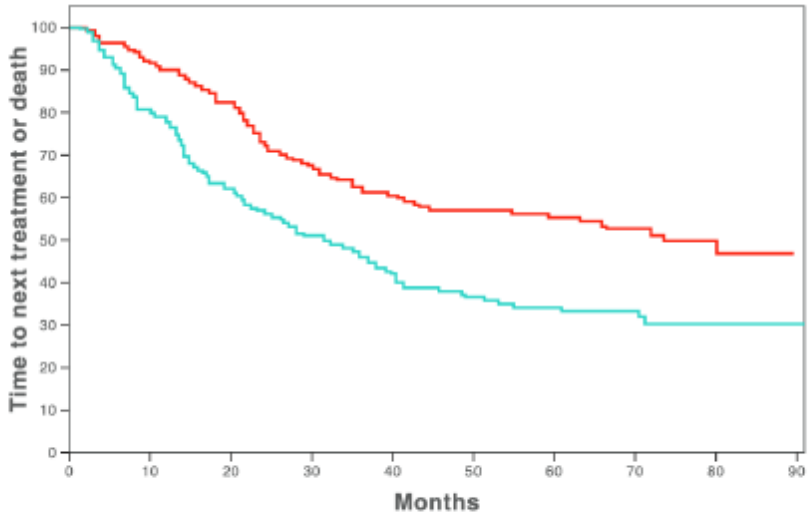
	HR (95% CI)
Lenalidomide + Rituximab vs Rituximab + Placebo	0.5 (0.38 - 0.66)



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)

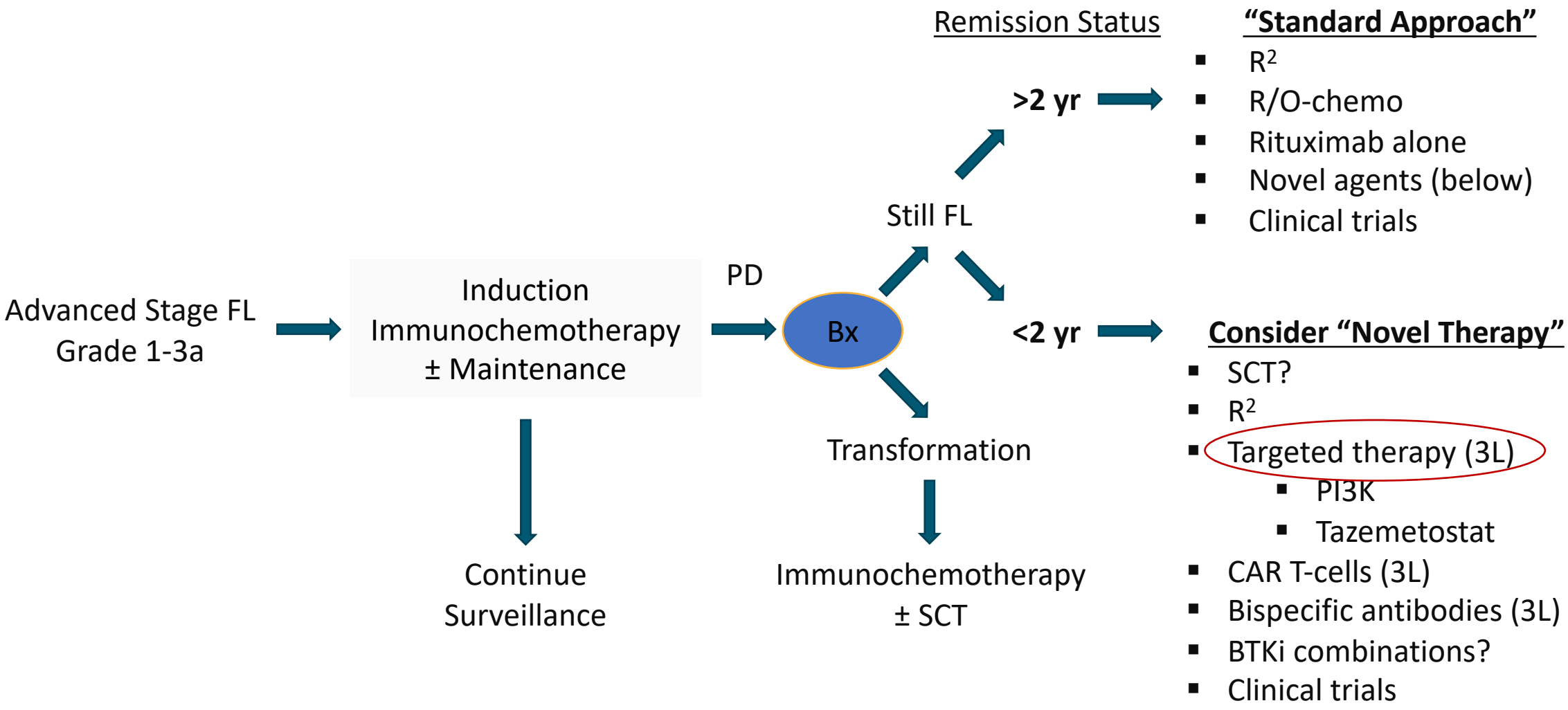
	HR (95% CI)
Lenalidomide + Rituximab vs Rituximab + Placebo	0.53 (0.39 - 0.71)

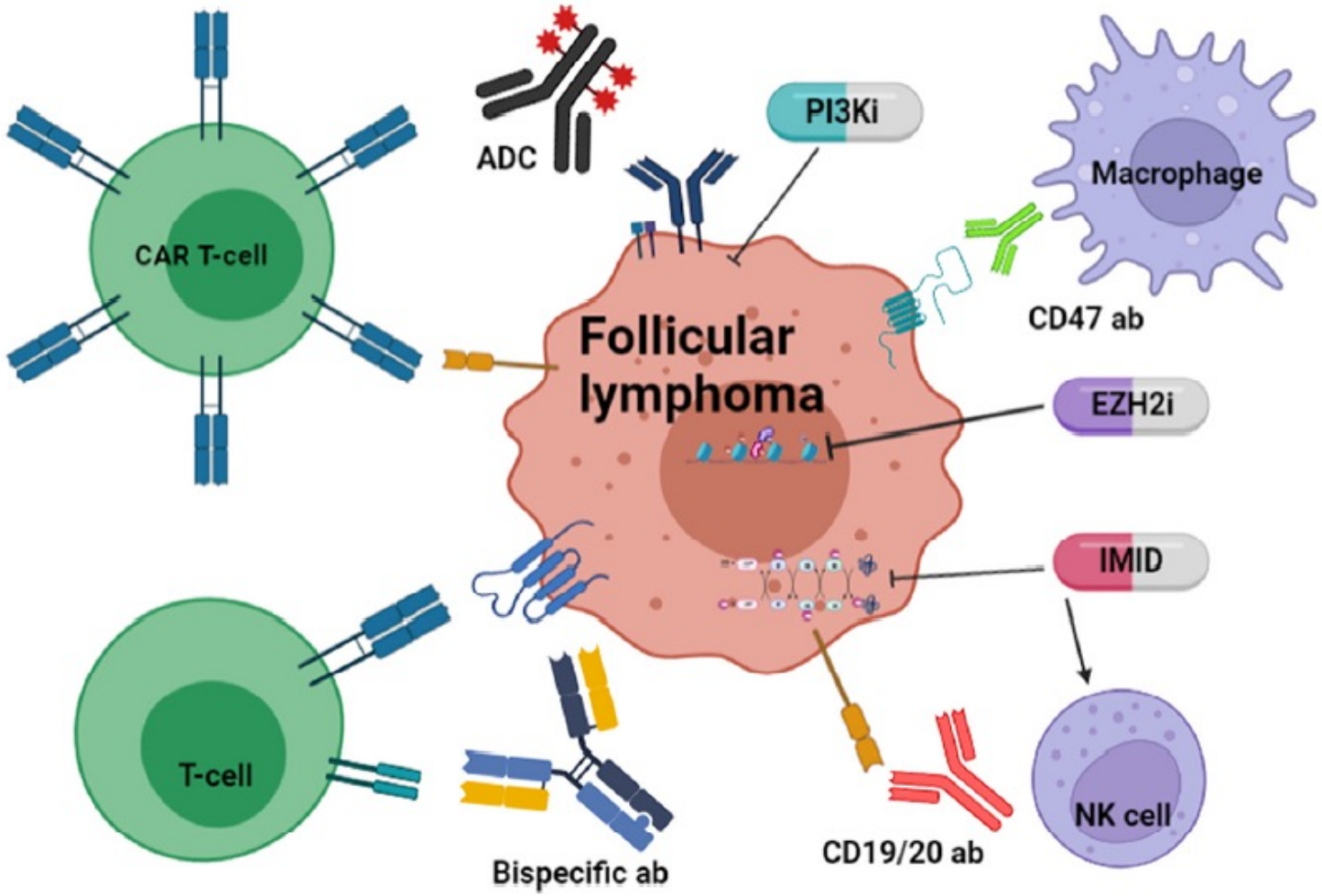
- SPMs occurred in 13 (7%) R2-treated and 21 (12%) control pts
- 9 pts died of SPM (n = 3 R2, n = 6 R-placebo)
- The incidence rate of SPMs per 100 y was 1.62 (95% CI, 0.94-2.78) in the R2 group vs 2.66 (95% CI, 1.73-4.07) in the control group.
- Fewer histological transformations occurred in the R2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

MAGNIFY STUDY (NCT01996865)

- Phase 3b multicenter open-label study of patients with grade 1-3b FL or transformed FL, MZL or MCL who received ≥ 1 prior therapy and had stage I-IV measurable desease
- ≈ 500 patients
- 12 cycles of R2 induction
- Randomization with 1:1 with ≥ SD after induction to maintenance Lenalidomide 10 mg/day (1-21/28, cycles 13-30), plus Rituximab D1 of cycles 13,15,17,19,21,23,25,27 and 29 (R2, Arm A) or Rituximab alone (Arm B)
- Primary end-point = PFS

Treatment of Follicular Lymphoma





Gordon MJ, Blood 2023

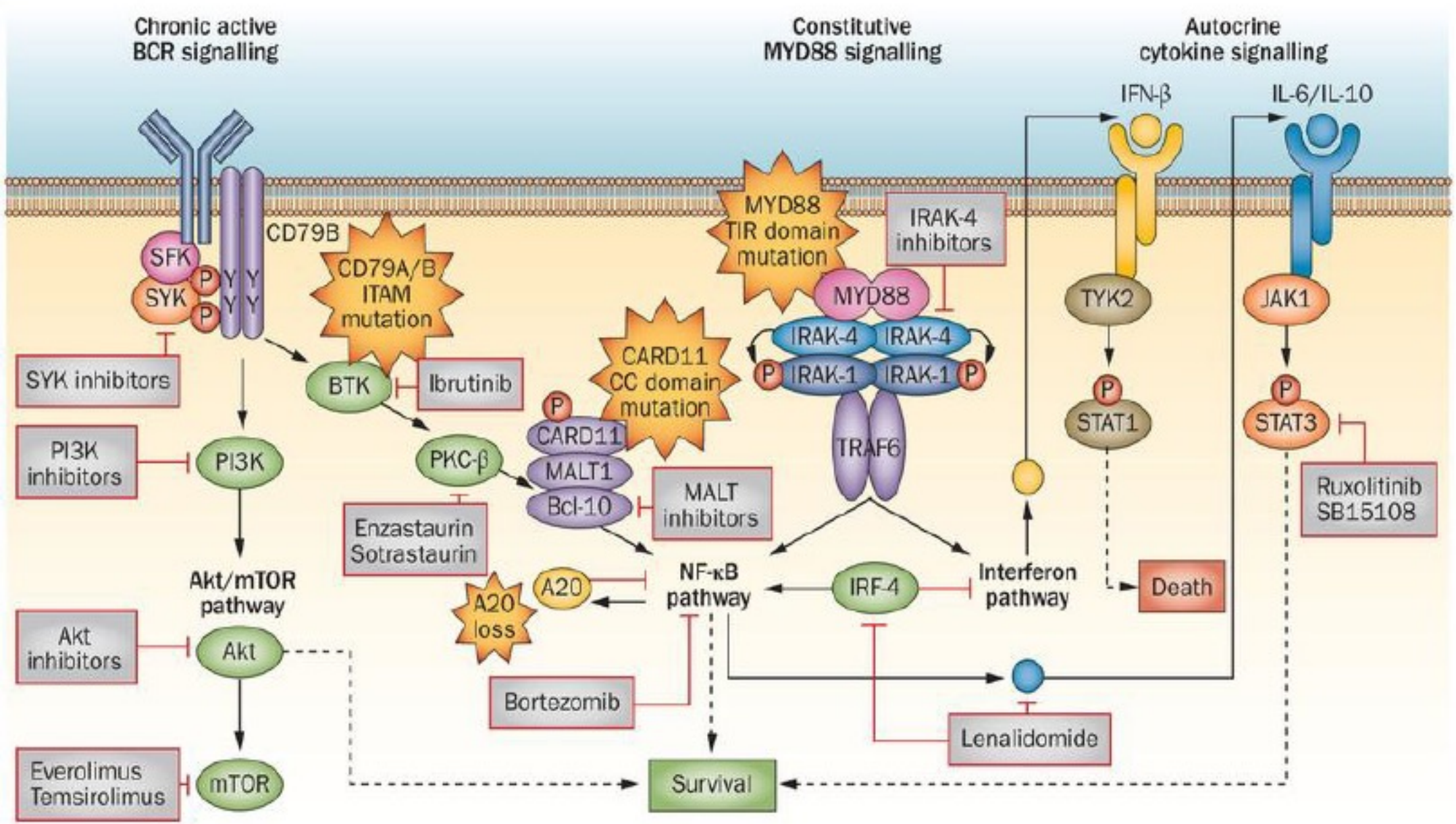
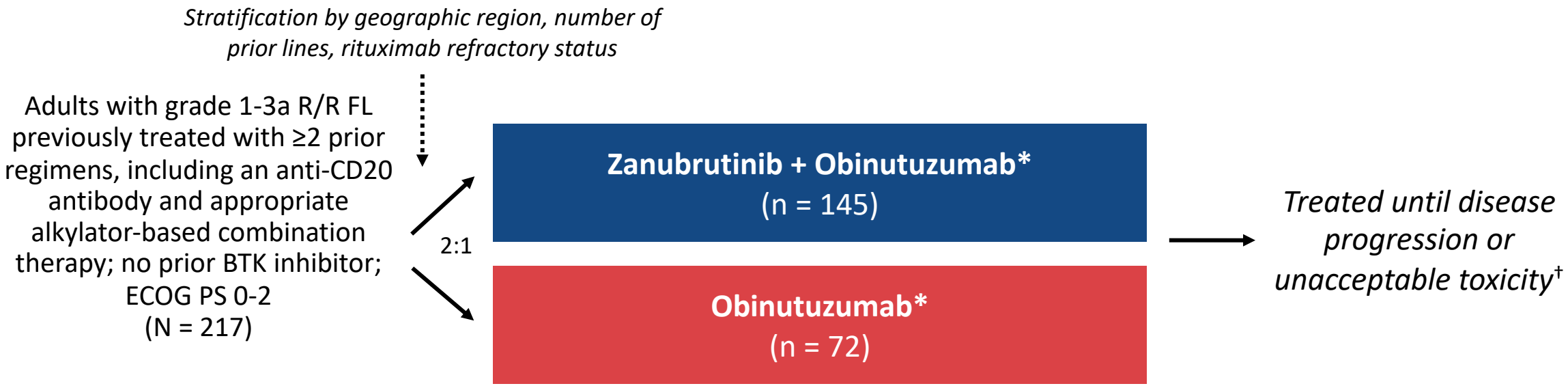


Figure from: Roschewski et al. Nat Rev Clin Oncol 2014;11:22–25.

