Neues zur Therapie lymphatischer Neoplasien

PD Dr. Andreas GÜNTHER

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Neue Zulassungen seit 2020

	1.Line	2.Line	>2. Line
CLL	Ibrutinib + Venetoclax Acalabrutinib +/- Obinutuzumab Zanubrutinib	Zanubrutinib	
Mantelzell-Lymphom	Zanubrutinib***	Zanubrutinib Pirtobrutinib****	Brexucabtagen Autoleucel****
Marginalzonen-lymphom		Zanubrutinib	
Waldenström	Zanubrutinib	Zanubrutinib	
Follikuläres Lymphom			Zanubrutinib + Obinutuzumab Mosunetuzumab Tisagenlecleucel Axicabtagen-Ciloleucel*
Aggressives B-NHL	Polatuzumab-Vedotin + Rituximab-CHP	Tafasitamab + Lenalidomid Axicabtagen-Ciloleucel**	Epcoritamab Glofitamab Axicabtagen-Ciloleucel, Tisagenlecleucel Lisocabtagen-Maraleucel Loncastuximab Tesirin

Antibody-Drug-Conjugate
Bispecific Antibody
CAR
BTKi
Antibody
BCL2i
IMiD

*4.Linie **POD12***
nicht CIT-geignet****nach BTKi

CLL

1.Line: Feste Dauer, maßgeschneidert ohne bis zum Progress?
≥ 2.Linie

Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI Flair Study

Peter Hillmen, David Cairns, Adrian Bloor, David Allsup, Kate Cwynarski, Andrew Pettitt, Shankara Paneesha, Christopher Fox, Toby Eyre, Francesco Forconi, Nagah Elmusharaf, Ben Kennedy, John Gribben, Nicholas Pemberton, Oonagh Sheehy, Gavin Preston, Anna Schuh, Dena Howard, Anna Hockaday, Sharon Jackson, Natasha Greatorex, Sean Girvan, Sue Bell, Julia M Brown, Nichola Webster, Surita Dalal, Ruth de Tute, Andrew Rawstron, Piers EM Patten, Talha Munir
on behalf of the NCRI CLL Subgroup.

Abstract No: 631, Oral Presentation, ASH Annual Meeting
Sunday, December 10th 2023

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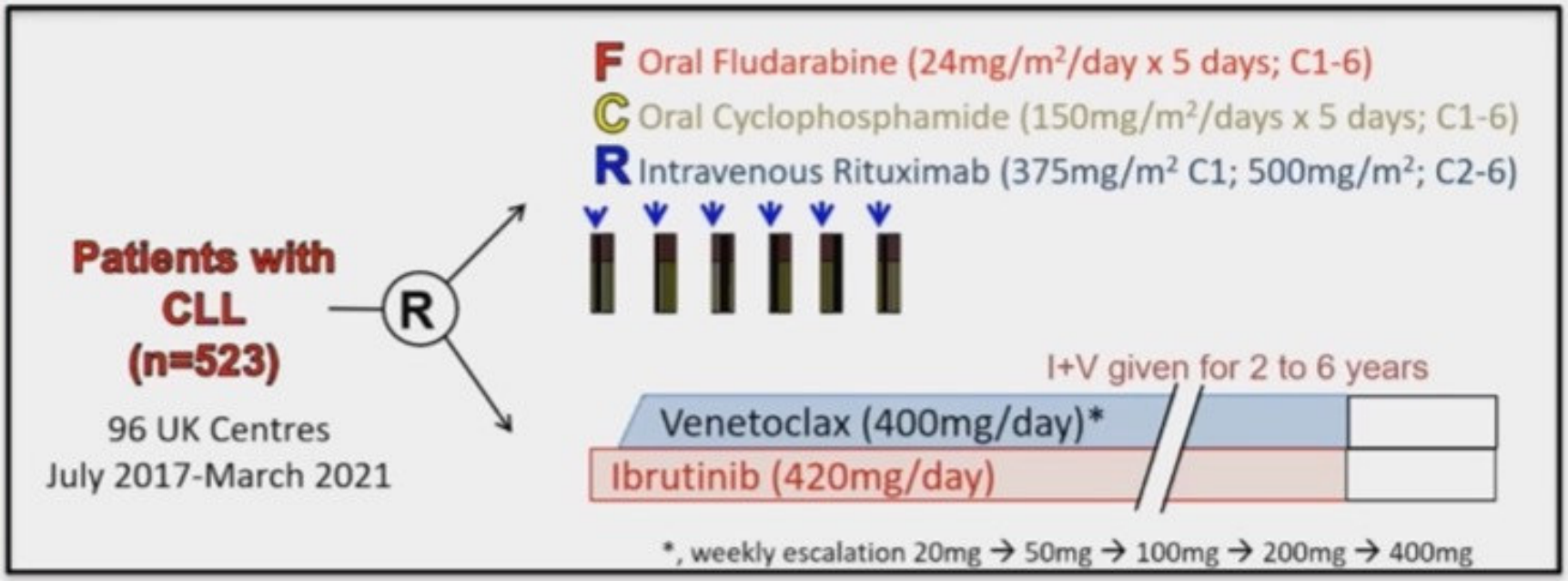
ORIGINAL ARTICLE

Chronic Lymphocytic Leukemia Therapy Guided by Measurable Residual Disease

T. Munir, D.A. Cairns, A. Bloor, D. Allsup, K. Cwynarski, A. Pettitt, S. Paneesha, C.P. Fox, T.A. Eyre, F. Forconi, N. Elmusharaf, B. Kennedy, J. Gribben, N. Pemberton, O. Sheehy, G. Preston, A. Schuh, R. Walewska, L. Duley, D. Howard, A. Hockaday, S. Jackson, N. Greatorex, S. Girvan, S. Bell, J.M. Brown, N. Webster, S. Dalal, R. de Tute, A. Rawstron, P.E.M. Patten, and P. Hillmen, for the National Cancer Research Institute Chronic Lymphocytic Leukemia Subgroup*