ROSEWOOD: Next-Generation BTK Inhibitor Zanubrutinib With Obinutuzumab in R/R FL

- Global, randomized, open-label phase II trial



*Zanubrutinib dosed at 160 mg PO BID. Obinutuzumab dosed at 1000 mg IV on Days 1,8,15 of cycle 1 and Day 1 of cycles 2-6, then Q8W to ≥20 doses.
†Patients assigned to obinutuzumab with centrally confirmed PD or no response at 12 mo could crossover to receive combination therapy.

- **Primary endpoint:** IRC-assessed ORR according to Lugano classification
- **Key secondary endpoints:** investigator-assessed ORR, CR, DoR, PFS, OS, safety

Zinzani. ASCO 2022. Abstr 7510.

ROSEWOOD: Response

Response by ICR	Zanubrutinib + Obinutuzumab (n = 145)	Obinutuzumab (n = 72)	*P* Value
ORR, %	68.3	45.8	.0017
Best overall response, n (%)			
▪ CR	54 (37.2)	14 (19.4)	.0083
▪ PR	45 (31.0)	19 (26.4)	--
▪ SD	25 (17.2)	14 (19.4)	--
▪ Nonprogressive disease	3 (2.1)	4 (5.6)	--
▪ PD	13 (9.0)	15 (20.8)	--
▪ D/c prior to first assessment	4 (2.8)	6 (8.3)	--
▪ NE	1 (0.7)	0 (0)	--

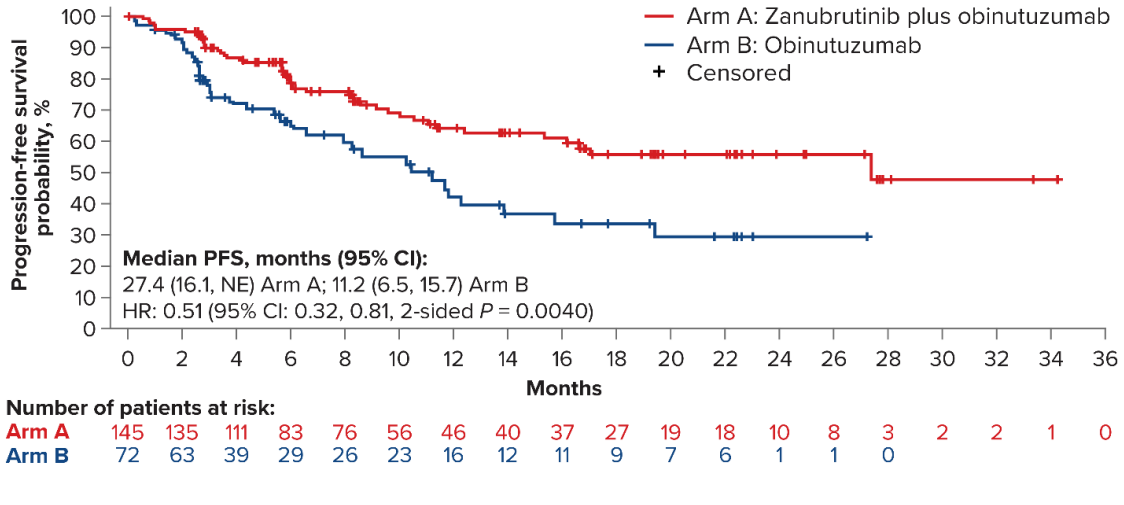
Median follow-up: 12.5 mo.

- Combination with improved ORR vs obinutuzumab across most patient subgroups, except in patients with bulky disease
- 29 patients in the obinutuzumab arm crossed over to receive zanubrutinib and obinutuzumab, with 7 patients (24.1%) achieving an objective response, including 2 patients with CR

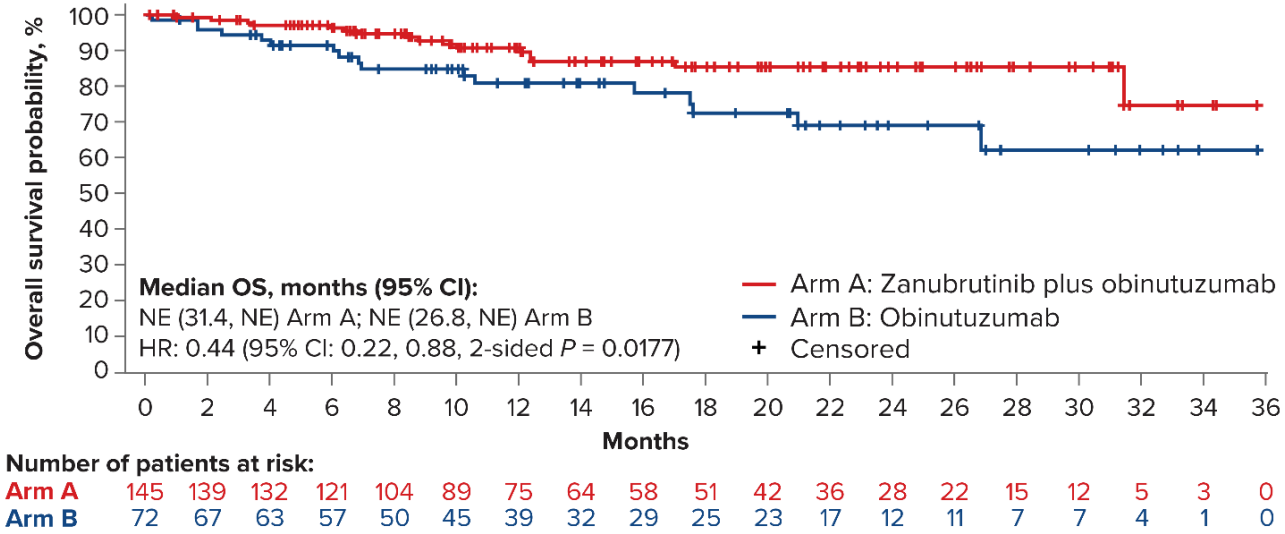
Zinzani. ASCO 2022. Abstr 7510.

ROSEWOOD: PFS and OS

PFS



OS



- Ongoing phase III MAHOGANY trial is evaluating zanubrutinib + obinutuzumab vs R^2 in patients with R/R FL after ≥1 line of systemic therapy including an anti-CD20 mAb (NCT05100862)

Zinzani. ASCO 2022. Abstr 7510.

Slide credit: clinicaloptions.com

PI3K Inhibitors: Established Agents

Agent	Idelalisib[1]	Duvelisib[2]	Copanlisib[3,4]
Isoform target	Delta	Delta, gamma	Alpha, delta
Trial	Phase II DELTA	Phase II DYNAMO	Phase II CHRONOS-1
Population (N)	iNHL with relapse ≤6 mo or refractory to R and alkylating agent (125 iNHL*)	iNHL with relapse ≤6 mo or refractory to R and either CT or RIT (129 iNHL‡/83 FL)	iNHL with relapse after or refractory to R and alkylating agent (142 iNHL†/104 FL)
Approval (yr)	≥2 prior therapies (2014)	≥2 prior therapies (2018)	≥2 prior therapies (2017)
ORR, n (%) ▪ CR, n (%)	71 (57) 7 (6)	61 (47)/35 (42) 2 (2)/1 (1)	86 (61)/61 (59) 24 (17)/21 (20)
Median PFS, mo	11	9.5	12.5
Median OS, mo	20.3	28.9	42.6
Grade ≥3 AEs	Diarrhea (13%), elevated ALT (13%), elevated AST (8%)	Diarrhea (15%), pneumonia (5%), fatigue (5%), elevated ALT (5.4%), elevated AST (3.1%)	Hyperglycemia (40%), pneumonia (11%), diarrhea (8.5%), elevated ALT (0.7%)

*Including FL, n = 72; SLL, n = 28; MZL, n = 15; LPL/WM, n = 10. †Including FL, n = 104; MZL, n = 23; SLL, n = 8; LPL/WM, n = 6; DLBCL, n = 1 (originally assessed as iNHL).
‡Including FL, n = 83, SLL, n = 28; MZL, n = 18.

1. Gopal. NEJM. 2014;370:1008. 2. Flinn. JCO. 2019;37:912. 3. Dreyling. JCO. 2017;35:3898. 4. Dreyling. Am J Hematol. 2020;95:362.

CHRONOS-1: Copanlisib in R/R iNHL

- Open-label, single arm phase II study

Patients with indolent B-cell lymphoma* R/R to ≥2 lines of therapy → **Copanlisib** 60 mg IV D1, 8, 15 (28-day cycle) → *Until PD or unacceptable toxicity*

*FL (grades 1-3a), MZL, SLL, LPL/WM.

- **Primary endpoint:** ORR by central radiologic review
- **Secondary endpoints:** PFS, DoR, OS, safety, QoL

Patient Characteristics	Patients (N = 142)
Median age, yr (range)	63 (25-82)
Male, n (%)	71 (50)
Median time from most recent progression, wk (range)	8.3 (1-73)
Median number of prior lines of anticancer therapy (range)	3 (2-9)
Prior rituximab, n (%)	142 (100)
Prior alkylating agents, n (%)	142 (100)
Refractory to last regimen, n (%)	86 (61)
Tumor histology, n (%)	
▪ FL	104 (73)
▪ MZL	23 (16)
▪ SLL	8 (6)
▪ WM/LPL	6 (4)
▪ DLBCL	1 (1)

Dreyling. Am J Hematol. 2020;95:362. Dreyling. JCO. 2017;35:3898. NCT01660451.

Slide credit: clinicaloptions.com

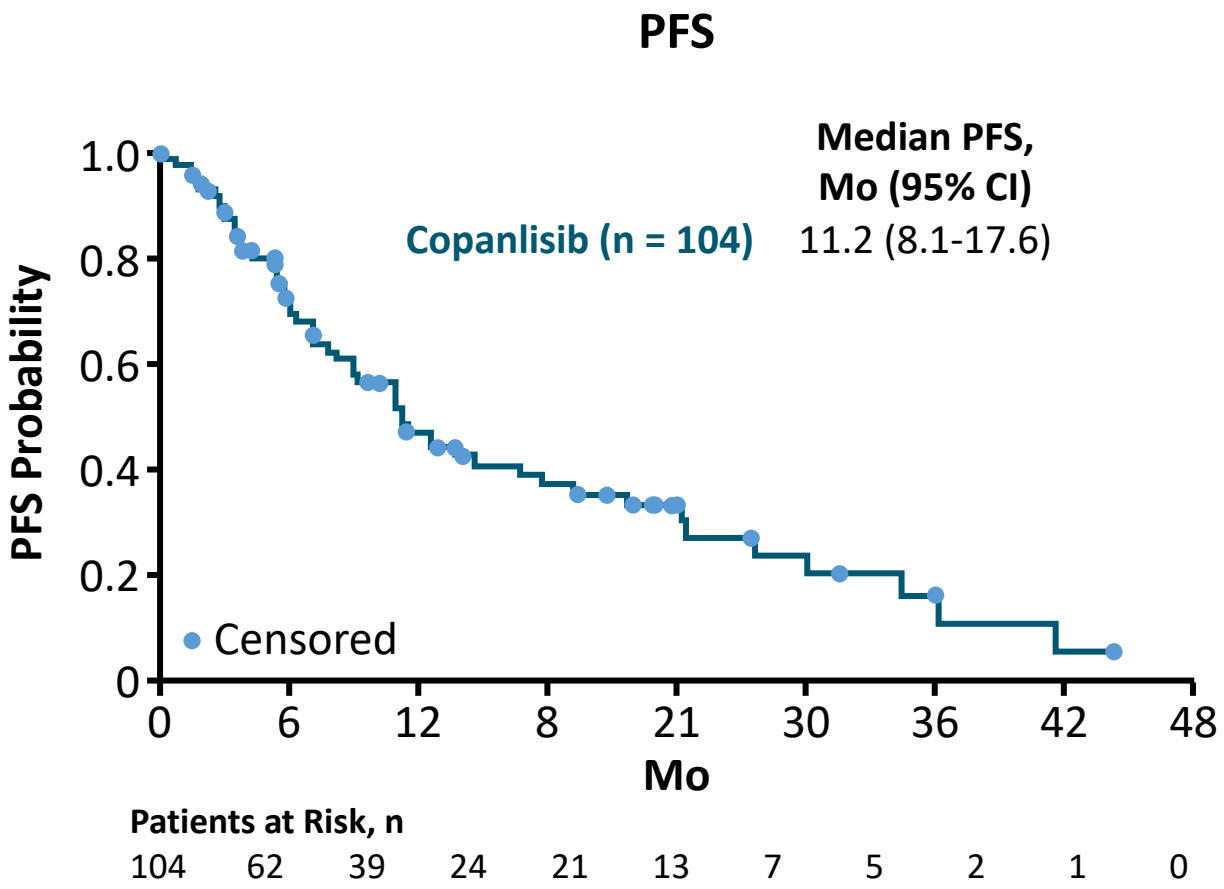
CHRONOS-1: Efficacy

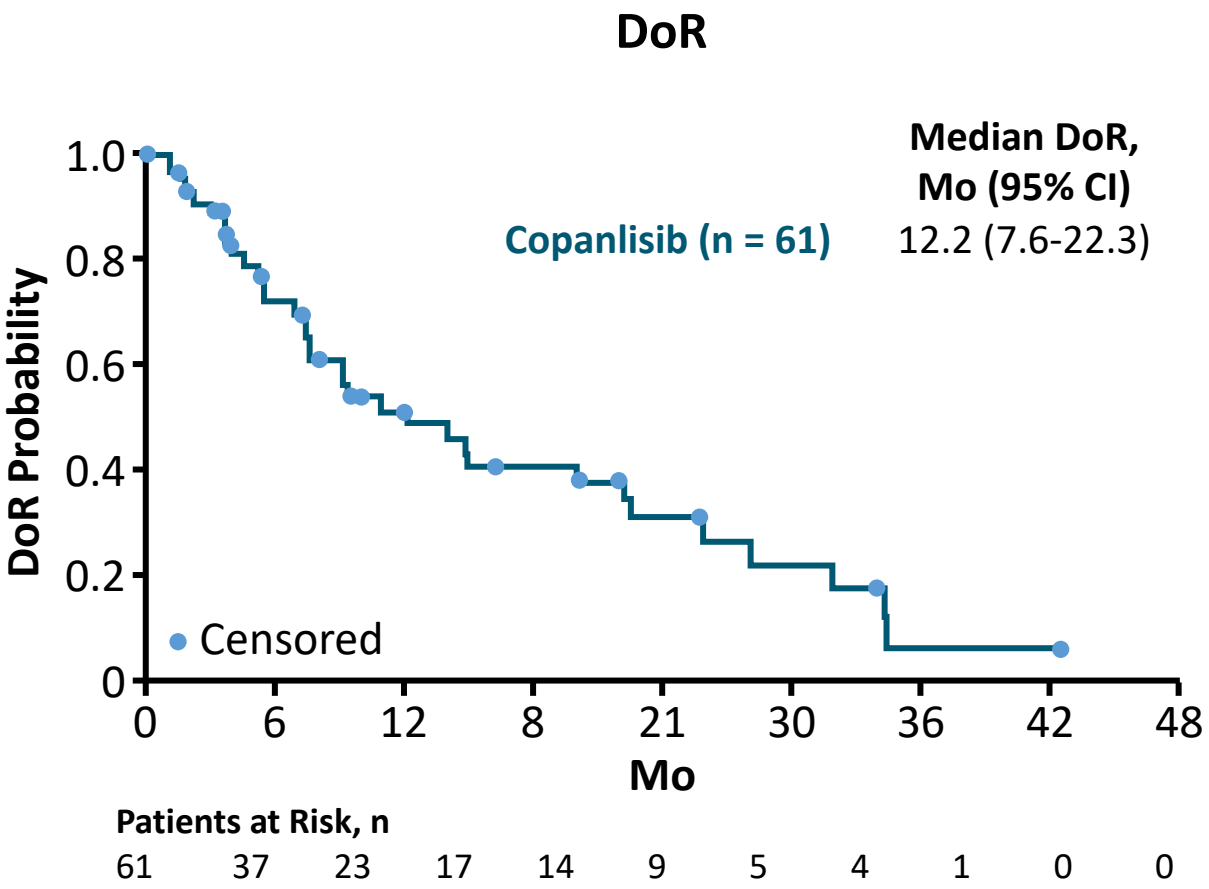
Response Outcome, n (%)	Total (N = 142)*	FL (n = 104)	MZL (n = 23)	SLL (n = 8)	LPL/WM (n = 6)
Best response					
▪ CR	24 (16.9)	21 (20.2)	3 (13.0)	0	0
▪ PR	62 (43.7)	40 (38.5)	15 (65.2)	6 (75.0)	1 (16.7)
▪ SD	41 (28.9)†	35 (33.7)†	2 (8.7)	1 (12.5)	3 (50.0)
▪ PD	3 (2.1)	2 (1.9)	0	1 (12.5)	0
▪ NE/NA	12 (8.5)	6 (5.8)	3 (13.0)	0	2 (33.3)
ORR	86 (60.6)	61 (58.7)	18 (78.3)	6 (75.0)	1 (16.7)
▪ 95% CI	52.0-68.7	48.6-68.2	56.3-92.5	34.9-96.8	0.4-64.1
DCR	122 (85.9)‡	91 (87.5)	20 (87.0)	7 (87.5)	4 (66.7)
▪ 95% CI	79.1-91.2	79.6-93.2	66.4-97.2	47.4-99.7	22.3-95.7

*n = 1 initially assessed as having iNHL was later confirmed to be DLBCL. †n = 1 with unconfirmed early SD.
‡n = 1 with unconfirmed SD, n = 4 with SD or PR recorded >35 days from last treatment excluded from the analysis.

Dreyling. Am J Hematol. 2020;95:362.

CHRONOS-1: Durable Responses in R/R FL





- Median OS: 38.3 mo (95% CI: 28.5-NE)

Leppa. ASCO 2019. Abstr 7553.

CHRONOS-1: Safety

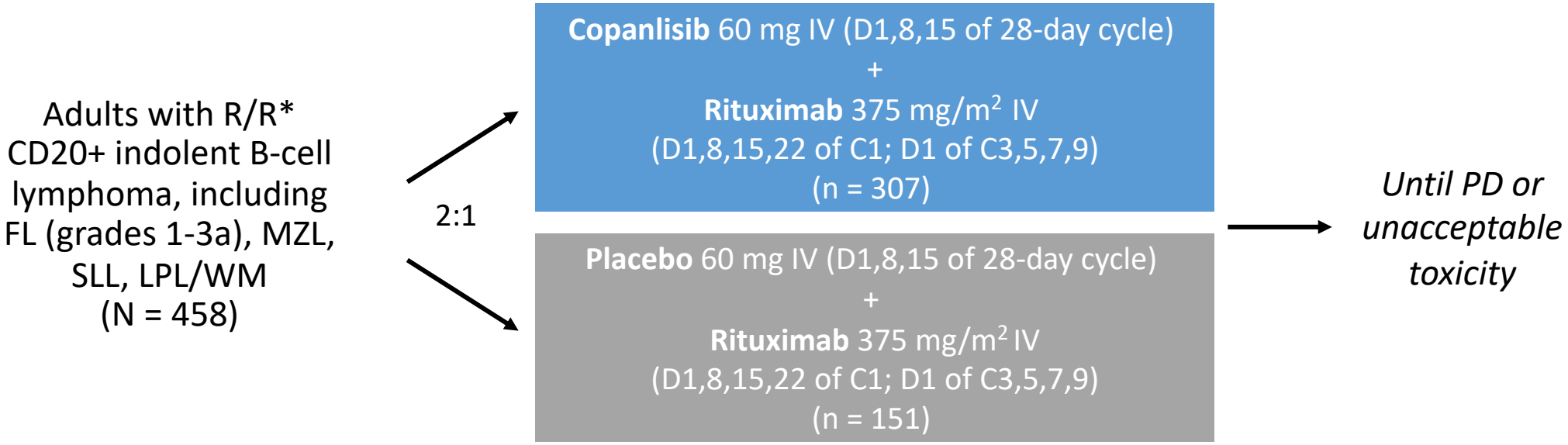
- For data cutoff of February 2018
  - Median duration of safety f/u: 6.7 mo (range: 0.2-44.1)
  - 26.1% received copanlisib for >1 yr
  - 21.1% d/c due to TRAE
- No new treatment-emergent mortality observed compared with original June 2016 data cutoff
  - 4.2% (6/142) experienced grade 5 AEs, with 2.1% (3/142) considered treatment related (n = 1 each; lung infection, respiratory failure, embolism)

TEAEs, n (%)	Patients (N = 142)		
	All	Grade 3	Grade 4
Any	140 (98.6)	77 (54.2)	41 (28.9)
AEs of special interest			
▪ Hyperglycemia	71 (50.0)	47 (33.1)	10 (7.0)
▪ Diarrhea	50 (35.2)	12 (8.5)	0
▪ Hypertension	42 (29.6)	34 (23.9)	0
▪ Pneumonitis	9 (6.3)	2 (1.4)	0
▪ Colitis	1 (0.7)	0	1 (0.7)
Infection-related events			
▪ URTI	21 (14.8)	2 (1.4)	0
▪ Pneumonia	20 (14.1)	13 (9.2)	2 (1.4)
Other AEs			
▪ Neutropenia	41 (28.9)	13 (9.2)	21 (14.8)
▪ Pyrexia	38 (26.8)	6 (4.2)	0
▪ Fatigue	37 (26.1)	3 (2.1)	0
▪ Nausea	33 (23.2)	1 (0.7)	0

Dreyling. Am J Hematol. 2020;95:362.

CHRONOS-3: Phase III Trial of Copanlisib + Rituximab vs Placebo + Rituximab in R/R iNHL

- Multicenter, randomized phase III study



*Relapsed after prior R, R biosimilar, or anti-CD20 mAb, whether as monotherapy or in a combination regimen, AND either progression and treatment free for ≥12 mo since last R-containing regimen or unwilling/unfit to receive CT and progression and treatment free for ≥6 mo since last R-containing regimen.

- **Primary endpoint:** PFS by central review
- **Secondary endpoints:** ORR, CR rate, DCR, DoR, TTP, OS, safety, PROs

Matasar. Lancet Oncol. 2021;22:678. NCT02367040.

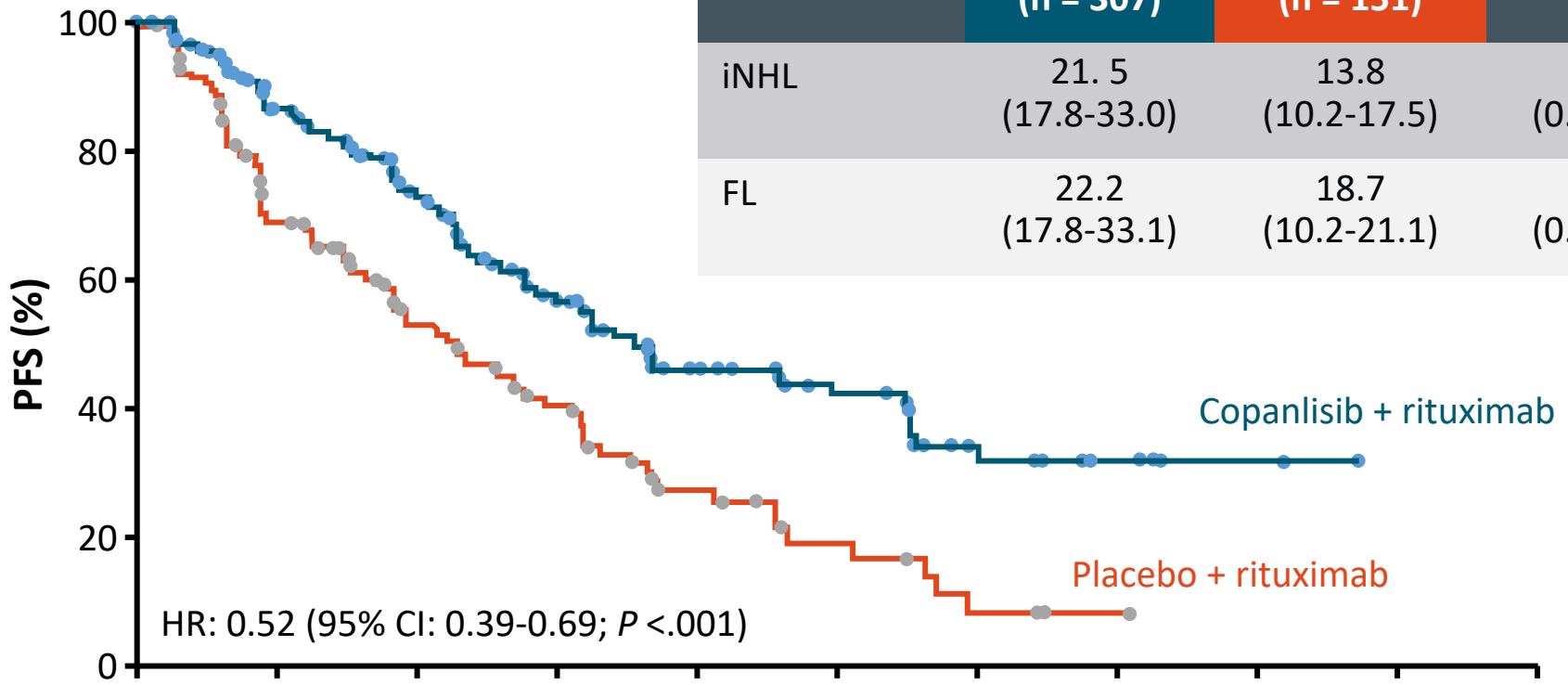
CHRONOS-3: Baseline Characteristics

Characteristics	Copanlisib + Rituximab (n = 307)	Placebo + Rituximab (n = 151)
Median age, yr (IQR)	63 (54-70)	62 (53-70)
Male, n (%)	153 (50)	85 (56)
Medical history of diabetes, n (%)	45 (15)	22 (15)
Medical history of hypertension, n (%)	114 (37)	53 (35)
Histology of lymphoma, n (%) ▪ FL ▪ MZL ▪ SLL ▪ LPL/WM	 184 (60) 66 (21) 35 (11) 22 (7)	 91 (60) 29 (19) 15 (10) 16 (11)
Median time since last systemic therapy, mo (IQR)	25.1 (15.7-45.8)	25.3 (15.3-42.8)
Median time from initial diagnosis, mo (IQR)	62.8 (36.4-101.7)	72.4 (35.2-110.9)
Progression- and treatment-free interval ≥12 mo from prior rituximab-containing regimen, n (%)	247 (80)	121 (80)
1 prior line of anticancer therapy, n (%)	150 (49)	71 (47)

Matasar. Lancet Oncol. 2021;22:678.

CHRONOS-3: PFS

Median PFS, Mo (95% CI)	Copanlisib + Rituximab (n = 307)	Placebo + Rituximab (n = 151)	HR (95% CI)	1-Sided *P* Value
iNHL	21. 5 (17.8-33.0)	13.8 (10.2-17.5)	0.52 (0.39-0.69)	<.0001
FL	22.2 (17.8-33.1)	18.7 (10.2-21.1)	0.58 (0.40-0.83)	.001

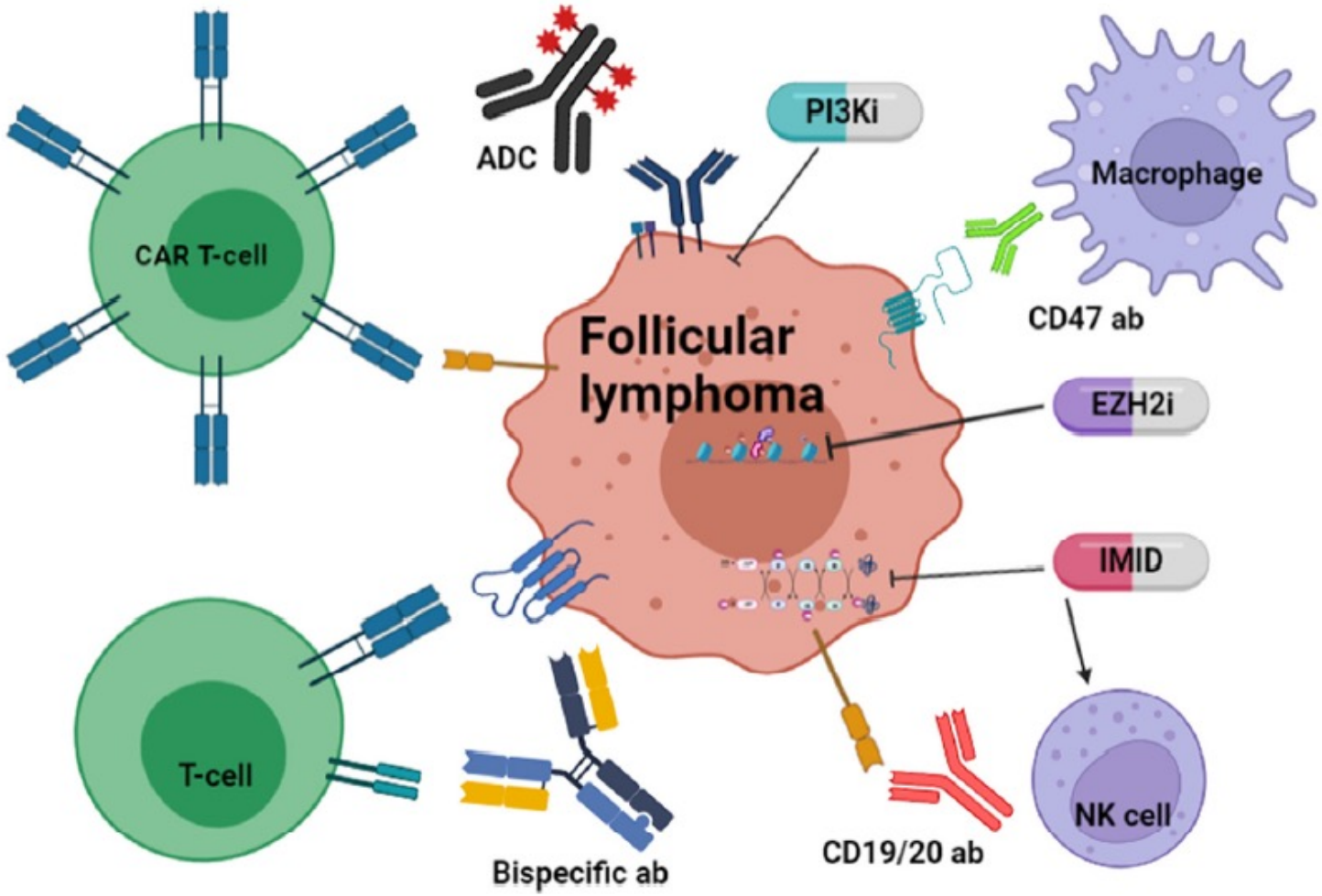


Patients at Risk, n (number censored)											
Copanlisib + rituximab	307 (0)	204 (67)	146 (97)	88 (125)	49 (149)	31 (164)	15 (175)	6 (183)	2 (187)	0 (189)	0 (189)
Placebo + rituximab	151 (0)	85 (26)	53 (41)	33 (49)	16 (56)	8 (60)	3 (61)	1 (63)	0 (64)	0 (64)	0 (64)

Matasar. Lancet Oncol. 2021;22:678.