Flair FCR vs I+V: Trial design



Primary end-point:
To assess whether I+V is superior to FCR in terms of PFS

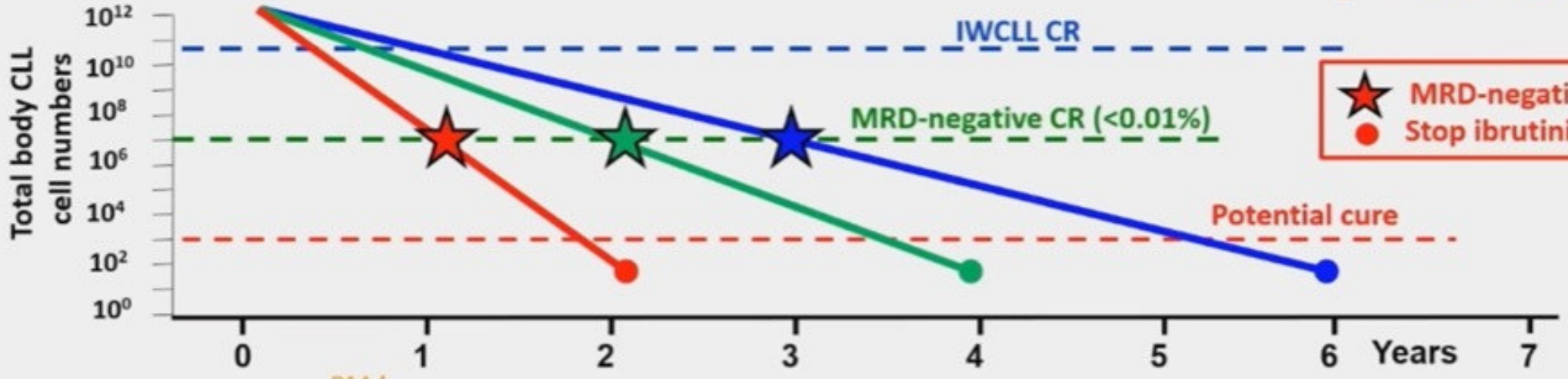
Key secondary end-points:
Overall survival
Response incl. MRD
Safety and toxicity

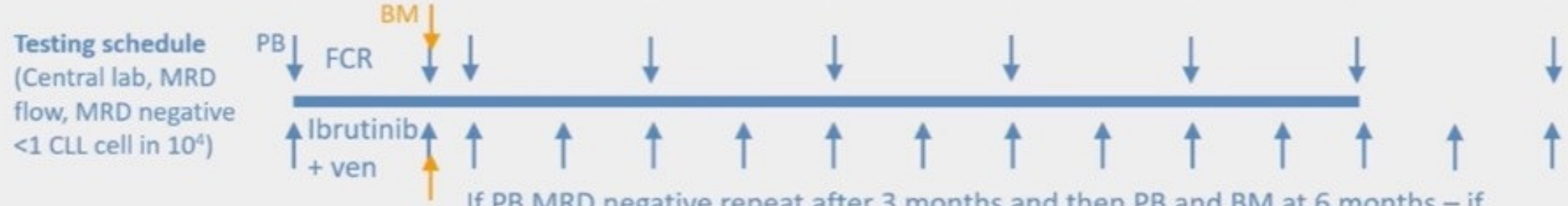
Key Inclusion Criteria:

- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

Stopping rules for ibrutinib + venetoclax in Flair





If PB MRD negative repeat after 3 months and then PB and BM at 6 months – if all MRD negative then first PB MRD negative result is time to MRD negativity

Defining treatment duration

2 to 6 years Ibrutinib or both ibr+venetoclax

Double time after MRD negative

Restart ibrutinib + venetoclax if becomes MRD positive prior to Year 6

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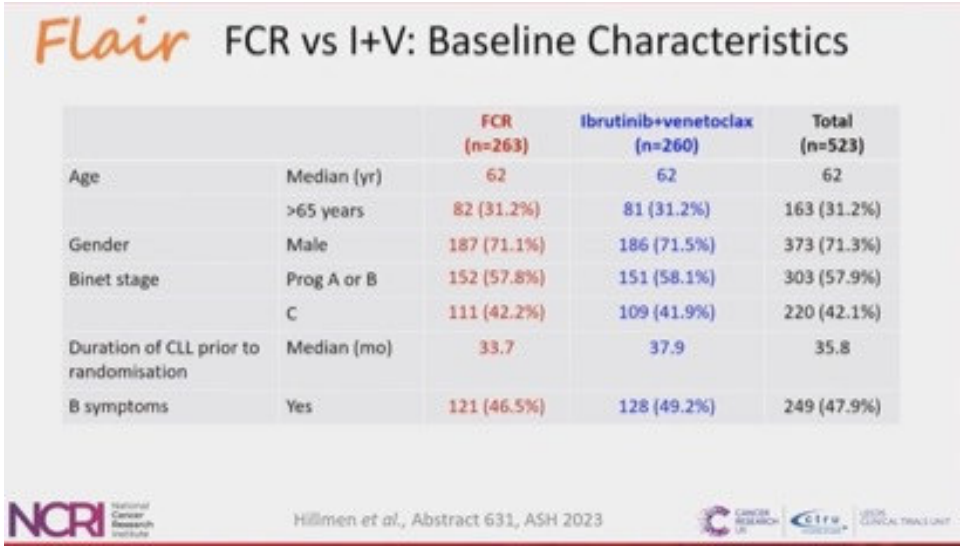
Baseline + Prognostic markers



Flair FCR vs I+V: Baseline Characteristics

		FCR (n=263)	Ibrutinib+venetoclax (n=260)	Total (n=523)
Age	Median (yr)	62	62	62
	>65 years	82 (31.2%)	81 (31.2%)	163 (31.2%)
Gender	Male	187 (71.1%)	186 (71.5%)	373 (71.3%)
Binet stage	Prog A or B	152 (57.8%)	151 (58.1%)	303 (57.9%)
	C	111 (42.2%)	109 (41.9%)	220 (42.1%)
Duration of CLL prior to randomisation	Median (mo)	33.7	37.9	35.8
B symptoms	Yes	121 (46.5%)	128 (49.2%)	249 (47.9%)

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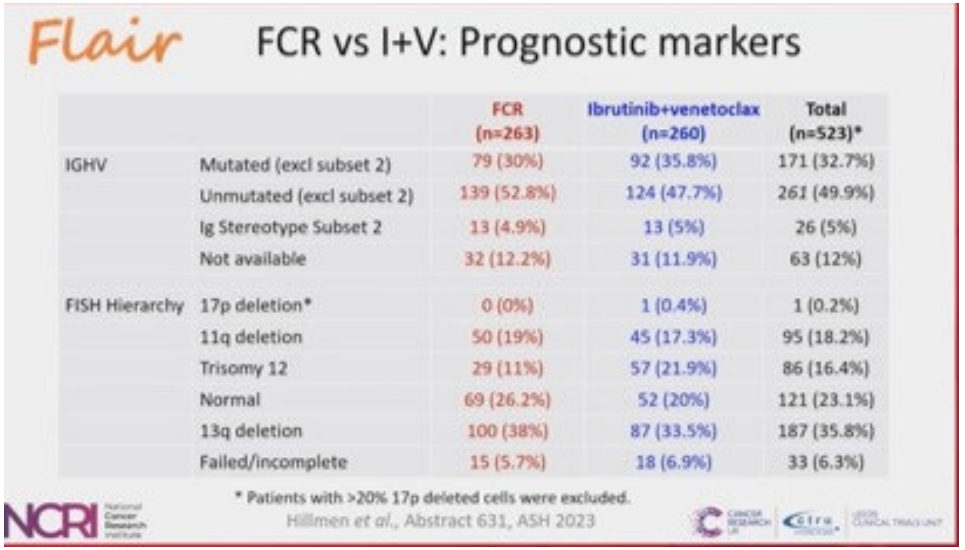