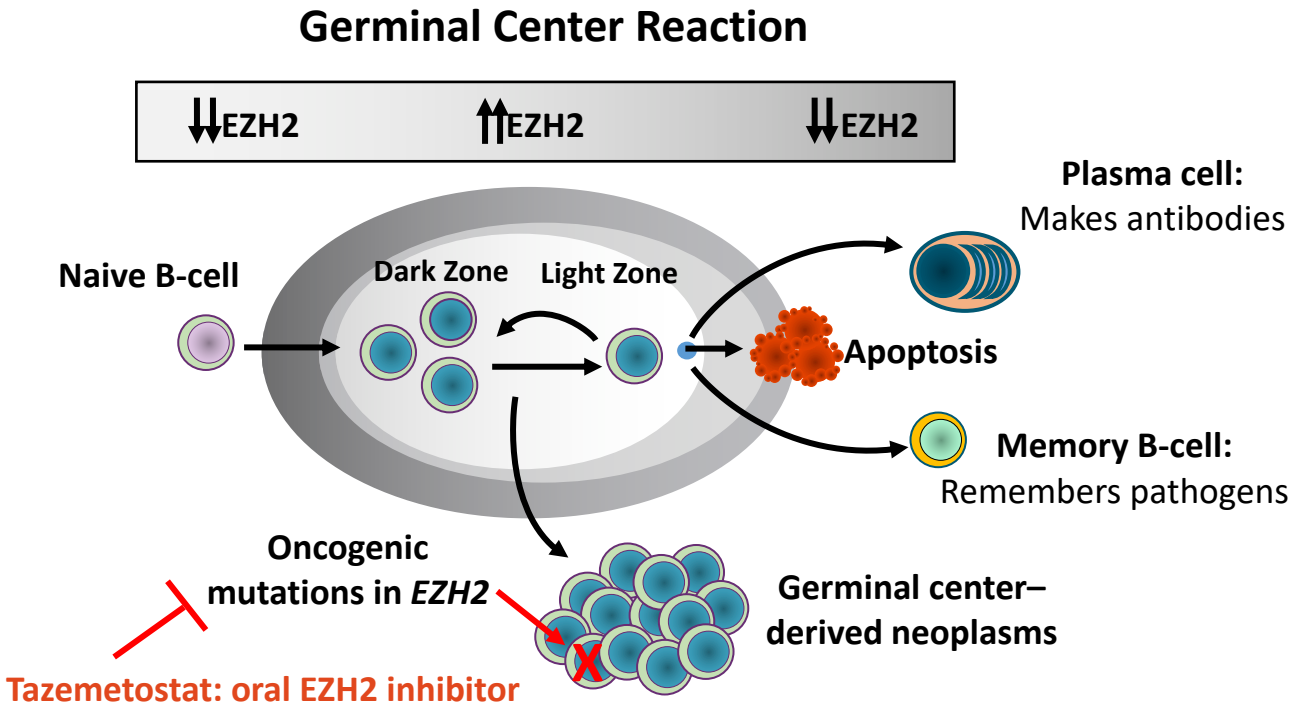
Status of PI3K Inhibitors in 2023

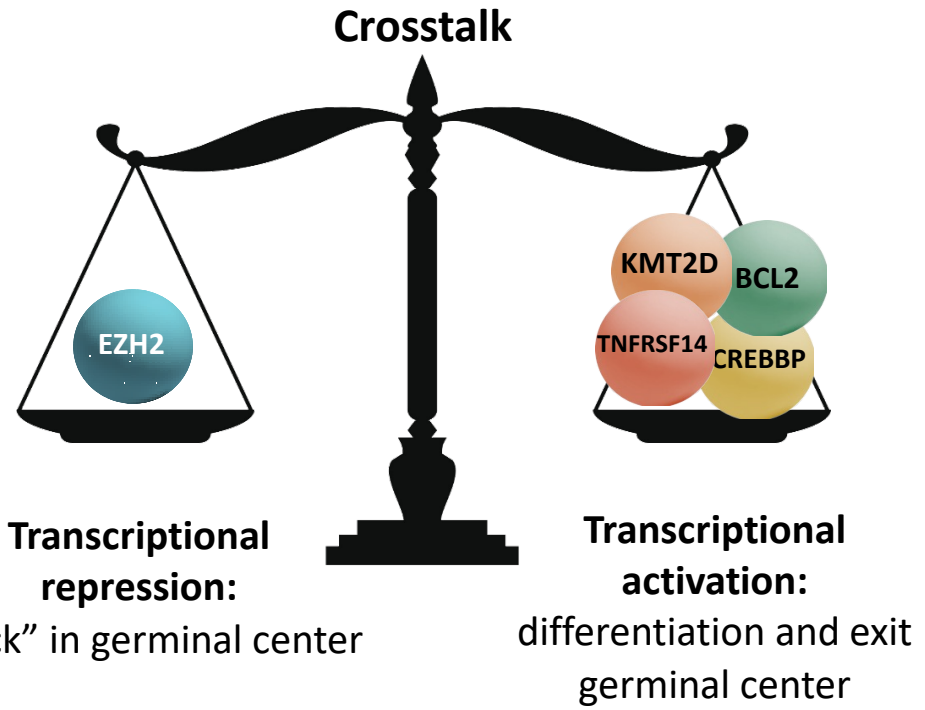
- Copanlisib is only commercially available PI3K inhibitor for R/R FL
  - Idelalisib and duvelisib withdrawn from market
  - Umbralisib approval withdrawn by FDA
- FDA has discouraged new applications without randomized trials
  - Parsaclisib New Drug Application withdrawn for FL, MZL, and MCL indications in US
  - Zandelisib only being developed in Japan
- Copanlisib under phase III investigation in combination with rituximab



Gordon MJ, Blood 2023

Follicular Lymphoma and *EZH2*: Tazemetostat





- EZH2: an epigenetic regulator of gene expression and cell fate decisions
  - In normal B-cell biology, EZH2 regulates germinal center formation
  - *EZH2* mutations can lead to oncogenic transformation by locking B-cells in germinal state and preventing terminal differentiation

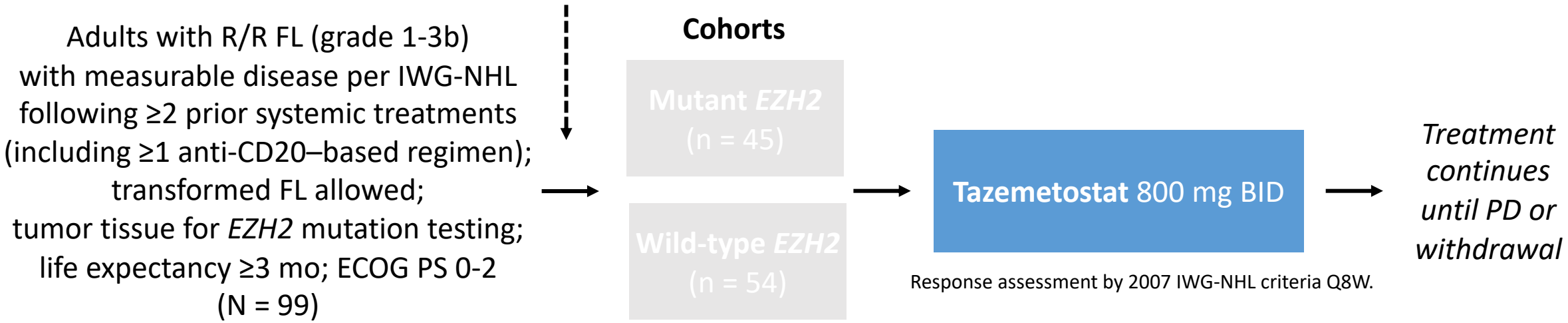
Gan. Biomark Res. 2018;6:10. Béguelin. Cancer Cell. 2013;23:677. Tazemetostat PI.

Slide credit: clinicaloptions.com

Phase II Study: Tazemetostat in R/R FL

- Open label, multicohort, single-arm phase II study conducted at 38 sites across NA, Europe, Australia (data cutoff for efficacy: August 9, 2019; for safety: May 24, 2019)

SCREENING: *Central testing of archival tissue for* EZH2 *hot spot activating mutations*



- **Primary endpoint:** ORR
- **Secondary endpoints:** DoR, PFS, safety/tolerability

Morschhauser. Lancet Oncol. 2020;21:1433. NCT01897571.

Phase II Study: Baseline Demographics (ITT)

Characteristic	Mut *EZH2* (n = 45)	WT *EZH2* (n = 54)
Median age, yr (IQR)	62 (57-68)	61 (53-67)
ECOG PS, n (%)	21 (47)	26 (48)
▪ 0	24 (53)	23 (43)
▪ 1	0	4 (7)
▪ 2	0	1 (2)
▪ Missing		
Median prior lines of anticancer tx,* n (IQR)	2 (2-4)	3 (2-5)
▪ 1, n (%)	2 (4)	1 (2)
▪ 2, n (%)	22 (49)	16 (30)
▪ 3, n (%)	10 (22)	11 (20)
▪ 4, n (%)	4 (9)	10 (19)
▪ ≥5, n (%)	7 (16)	16 (30)

Characteristic	Mut *EZH2* (n = 45)	WT *EZH2* (n = 54)
GELF criteria, n (%)	31 (69)	40 (74)
Refractory† to last regimen, n (%)	22 (49)	22 (41)
Poor-risk features, n (%)	22 (49)	32 (59)
▪ Refractory to R-containing regimen‡	9 (20)	15 (28)
▪ Double refractory§	4 (9)	21 (39)
▪ Prior HSCT	19 (42)	32 (59)
▪ POD24		

*Excludes maintenance, consolidation, adjuvant, neoadjuvant tx when counted as their own line. †SD or PD. ‡Refractory to or PD <6 mo of completion of rituximab monotherapy or rituximab-containing tx. §Refractory to or PD <6 mo of completion of rituximab monotherapy or as part of combination and chemotherapy induction regimen containing ≥1 alkylating agent or purine nucleoside antagonist.

Morschhauser. Lancet Oncol. 2020;21:1433.

Phase II Study: Safety (ITT)

TEAEs, %	All TEAEs (N = 99)		Treatment-Related TEAEs (N = 99)	
	All Grades*	Grade ≥3	All Grades	Grade ≥3
Nausea	23	0	19	0
Diarrhea	18	0	12	0
Alopecia	17	0	14	0
Cough	16	0	2	0
Asthenia	15	3	13	1
Fatigue	15	2	11	1
URTI	15	0	1	0
Bronchitis	15	0	3	0
Abdominal pain	12	1	2	0
Headache	12	0	5	0
Vomiting	11	1	6	0
Back pain	11	0	0	0
Pyrexia	10	0	2	0
Anemia	9	5	7	2
Thrombocytopenia	5	5	5	3
Neutropenia	3	4	3	3

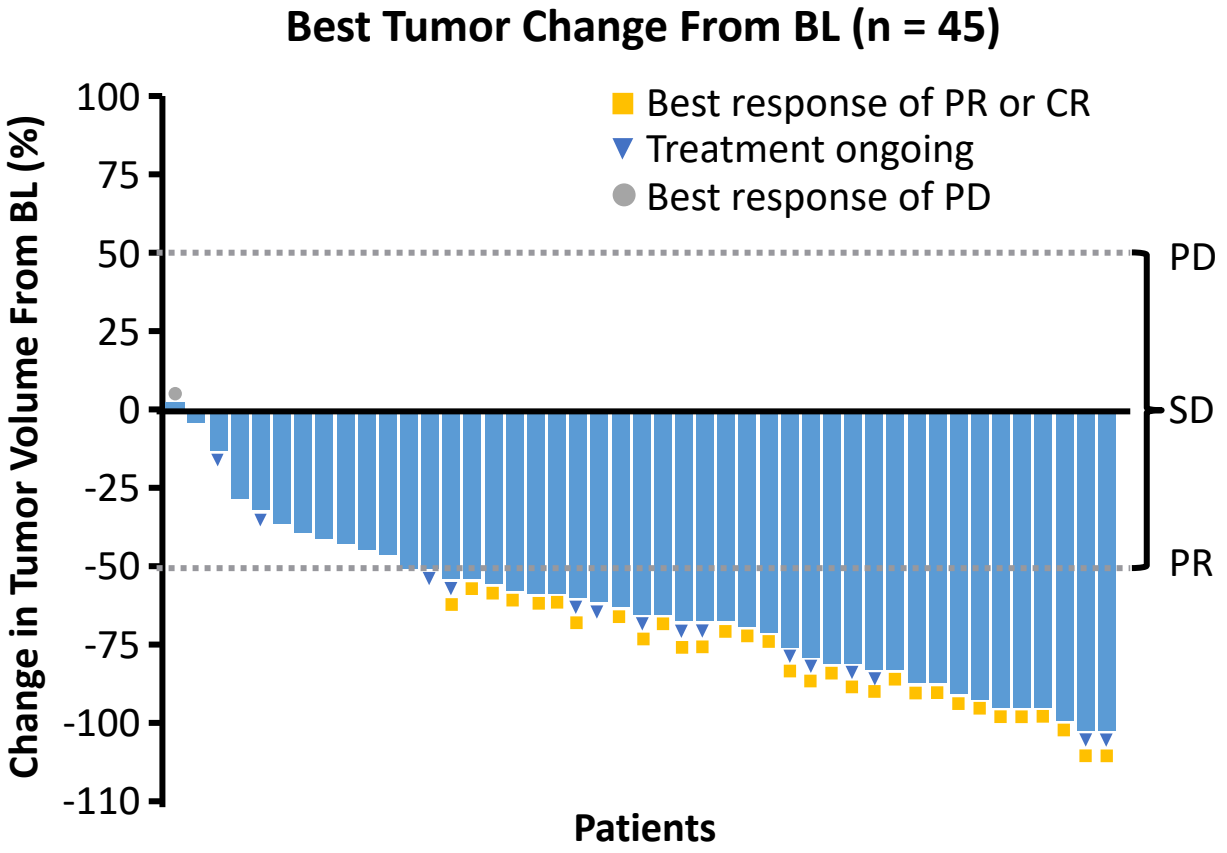
- Tazemetostat was generally well tolerated
  - 8% discontinued due to TEAEs
  - 9% had a dose reduction due to TEAEs
  - 27% had a dose interruption due to TEAEs
  - Low rate of grade ≥3 treatment-related TEAEs
- No treatment-related deaths

Morschhauser. Lancet Oncol. 2020;21:1433.

Phase II Study: Response in Mutant *EZH2* Cohort

Response	Mutant *EZH2* (n = 45)	
	IRC	INV
ORR, n (%) (95% CI)	31 (69) (53-82)	35 (78) (63-89)
▪ CR, n (%)	6 (13)	4 (9)
▪ PR, n (%)	25 (56)	31 (69)
SD, n (%)	13 (29)	10 (22)
PD, n (%)	1 (2)	0

High concordance between IRC- and INV-assessed response rates.