Flair FCR vs I+V: Prognostic markers

		FCR (n=263)	Ibrutinib+venetoclax (n=260)	Total (n=523)*
IGHV	Mutated (excl subset 2)	79 (30%)	92 (35.8%)	171 (32.7%)
	Unmutated (excl subset 2)	139 (52.8%)	124 (47.7%)	261 (49.9%)
	Ig Stereotype Subset 2	13 (4.9%)	13 (5%)	26 (5%)
	Not available	32 (12.2%)	31 (11.9%)	63 (12%)
FISH Hierarchy	17p deletion*	0 (0%)	1 (0.4%)	1 (0.2%)
	11q deletion	50 (19%)	45 (17.3%)	95 (18.2%)
	Trisomy 12	29 (11%)	57 (21.9%)	86 (16.4%)
	Normal	69 (26.2%)	52 (20%)	121 (23.1%)
	13q deletion	100 (38%)	87 (33.5%)	187 (35.8%)
	Failed/incomplete	15 (5.7%)	18 (6.9%)	33 (6.3%)

* Patients with >20% 17p deleted cells were excluded.

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Flair

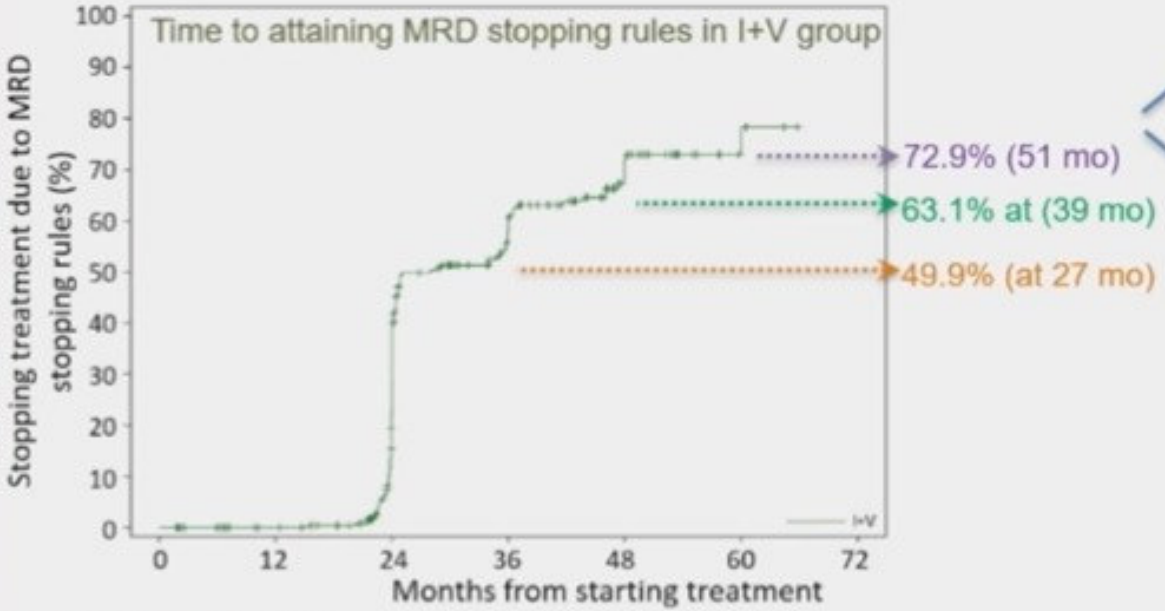
iwCLL response and MRD stopping rules

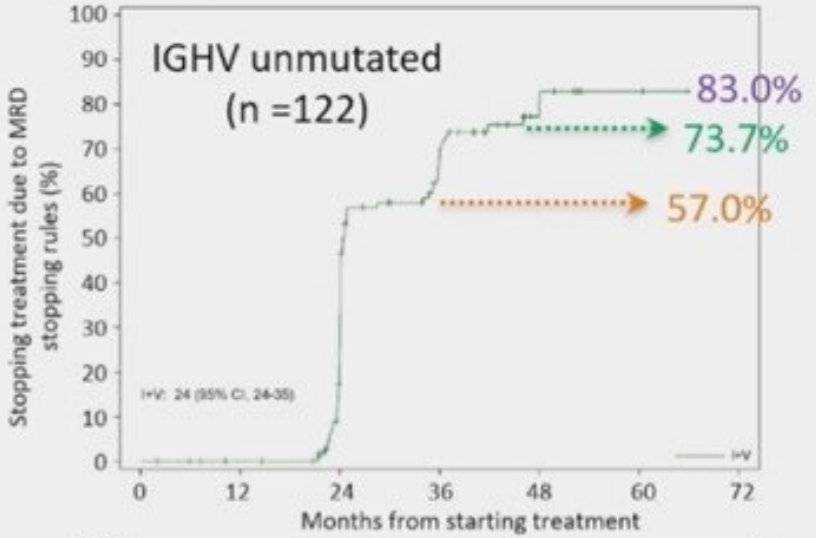
iwCLL Responses

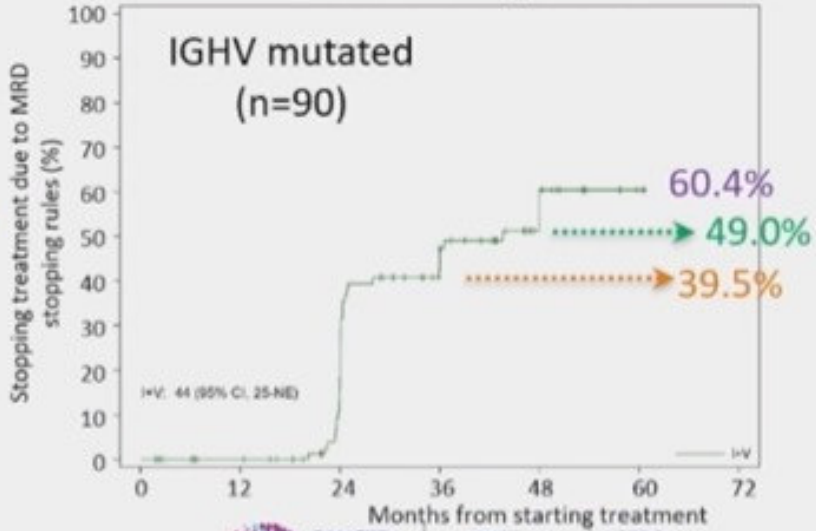
	Complete Response/CRi		Overall Response		BM uMRD
	9 months	Anytime	9 months	Anytime	Anytime
FCR	49%	71.5%	76.4%	83.7%	40.3%
I+V	59.2%	92.3%	86.5%	95.4%	61.9%

Odds ratio: 1.51
P<0.05

Odds ratio: 2.0
P<0.005







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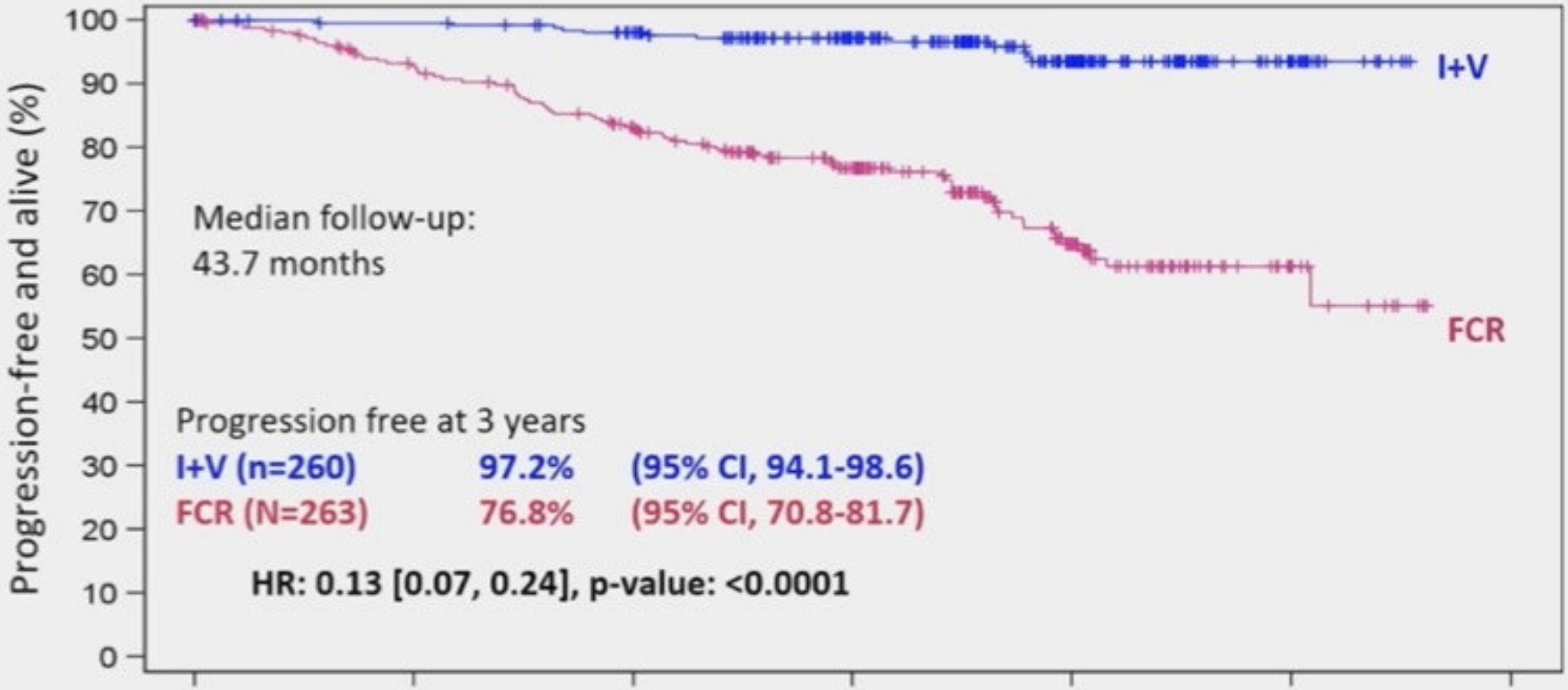
Flair Primary end-point: PFS for FCR versus I+V