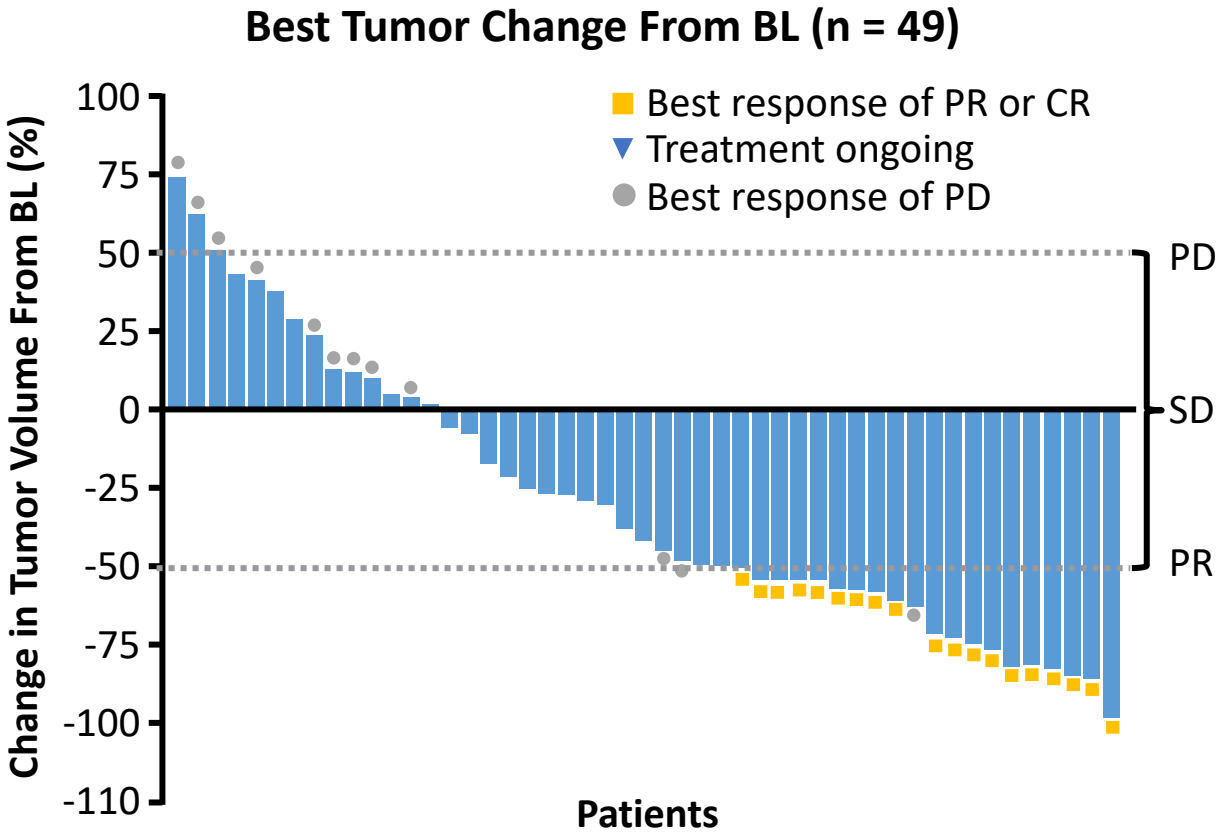
- 98% (44/45) of patients had evidence of tumor reduction by IRC

Morschhauser. Lancet Oncol. 2020;21:1433.

Phase II Study: Response in Wild-type *EZH2* Cohort

Response	WT *EZH2* (n = 54)	
	IRC	INV
ORR, n (%) (95% CI)	19 (35) (23-49)	18 (33) (21-48)
▪ CR, n (%)	2 (4)	3 (6)
▪ PR, n (%)	17 (31)	15 (28)
SD, n (%)	18 (33)	16 (30)
PD, n (%)	12 (22)	16 (30)
NE/missing/unknown,* n (%)	5 (9)	4 (7)

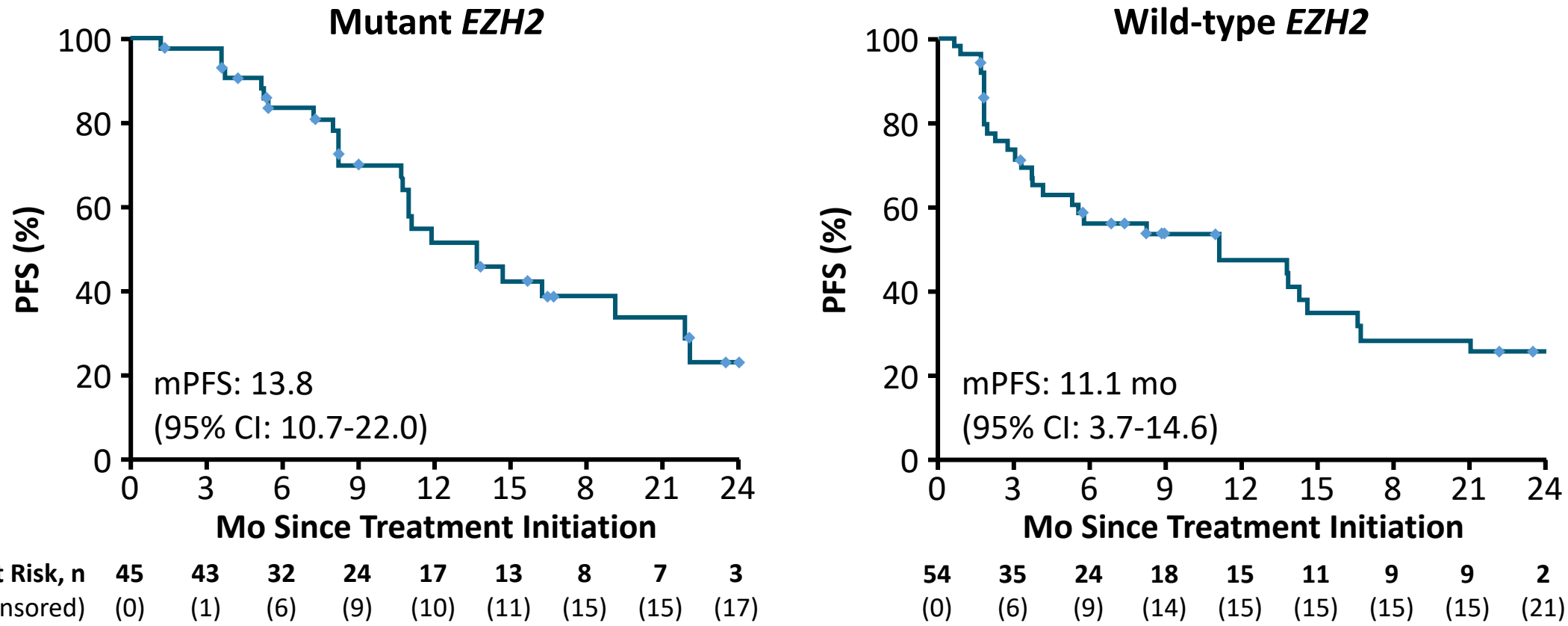
High concordance between IRC- and INV-assessed response rates.
*n = 4 missing post-BL values; n = 1 with poor image.



- 69% (37/49) of patients had evidence of tumor reduction by IRC

Morschhauser. Lancet Oncol. 2020;21:1433.

Phase II Study: PFS by IRC



- Approved by FDA for adults with *EZH2*mut+ R/R FL after ≥2 prior systemic therapies or any adult with R/R FL without alternative treatment options

Morschhauser. Lancet Oncol. 2020;21:1433. Tazemetostat PI.

SYMPHONY-1 Phase Ib: Tazemetostat + R^2 in R/R FL

- Phase Ib safety run-in analysis (stage 1) of international, randomized, double-blind phase Ib/III trial (median follow-up: 11.2 mo)
  - Stage 2: phase III design comparing tazemetostat at RP3D + R^2 vs placebo + R^2 in patients with R/R FL
  - Stage 3 (to be executed if stage 2 futility analysis finds that efficacy fails in overall population but is promising for *EZH2*-mutated subpopulation): in patients with *EZH2*-mutated R/R FL

Adults with R/R FL grades 1-3A;
tumor tissue for *EZH2* mut testing;
≥1 prior systemic CT, IO, or CIT;
prior HSCT, CAR T-cell tx permitted;
no prior lenalidomide, tazemetostat,
or other EZH2 inhibitor;
measurable disease per Lugano;
ECOG PS 0-2
(N = 44)

→

Phase Ib: Dose Escalation (3 + 3 Design)

Tazemetostat 400/600/800 mg BID x 28-d cycles +
Rituximab 375 mg/m^2 IV on D1,8,15,22 of cycle 1, then D1 of cycles 2-5 +
Lenalidomide 20 mg* PO QD on D1-21 of 28-d cycles x 12

*10 mg if CrCl <60 mL/min.

- **Primary endpoints:** safety/tolerability, tazemetostat RP3D
- **Secondary endpoint:** safety PK parameters

SYMPHONY-1 Phase Ib: Baseline Characteristics

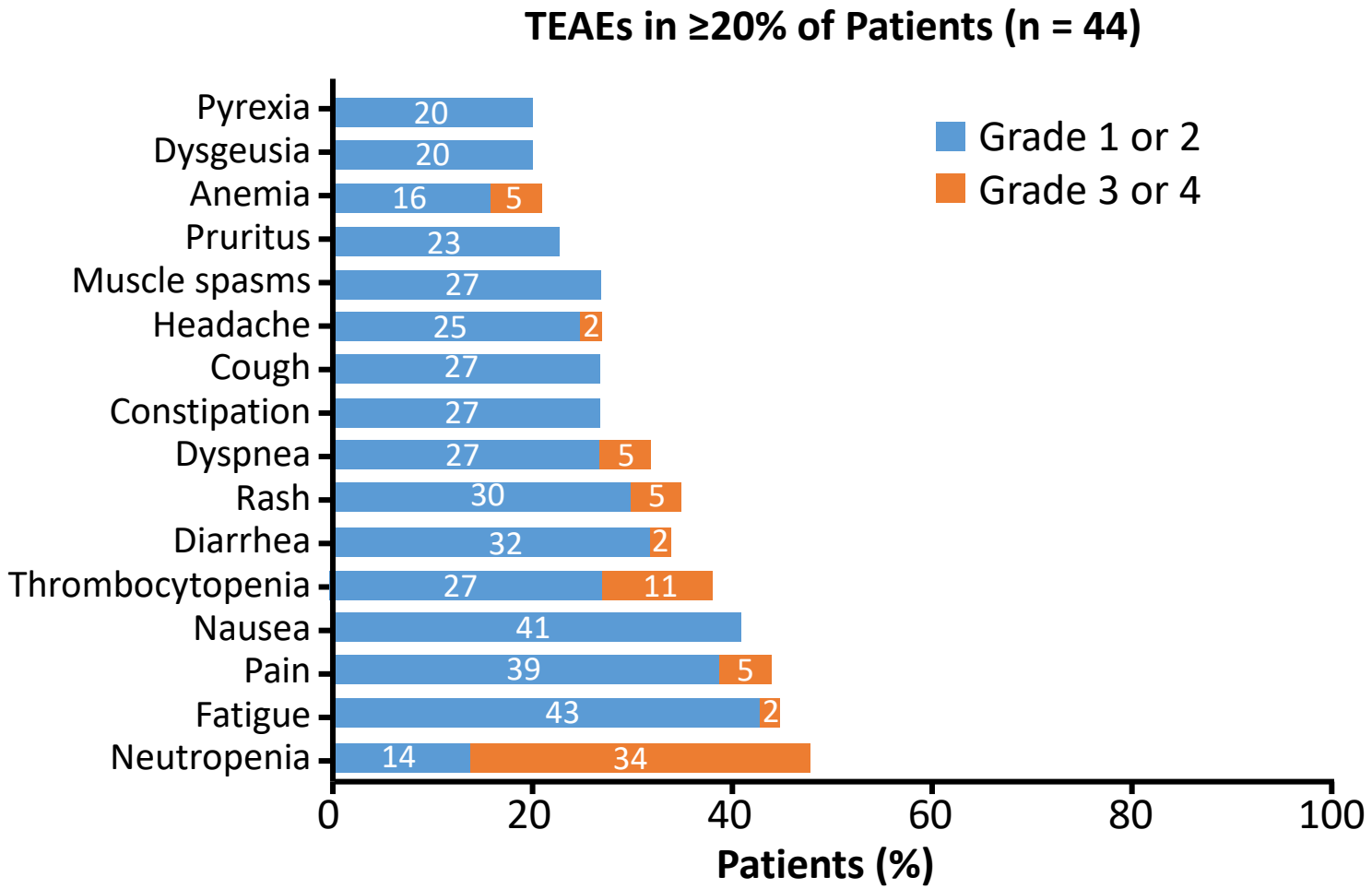
Characteristic	Tazemetostat + R^2 (N = 44)
Median age, yr (range) ▪ Age ≥65 yr, n (%)	67 (39-83) 26 (59.1)
Male, n (%)	26 (59.1)
ECOG PS, n (%) ▪ 0 ▪ 1	 33 (75.0) 11 (25.0)
Grade at diagnosis, n (%) ▪ 1 ▪ 2 ▪ 3A ▪ Unknown/not reported	 11 (25.0) 20 (45.5) 12 (27.3) 1 (2.3)
LDH > ULN, n (%)	7 (15.9)
B symptoms, n (%)	6 (13.6)
Transformed from DLBCL to FL, n (%)	4 (9.1)

Characteristic	Tazemetostat + R^2 (N = 44)
Median time from last tx, mo (range)*	15.7 (0.6-193.6)
Median prior lines of systemic tx (range)[†] ▪ 1 ▪ 2 ▪ 3 ▪ 4	1 (1-4) 30 (68.2) 7 (15.9) 2 (4.5) 5 (11.4)
Prior classes of tx, n (%) ▪ Anti-CD20 mAb + CT[‡] ▪ Anti-CD20 mAb as only tx	 33 (75) 11 (25)
Refractory to rituximab at BL,[§] n (%)	15 (34.1)
POD24, n (%)	12 (27.3)
EZH2 mutation status,[‖] n/N (%) ▪ Mutated ▪ Wild-type	 7/42 (16.7) 35/42 (83.3)

*n = 1 not available. [†]n = 14 received rituximab maintenance, which was not considered separate line of tx. [‡]R/O-bendamustine, R/O-CHOP–based tx.
[§]No response to single-agent or combination rituximab therapy or PD within 6 mo of completing rituximab-based tx. [‖]Unknown *EZH2* status, n = 2.

Batlevi. ASH 2022. Abstr 954.

SYMPHONY-1 Phase Ib: Safety



- Neutropenia most common high-grade TEAE
  - Prophylactic G-CSF not permitted in phase Ib; n = 14 received secondary G-CSF after 1 occurrence of neutropenia
- 36.4% (16/44) of patients had serious TEAEs, with COVID-19 being most common (9.1%)
- 1 case of B-ALL developed after data cutoff*

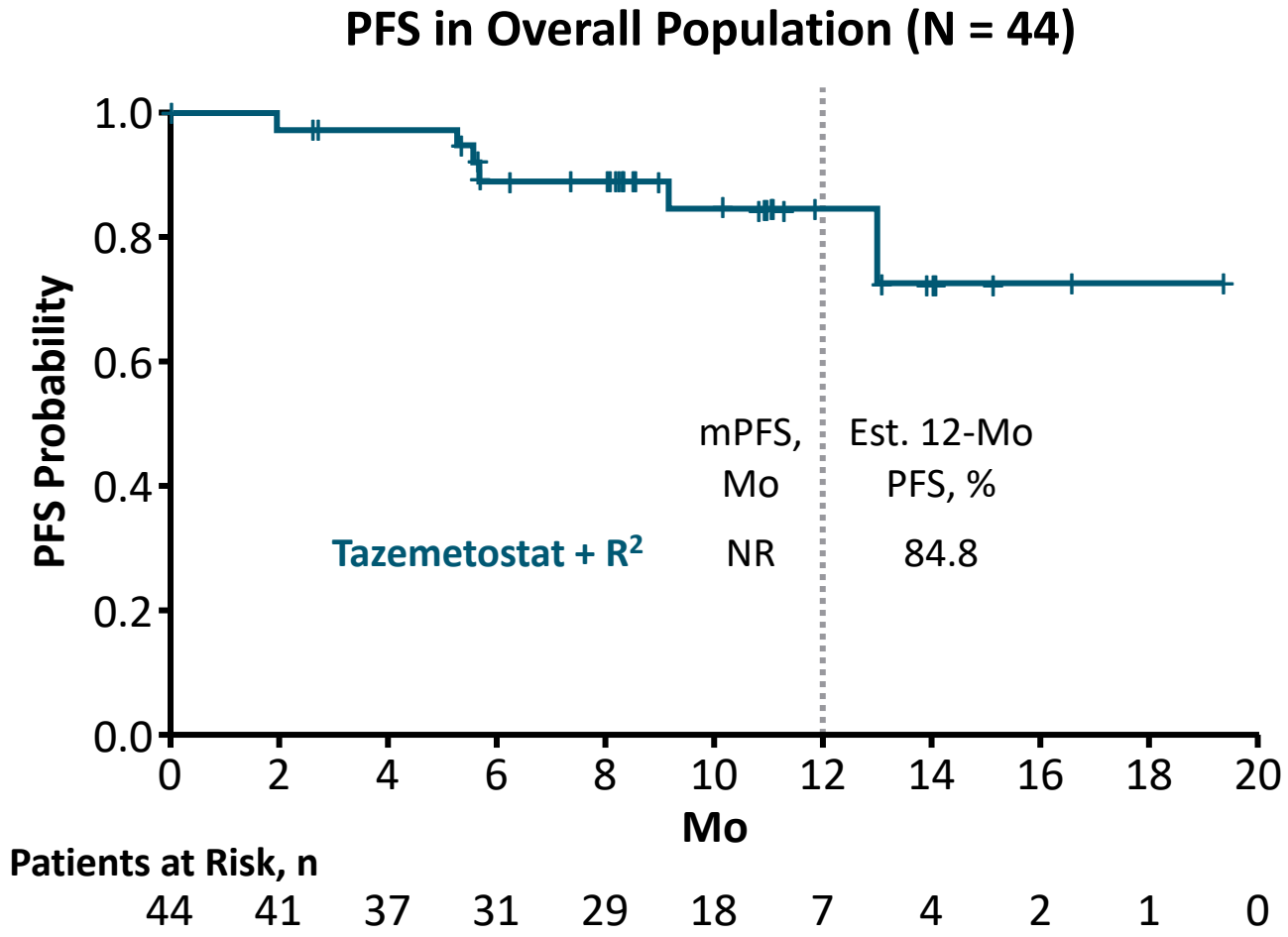
*69-yr-old man with R/R FL previously treated with BR x 6 cycles received tazemetostat + R^2 → tazemetostat; developed B-ALL after 590 days on study and discontinued tx.