No. at risk						
I+V	260	253	239	183	99	21	0
FCR	263	227	194	145	68	12	0

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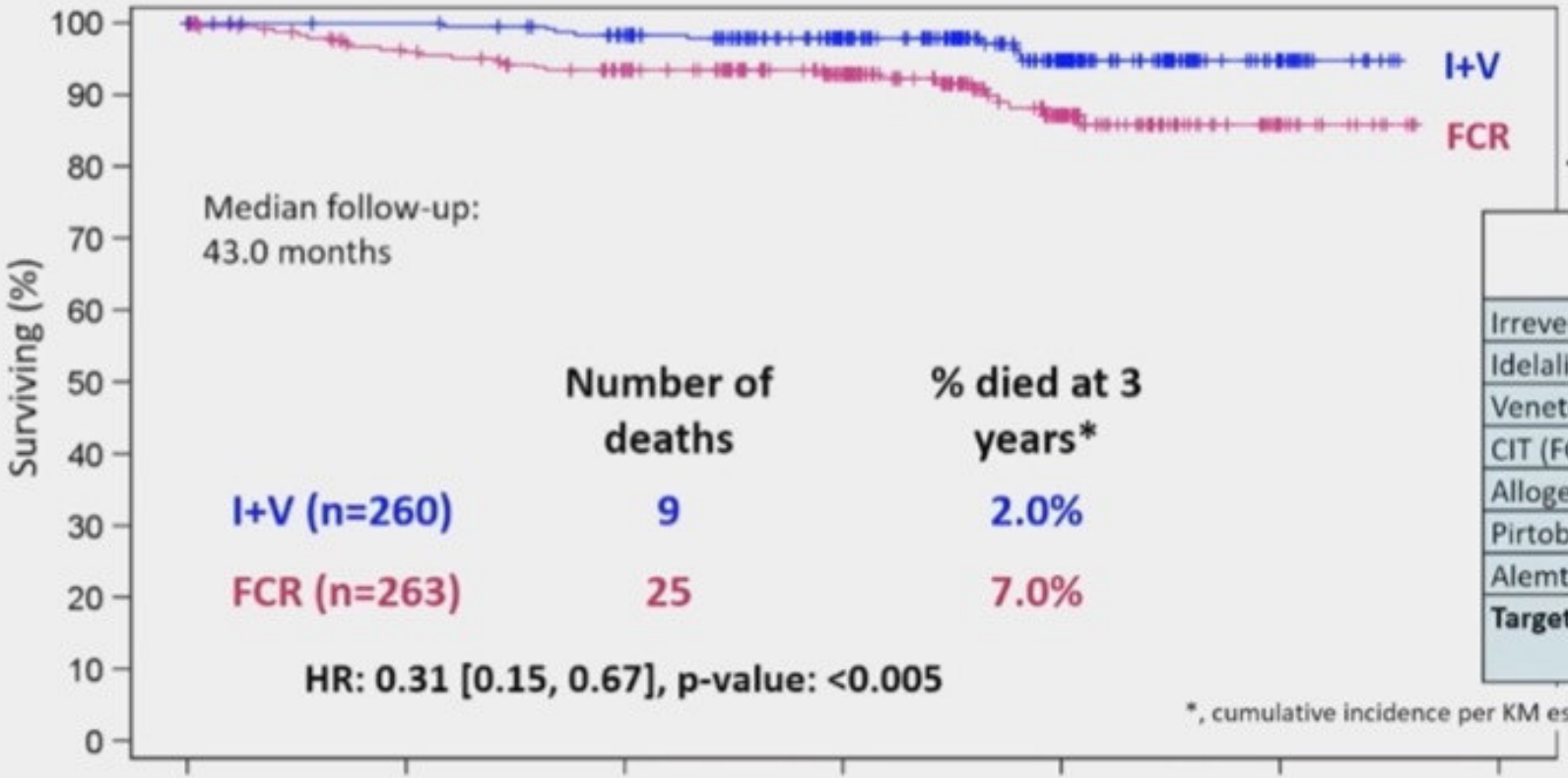
Overall Survival in FCR versus I+V



Treatment after progression

	FCR (n=42)	I+V (n=5)
Irreversible BTKi	23	2
Idelalisib + R	1	0
Venetoclax + R	11	0
CIT (FCR/BR/ChlR)	6	1
Allogeneic SCT	1	0
Pirtobrutinib	0	1
Alemtuzumab	0	1
Targeted therapy for CLL	**35/42 (83%)**	**3/5 (60%)**

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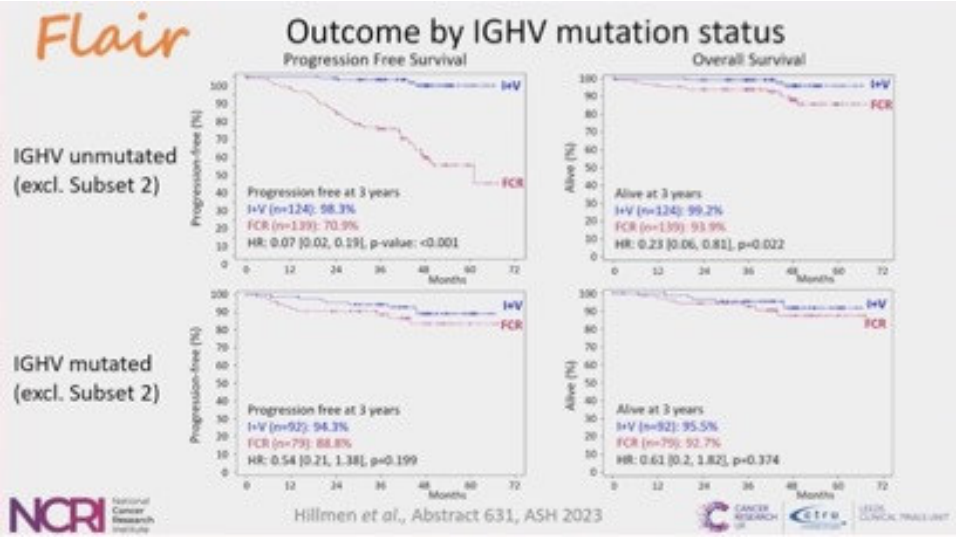
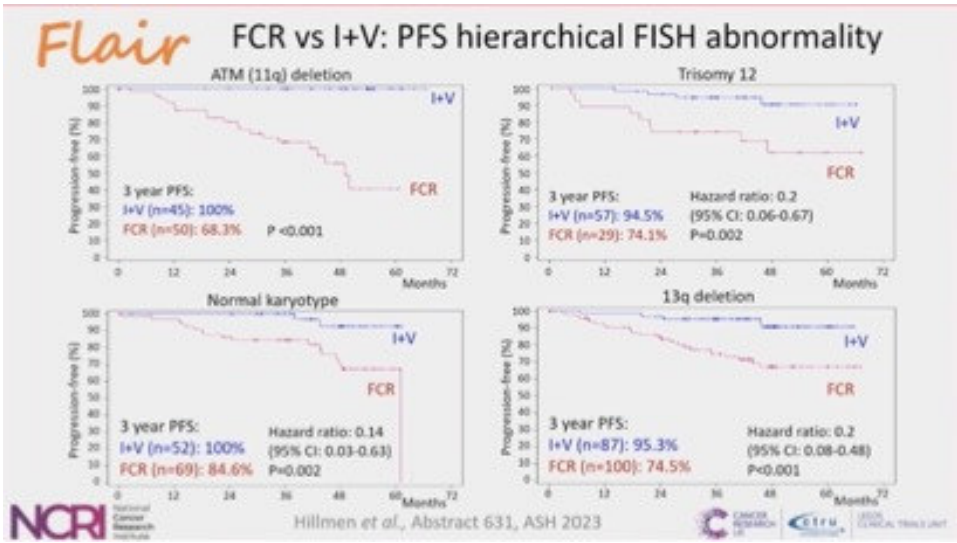
IGHV mutation status & FISH abnormality





Safety

Flair

Serious Adverse Events & malignancies

SAEs, by MedDRA System organ class

	Number of participants reporting ≥1 SAE	
	FCR (n=239)	I+V (n=252)
Infections and infestations	45 (18.8%)	56 (22.2%)
Blood and lymphatic system disorders	**74 (31%)**	**13 (5.2%)**
Cardiac disorders	**1 (0.4%)**	**27 (10.7%)**
Gastrointestinal disorders	19 (7.9%)	9 (3.6%)
General disorders and administration site conditions	**12 (5%)**	**4 (1.6%)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (2.1%)	6 (2.4%)
Metabolism and nutrition disorders	**0 (0%)**	**10 (4%)**
Respiratory, thoracic and mediastinal disorders	6 (2.5%)	4 (1.6%)
Musculoskeletal and connective tissue disorders	3 (1.3%)	6 (2.4%)
Skin and subcutaneous tissue disorders	5 (2.1%)	4 (1.6%)
Nervous system disorders	2 (0.8%)	5 (2%)
Eye disorders	**0 (0%)**	**6 (2.4%)**

Secondary malignancies (SM)

	FCR	I+V
Incidence rate of cancers per 100 person-years (95% CIs)	**5.4** (5.11, 5.68)	**2.6** (2.40, 2.79)

	FCR	I+V
BCC/SCC	16	13
MDS/AML	8	1
Lymphoma	5	3
Prostate/urological	5	1
Lung	3	0
GI	3	1
Breast	1	1
Melanoma	1	1
Myeloma	1	0
Endocrine	0	1
Other	5	2
Total patients*	**39**	**17**

*, some patients had more than one SM

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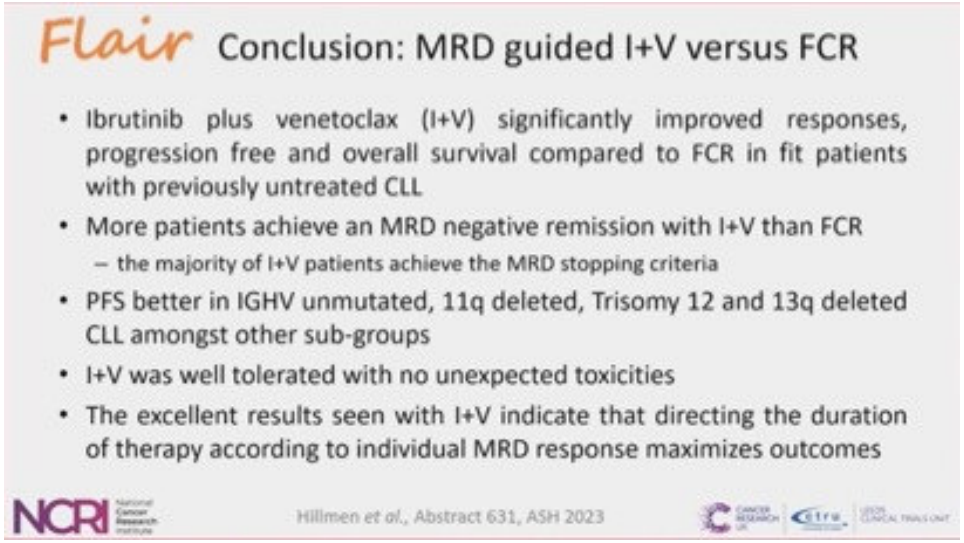
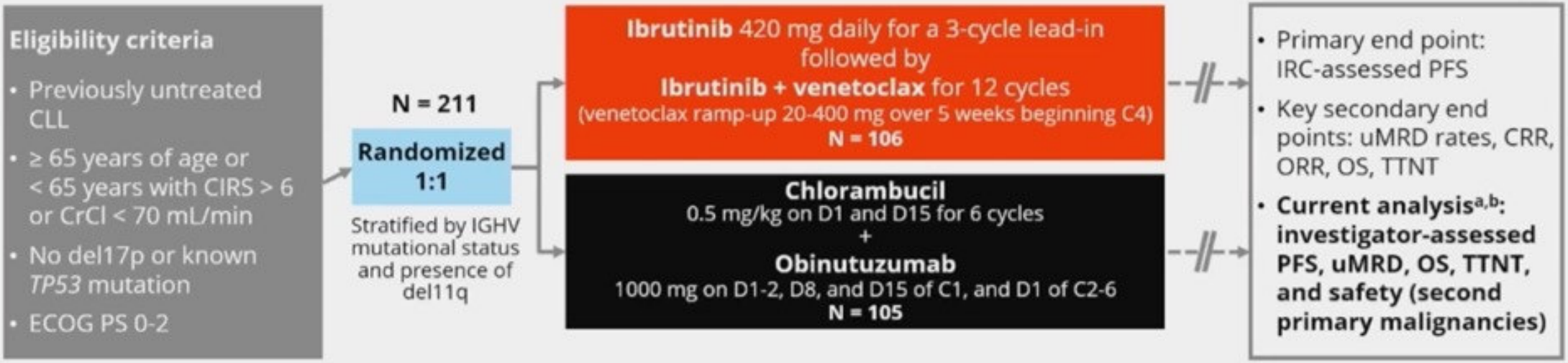
Conclusion



- IV in PFS, OS + Response Rate besser als FCR
- Effekt in allen Subgruppen, aber vor allem IgHV unmutated / TP53 affected
- Toxizität geringer als FCR (aber kardiale Events!)
- Deutlich längere Behandlungszeit im IV-Arm !
- Kein Vergleich zu open end/fixed duration IV !

GLOW: Phase 3 Study (NCT03462719) Evaluating Fixed-Duration Ibr+Ven in Previously Untreated CLL