Batlevi. ASH 2022. Abstr 954.

SYMPHONY-1 Phase Ib: Efficacy in Overall Population

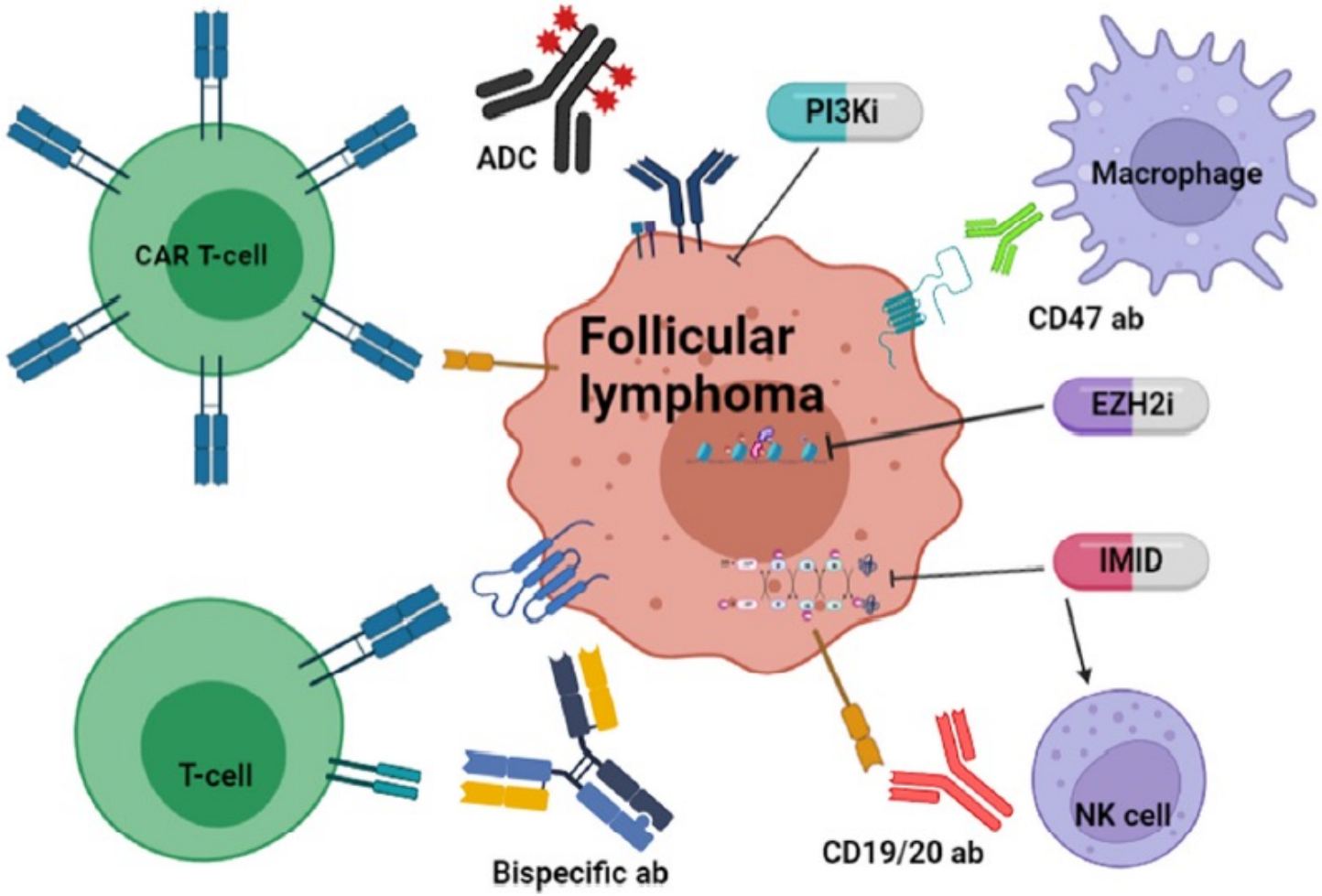
Response	Tazemetostat + R^2 (n = 41)
ORR, n (%)	40 (97.6)
▪ CR	21 (51.2)
▪ PR	19 (46.3)
▪ SD	1 (2.4)
Median DoR, mo	NR

- At data cutoff (June 14, 2022), 56.8% (25/44) had treatment ongoing, 6.8% (3/44) had PD



Conclusions: Tazemetostat

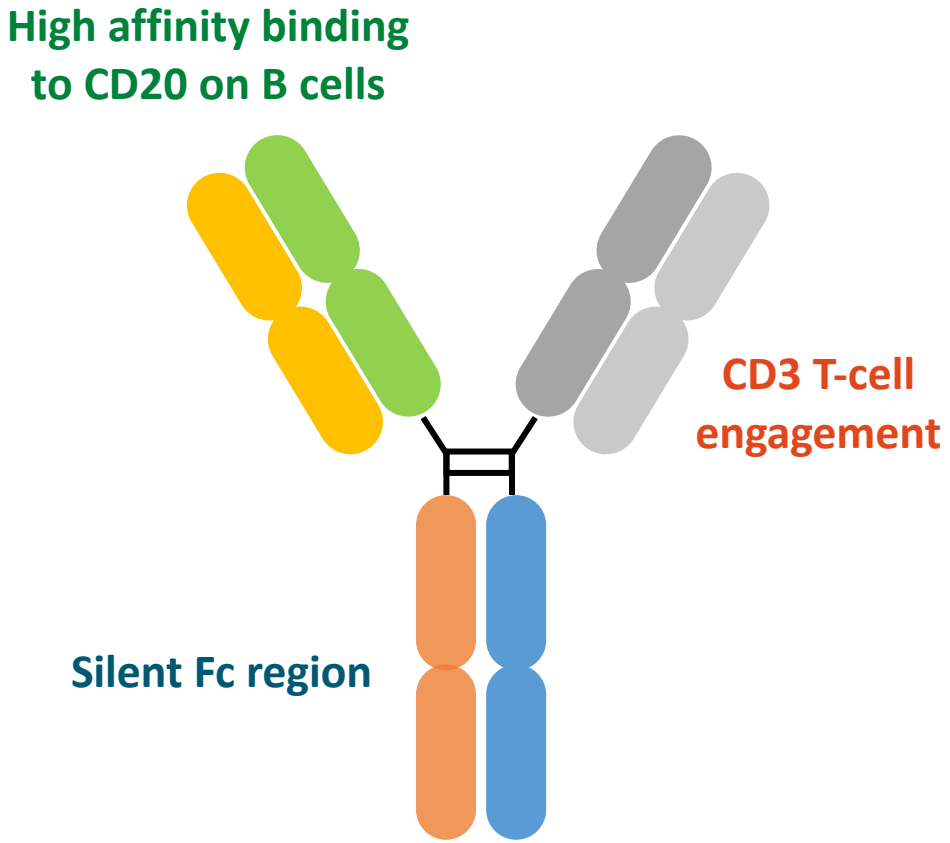
- Single-agent tazemetostat active in patients with R/R FL
  - ORR greater in patients with *EZH2* mutation
- Combination of tazemetostat with R^2 was generally well tolerated and demonstrated preliminary antitumor activity in patients with R/R FL
  - RP3D identified as 800 mg BID
  - ORR in overall population was 97.6% and ranged from 96.2% to 100% across subgroups (including *EZH2* mutation status, rituximab sensitivity, POD24)
  - Median DoR not reached
- Randomized phase III portion of SYMPHONY-1 will compare tazemetostat 800 mg BID + R^2 vs placebo + R^2 in patients with R/R FL after ≥1 prior therapy



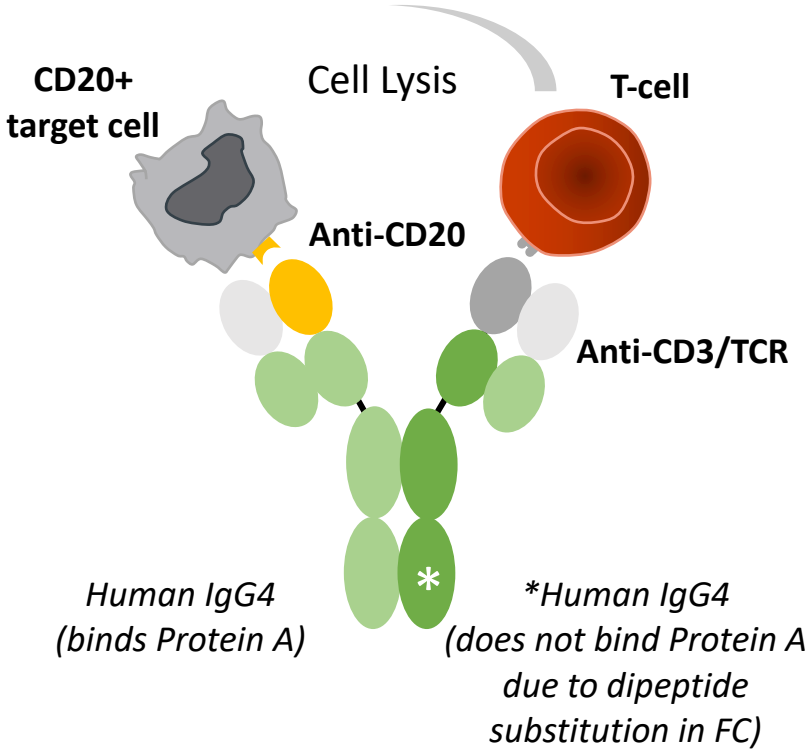
Gordon MJ, Blood 2023

CD20/CD3 Bispecific Antibody Structure

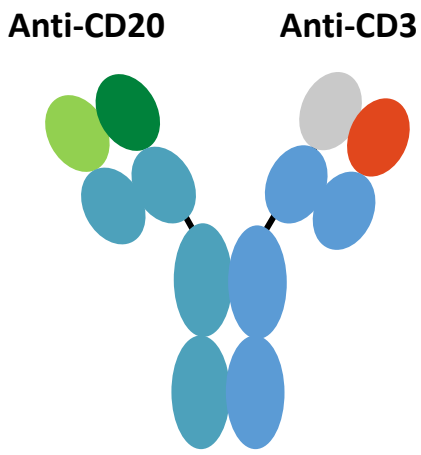
- Full-length, fully humanized IgG1 bispecific antibody
- Redirects T-cells to engage and redirect B-cells
- Off-the-shelf treatment, potentially fixed duration



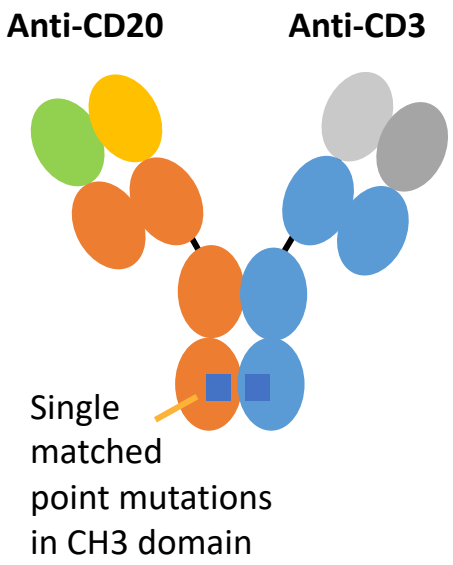
CD20/CD3 Bispecific Antibodies in B-Cell Lymphomas



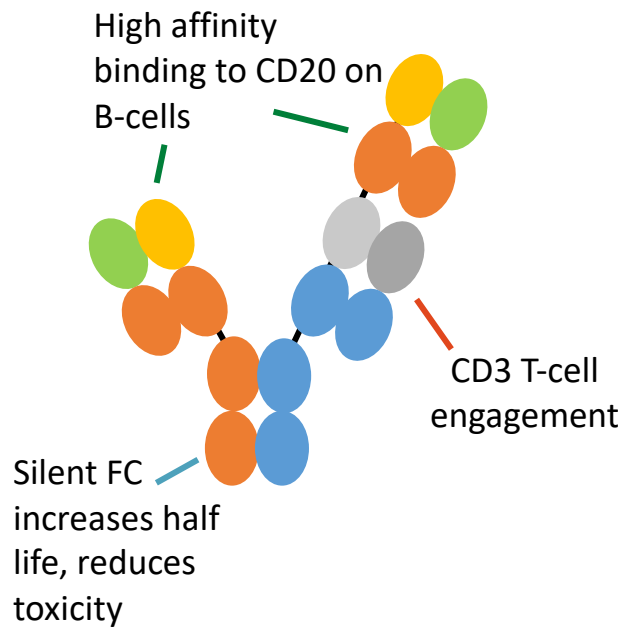
Odronextamab
(IV)



Mosunetuzumab
(IV/SC)



Epcoritamab
(SC)



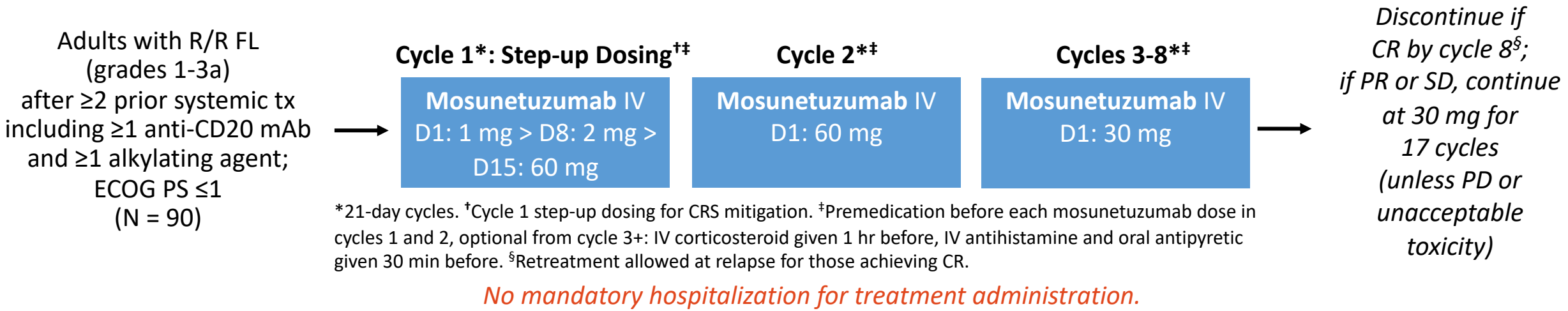
Glofitamab
(IV)

Humanized mouse IgG1-based mAb

Castaneda-Puglianni. Drugs Context. 2021;10:2021. Bannerji. ASH 2020. Abstr 42. Budde. ASH 2018. Abstr 399.
Hutchings. Lancet. 2021;398:1157. Engelberts. eBioMedicine. 2020;52:102625. Hutching. ASH 2020. Abstr 403.