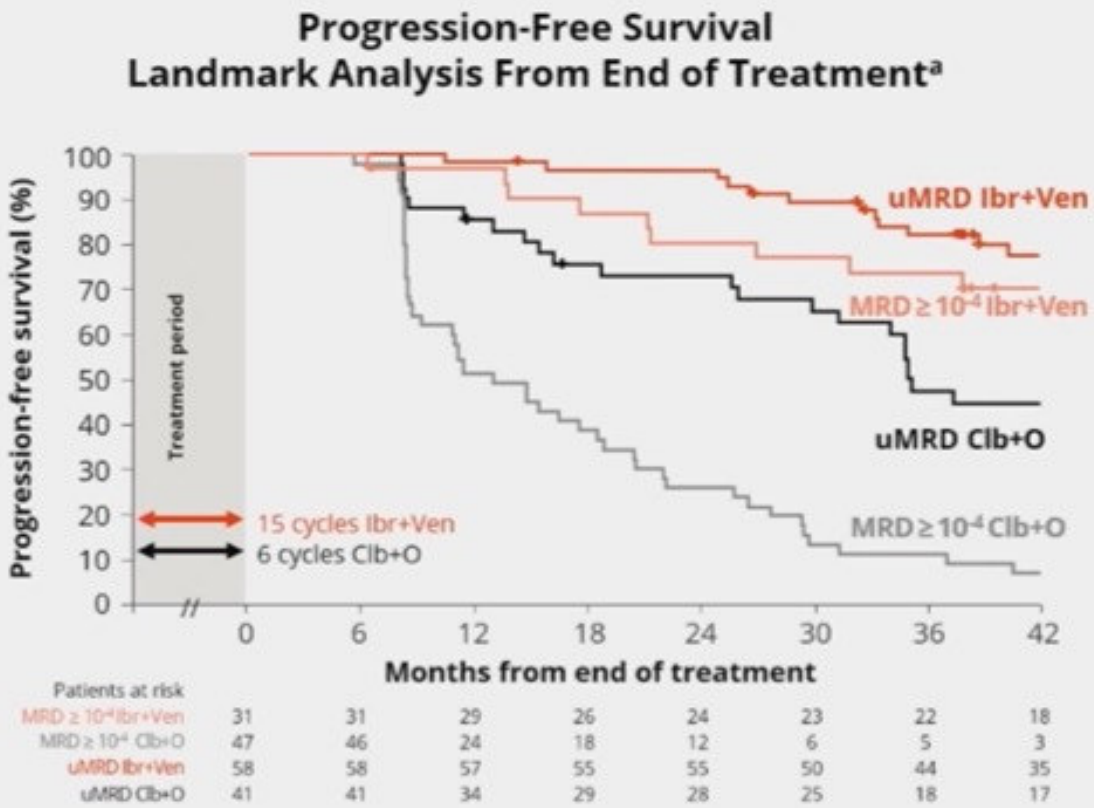
- **Here we present the updated clinical outcomes at a median follow-up of 57.3 months (range, 1.7-65.2)**
- Baseline characteristics (presented previously) were generally balanced between arms and reflective of an elderly and/or comorbid population[1]
- IGHV status at baseline:
  - Ibr+Ven arm: mIGHV 30.2%, uIGHV 63.2%
  - Clb+O arm: mIGHV 33.3%, uIGHV 54.3%

[a]All *p* values are nominal. [b]uMRD in PB by NGS via Clonoseq assay.
C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; CRR, complete response rate; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, Independent review committee; mIGHV, mutated IGHV; NGS, next-generation sequencing; ORR, overall response rate; PB, peripheral blood; uIGHV, unmutated IGHV.

1. Niemann CU, et al. *Lancet Oncol*. 2023;24:1423-1433.

Presented by G. Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

GLOW: At 57 Months of Follow-up, Ibr+Ven Improved PFS Versus Clb+O Regardless of MRD Status at EOT+3

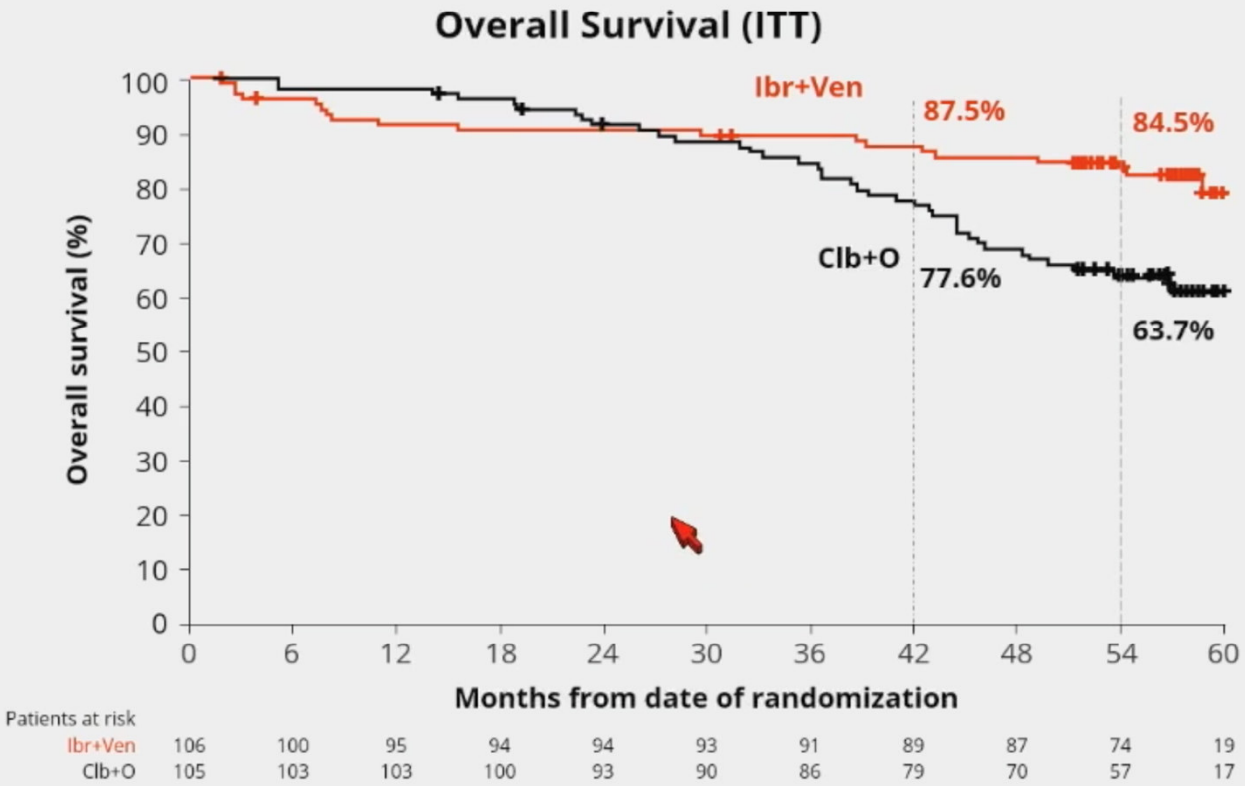


- Estimated PFS rates at 42 months post treatment:
  - **Ibr+Ven:**
    - 78% for patients with uMRD at EOT+3
    - 70% for patients with MRD ≥ 10^{-4} at EOT+3
  - **Clb+O:**
    - 44% for patients with uMRD at EOT+3
    - 6% for patients with MRD ≥ 10^{-4} at EOT+3

*Curves generated from EOT (C15 for Ibr+Ven, C6 for Clb+O).
Investigator-assessed progression-free survival was analyzed. All patients who had MRD outcome at EOT+3 were included in this analysis; uMRD was defined as < 1 CLL cell per 10,000 leukocytes (< 10^{-4}).
MRD, minimal residual disease.