Phase II Study Update: Mosunetuzumab Monotherapy in R/R Follicular Lymphoma (ASH 2022)

- Single-arm, pivotal phase II expansion study
  - Primary endpoint met: 60% CR vs 14% historical control (*P* <.0001) at 10-mo follow-up[2]
  - Current analysis reports updated safety and efficacy at median follow-up of 28.3 mo



*21-day cycles. †Cycle 1 step-up dosing for CRS mitigation. ‡Premedication before each mosunetuzumab dose in cycles 1 and 2, optional from cycle 3+: IV corticosteroid given 1 hr before, IV antihistamine and oral antipyretic given 30 min before. §Retreatment allowed at relapse for those achieving CR.

No mandatory hospitalization for treatment administration.

- **Primary endpoint:** CR (best response) rate by IRF, assessed vs 14% historical control CR rate
- **Secondary endpoints:** ORR, DoR, PFS, safety, and tolerability

1. Bartlett. ASH 2022. Abstr 610. 2. Budde. Lancet Oncol. 2022;23:1055. NCT02500407. Mosunetuzumab.

Phase II Study Update: Baseline Characteristics

Characteristic	Mosunetuzumab (N = 90)
Median age, yr (range)	60 (29-90)
Male, n (%)	61
ECOG PS 0/1, n (%)	59/41
Ann Arbor stage, n (%)	
▪ I-II	23
▪ III-IV	77
Median prior lines, n (range)	3 (2-10)
Refractory to last prior therapy, %	69
Refractory to any prior anti-CD20 therapy, %	79
PD within 24 mo from start of first-line therapy (POD24), %	52
Double refractory to prior anti-CD20 therapy and alkylator, %	53
Prior ASCT, %	21

Bartlett. ASH 2022. Abstr 610.

Slide credit: clinicaloptions.com

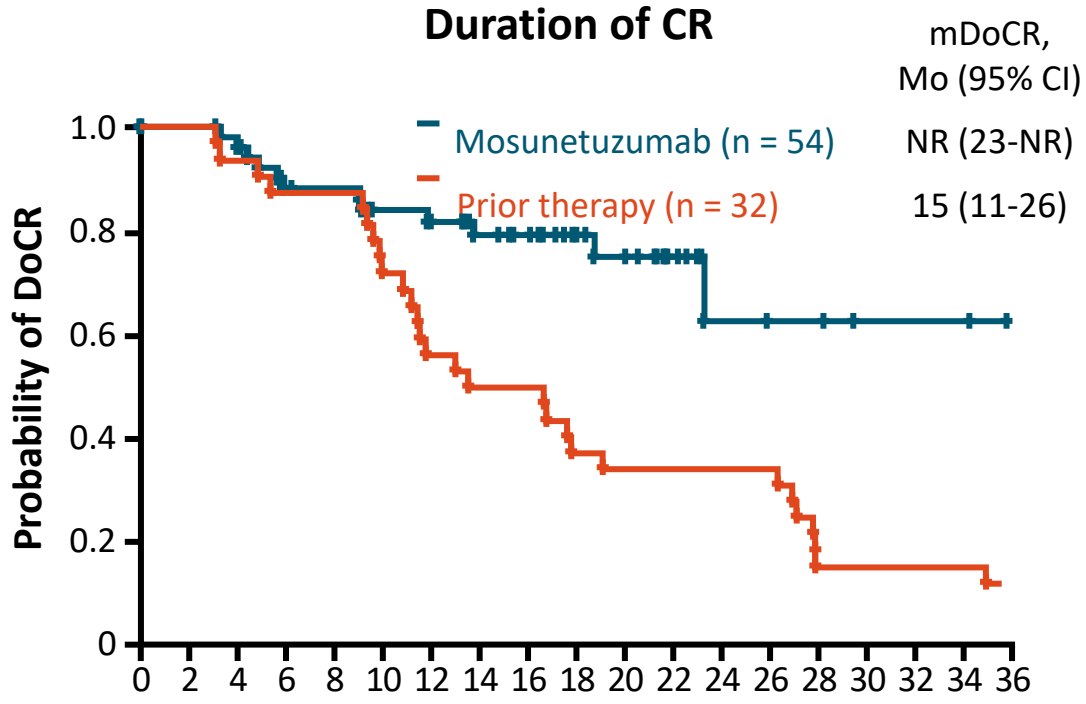
Phase II Study Update: Response

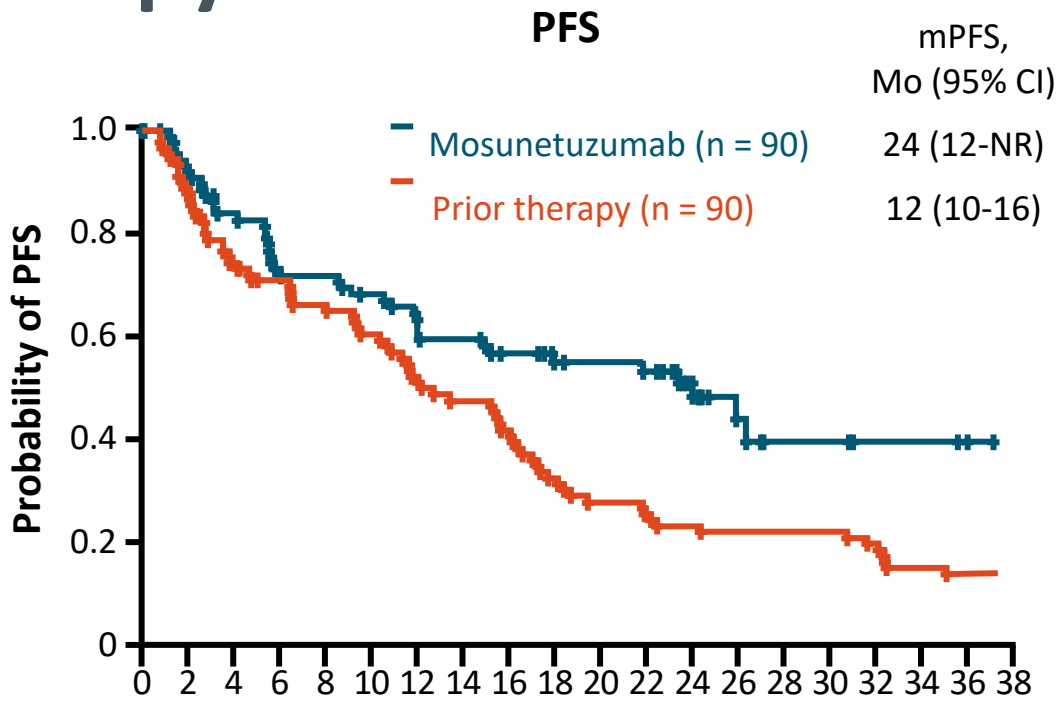
Response Outcome by Investigator	Mosunetuzumab (N = 90)
ORR, % (95% CI)	78 (68-86)
▪ Median time to first response, mo (range)	1.4 (1.0-11)
CR, % (95% CI)	60 (49-70)
▪ Median time to first CR, mo (range)	3.0 (1.0-19)

- High overall response and CR rates consistent with previous report

Bartlett. ASH 2022. Abstr 610. Budde. Lancet Oncol. 2022;23:1055.

Phase II Study Update: Duration of CR and PFS With Mosunetuzumab vs Last Prior Therapy





Patients at Risk, n																			
Prior therapy	32	32	30	28	28	23	18	16	16	12	11	11	11	11	5	5	5	5	4
Mosunetuzumab	54	53	50	43	42	37	35	31	28	22	19	10	5	4	4	2	2	2	NR

Patients at Risk, n																									
Prior therapy	90	80	66	61	56	52	44	41	36	28	24	22	20	19	19	19	16	13	12	12					
Mosunetuzumab	90	80	71	60	59	55	47	46	40	33	32	31	18	10	5	5	3	3	1	NR					

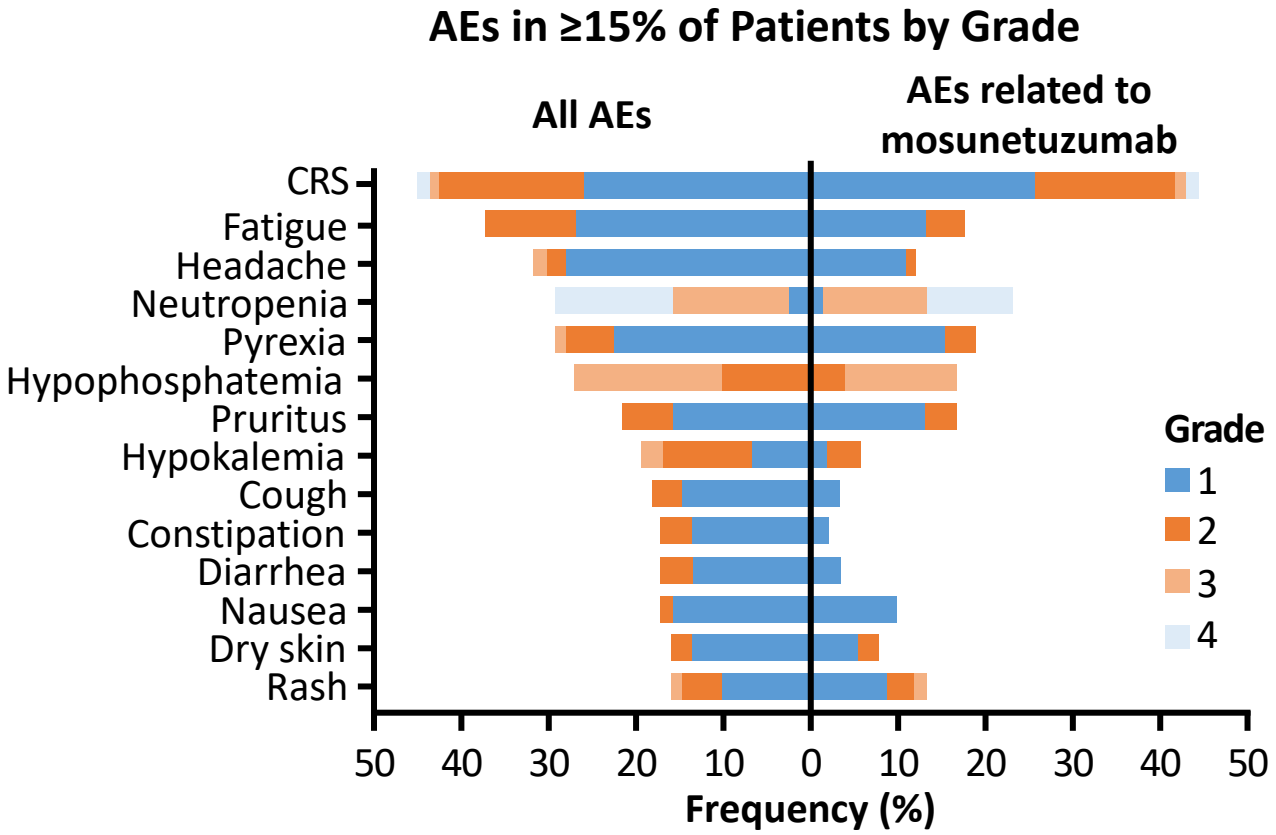
- Extended duration of CR and 12-mo improvement in median PFS with mosunetuzumab compared with last prior therapy

Bartlett. ASH 2022. Abstr 610.

Phase II Study Update: Safety

AE, %	Mosunetuzumab(N = 90)
Any	100
▪ Mosunetuzumab related	92
Grade 3/4	70
▪ Mosunetuzumab related	51
Serious AE	47
▪ Mosunetuzumab related	33
Fatal*	2
▪ Mosunetuzumab related	0
Leading to treatment d/c†	4
▪ Mosunetuzumab related	2

*Fatal AEs: malignant neoplasm progression and unexplained.
†D/c: mosunetuzumab related, CRS (n = 2); unrelated to mosunetuzumab, EBV viremia (n = 1), Hodgkin disease (n = 1).

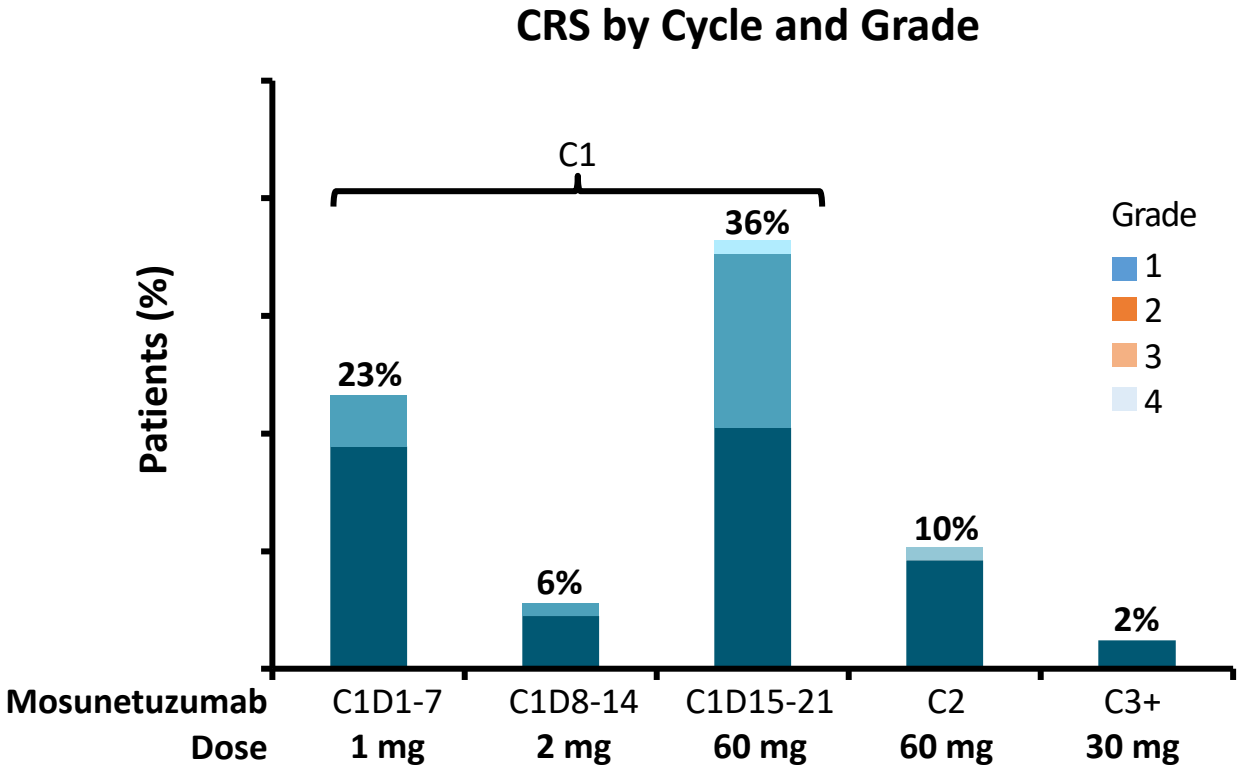


- No new serious AEs, grade ≥3 AEs, or TRAEs with additional 10 mo of follow-up

Bartlett. ASH 2022. Abstr 610.

Phase II Study Update: CRS

CRS per ASTCT Criteria	Mosunetuzumab(N = 90)
Any grade, % ▪ Grade 1 ▪ Grade 2 ▪ Grade 3 ▪ Grade 4	44 26 17 1 1
Median time to onset, hr (range) ▪ Cycle 1, Day 1 ▪ Cycle 1 Day 15	 5.2 (1.2-24) 27 (0.1-391)
Median duration, days (range)	3 (1-29)
Patients who received tx for CRS, % ▪ Corticosteroids only ▪ Tocilizumab only	 11 8
Events resolved, %	100



- Most CRS events low grade and occurred during cycle 1; all resolved
- No new events with additional 10-mo f/u

Bartlett. ASH 2022. Abstr 610. Lee. Biol Blood Marrow Transplant. 2019;25:625.

Slide credit: clinicaloptions.com

FDA Approval of First Bispecific Antibody for R/R FL

- In December 2022, FDA granted accelerated approval to CD20-directed CD3 T-cell engager mosunetuzumab IV for adult patients with R/R FL after ≥2 lines of systemic therapy
- Recommended dosing (21-day cycles)
  - Step up dosing in cycle 1: 1 mg on Day 1, 2 mg on Day 8, 60 mg on Day 15
  - Cycle 2: 60 mg Day 1
  - Subsequent cycles: 30 mg on Day 1
    - Administer for 8 cycles in patients achieving CR
    - Administer for up to 17 cycles in patients with PR/SD
    - Discontinue if PD or unacceptable toxicity
- Black box warning for CRS
  - Mitigate CRS risk with step-up dosing in cycle 1, premedication (ie, corticosteroid, antihistamine, antipyretic); if CRS occurs, withhold drug until CRS resolves or permanently discontinue based on CRS severity

Bartlett. ASH 2022. Abstr 610. Budde. Lancet Oncol. 2022;23:1055.

Phase Ib/II Study: Mosunetuzumab + Lenalidomide in R/R Follicular Lymphoma

- Multicenter, open label phase Ib/II study
  - Current analysis reports initial data from phase Ib (median follow-up: 5.4 mo)

Adults with CD20+ R/R FL (grades 1-3a) after ≥1 prior CIT regimen, including an anti-CD20 mAb; prior lenalidomide allowed; ECOG PS ≤2 (Planned N = 169)

→

Cycle 1*: Step-up Dosing	Cycles 2-12
Mosunetuzumab IV D1: 1 mg > D8: 2 mg > D15: 30 mg (21-day cycle)	**Mosunetuzumab** 30 mg IV D1 + **Lenalidomide** 20 mg PO QD D1-21 (28-day cycle)

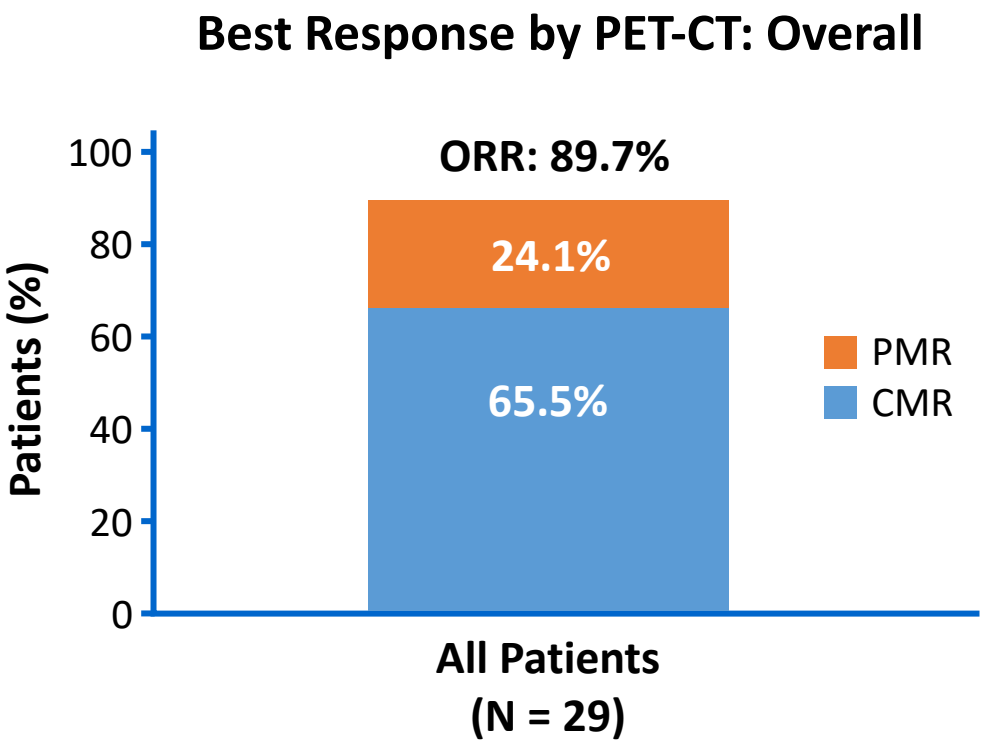
No mandatory hospitalization for treatment administration

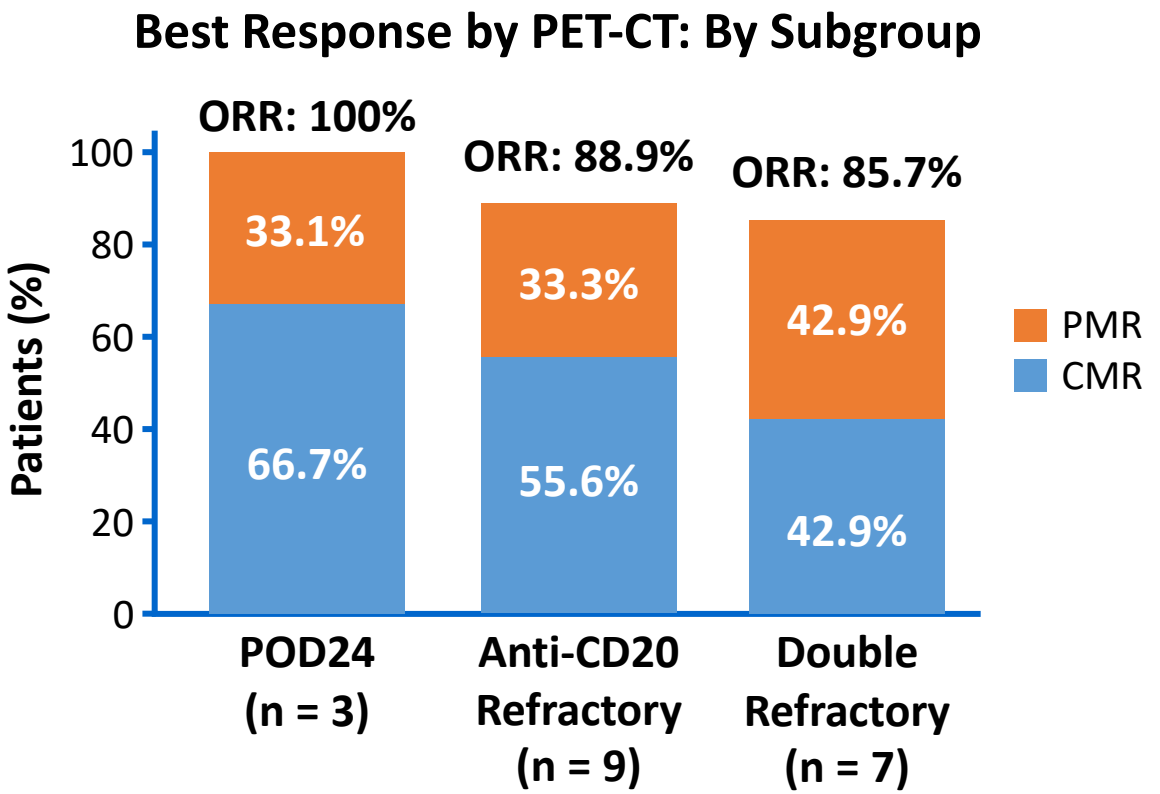
- **Primary endpoint:** safety/tolerability
- **Secondary endpoints:** efficacy (CR, ORR, DoR, DoCR), PK

Morschhauser. ASH 2021. Abstr 129. NCT04246086.

Slide credit: clinicaloptions.com

Mosunetuzumab + Lenalidomide in R/R FL: Response





- Median time to first/best response: 2.5 mo (range: 1.4-5.3)/2.5 mo (range: 1.4-10.7)
- High ORR and CMR rate in overall population, including those with high-risk disease
- Ongoing phase III CELESTIMO study evaluating mosunetuzumab + lenalidomide vs R^2 in R/R FL after ≥1 prior line of systemic therapy (NCT04712097)

Morschhauser. ASH 2021. Abstr 129.

EPCORE NHL-2: Epcoritamab + R^2 in R/R Follicular Lymphoma (ASH 2022)

- Multicohort, open-label phase Ib/II study of epcoritamab combination tx in FL and DLBCL
  - Current analysis reports updated results from R/R FL cohort receiving epcoritamab + R^2 (arm 2b)

Adults with CD20+ R/R FL (grades 1-3a, stage II-IV); measurable disease and requiring treatment; ECOG PS ≤2

→

Epcoritamab* 48 mg SC
QW for C1-2, then Q4W for C6-C12
+
$R^{2\dagger}$ C1-12

→

Continue epcoritamab Q4W for ≤2 yr

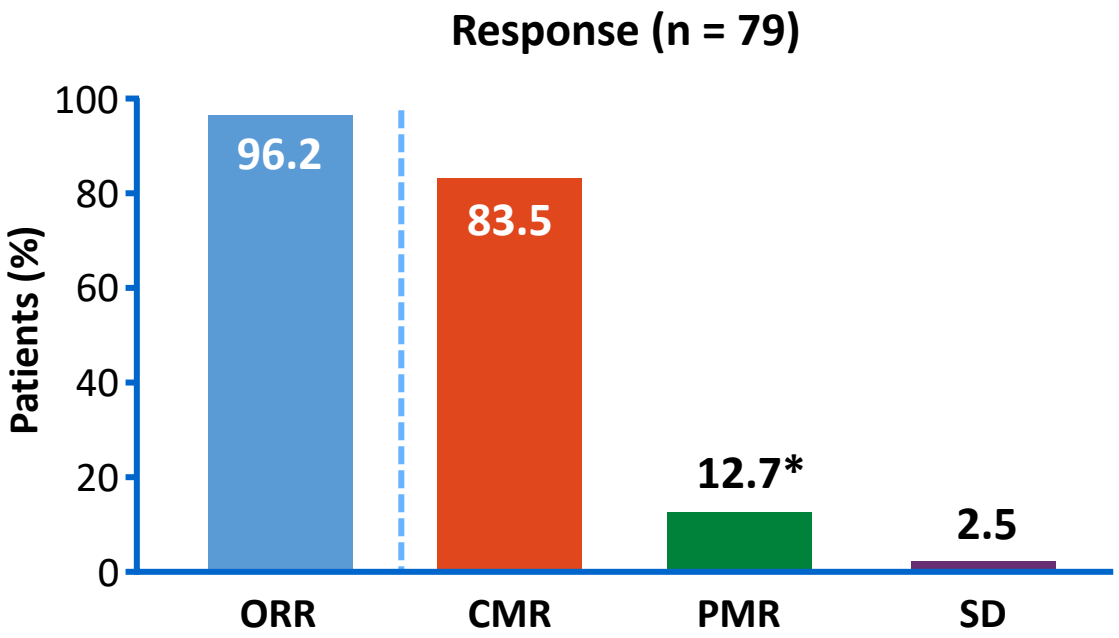
*Epcoritamab administered in 28-day cycles, with step-up dosing comprising priming and intermediate doses prior to first full dose, along with corticosteroid as CRS prophylaxis and protocol mandated hospitalization for 24 hr after.
†Rituximab: 375 mg/m^2 IV; QW for C1, Q4W for C2-5 (21-day cycles); lenalidomide: 20 mg PO QD for C1-C12 (21-day cycles).

- **Primary endpoint:** safety, antitumor activity (ORR)
- **Secondary endpoints:** PK, DoR, TTR, PFS, OS, TTNT

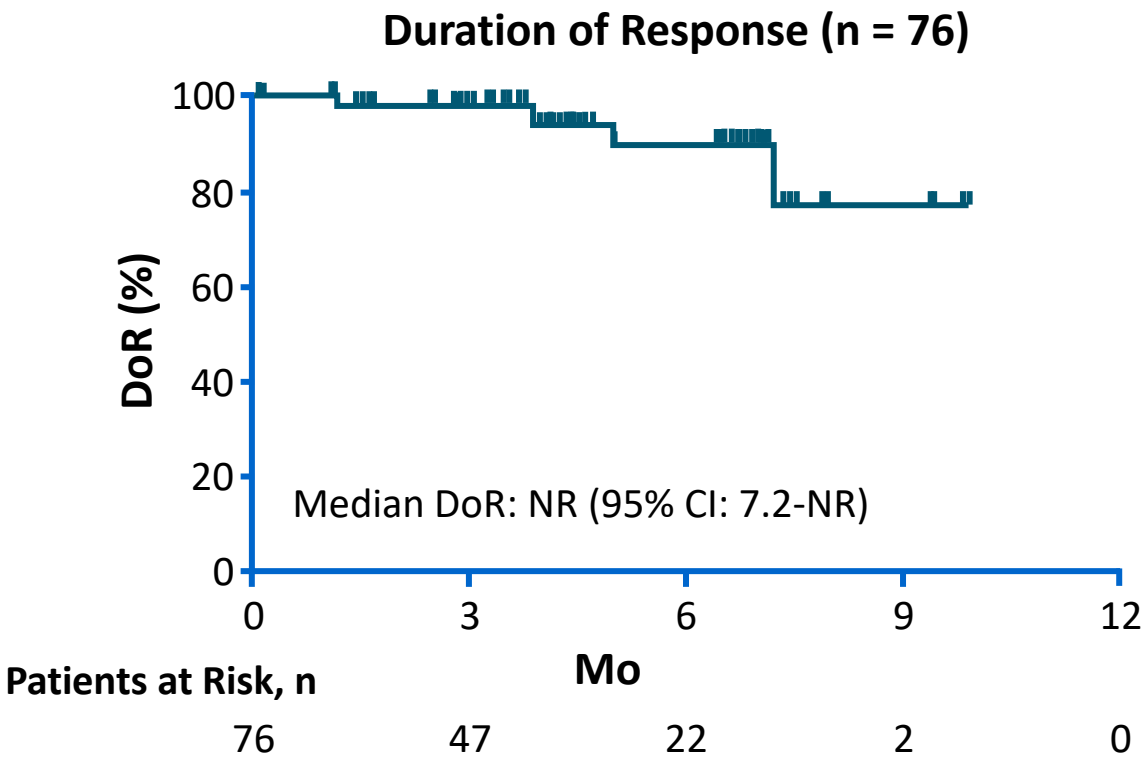
Falchi. ASH 2022. Abstr 609. NCT04663347.

Slide credit: clinicaloptions.com

EPCORE NHL-2: Updated Response



*n = 6 with ongoing PMR.



Median follow-up: 5.6 mo (range: 1.2-11.5+).

Bispecific Antibodies in R/R FL: Summary

- Bispecific antibodies represent a novel immunotherapy for patients with R/R FL
- In December 2022, the FDA approved the first CD20-directed CD3 T-cell engager, mosunetuzumab, for treatment of adult patients with R/R FL after ≥2 lines of systemic therapy
  - In pivotal phase II trial, mosunetuzumab achieved a CR rate of 60%, ORR of 80% by IRC
  - Safety profile manageable; CRS primarily low grade and mostly occurred in cycle 1
  - Risk of CRS mitigated by step-up dosing and premedication
- Additional CD20-directed CD3 T-cell engagers are under development, including in combination regimens and earlier lines of therapy

trattamenti chemo-free

CONSIDERAZIONI FINALI

- Diversi approcci chemo-free si sono dimostrati efficaci e con un accettabile profilo di tossicità, arricchendo l'armamentario terapeutico nella malattia ricaduta/refrattaria, possibilmente in una linea di terapia precoce (ovviamente da confrontare con i CAR-T)

- Oltre all'efficacia, altri fattori vanno tenuti in