Presented by G. Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

GLOW: Ibr+Ven Remained Associated With Improved Overall Survival at 57 Months of Study Follow-up



- **Ibr+Ven reduced the risk of death by 55%** versus Clb+O
  - HR 0.453 (95% CI, 0.261-0.785); $p = 0.0038$
- Estimated 54-month OS rates:
  - **84.5%** for patients treated with Ibr+Ven
  - **63.7%** for patients treated with Clb+O

p value is nominal.

GLOW: Summary of Deaths

	Ibr+Ven (n = 106)		Clb+O (n = 105)	
Total number of deaths	**19**		**39**	
Reasons for deaths	**On treatment**	**Post randomized treatment[a]**	**On treatment**	**Post randomized treatment[a]**
Infection related[b]	1	3	1	13
Second primary malignancy	1	1	0	7
Cardiac	2[c]	0	0	4
Sudden/unknown	2	3	0	4
Progressive disease	0	1	0	2
Vascular disorders	1	2	0	3
Other	0	2	1	4
Total	**7**	**12**	**2**	**37**

- **At 57 months of follow-up, there were 19 deaths in Ibr+Ven versus 39 in Clb+O arms**
  - 3 deaths in Ibr+Ven and 13 in Clb+O were due to post-treatment infections
  - 2 deaths in Ibr+Ven and 7 in Clb+O were due to second primary malignancies

[a]Either before or after initiation of subsequent antileukemic therapy. [b]Including 2 and 7 deaths due to COVID-19 in the Ibr+Ven and Clb+O arm, respectively. [c]1 patient had 3 causes of death: tachy-brady syndrome, cardiac failure, and pneumonia.

GAIA/CLL13

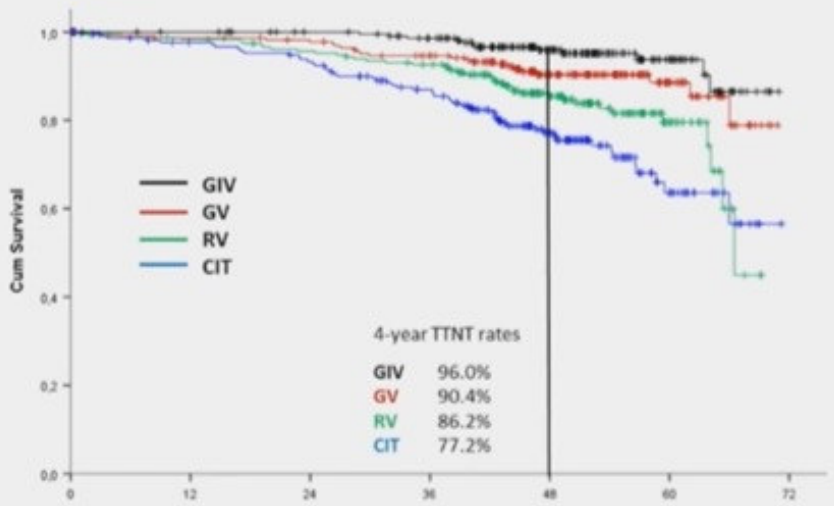
First-line venetoclax combinations in CLL:
4-year follow-up from the phase 3 GAIA/CLL13 trial

Moritz Fürstenau, Matthias Ritgen, Sandra Robrecht, Julia von Tresckow, Can Zhang, Anke Schilhabel, Michael Gregor, Patrick Thornton, Philipp B. Staber, Tamar Tadmor, Vesa Lindström, Gunnar Juliusson, Ann Janssens, Mark David Levin, Caspar da Cunha-Bang, Christof Schneider, Neta Goldschmidt, Elisabeth Vandenberghe, Davide Rossi, Rudolf Benz, Daniel Heintel, Christian B Poulsen, Ilse Christiansen, Henrik Frederiksen, Lisbeth Enggaard, Eduardus FM Posthuma, Djamila E Issa, Hein PJ Visser, Mar Bellido, Nadine Kutsch, Jan Dürig, Alexander Stehle, Matthias Vöhringer, Sebastian Böttcher, Clemens Schulte, Florian Simon, Maria Fink, Kirsten Fischer, Emily Holmes, Karl-Anton Kreuzer, Matthias Ritgen, Monika Brüggemann, Eugen Tausch, Stephan Stilgenbauer, Michael Hallek, Arnon P Kater, Carsten U Niemann, Barbara Eichhorst

Efficacy – TTNT

Oganatuzumab

Time to next treatment



Patients at risk

CIT	229	205	195	170	96	25
RV	237	229	220	210	127	30
GV	229	224	219	205	125	38
GIV	231	228	220	208	136	46

TTNT comparisons

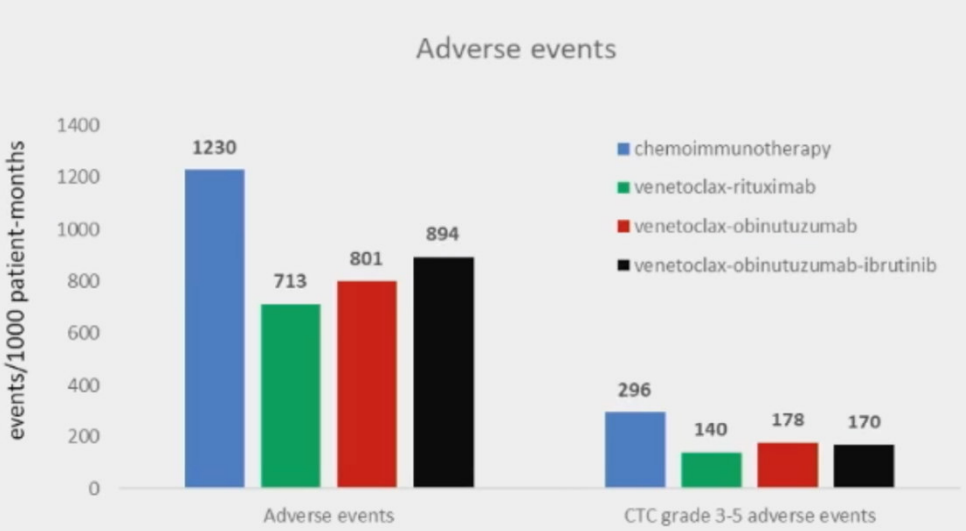
GIV *vs* CIT: HR 0.17, 97.5%CI: 0.09-0.36, ***p<0.001***
GIV *vs* RV: HR 0.27, 97.5%CI: 0.13-0.57, ***p<0.001***
GIV *vs* GV: HR 0.50, 97.5%CI: 0.23-1.12, p=0.049

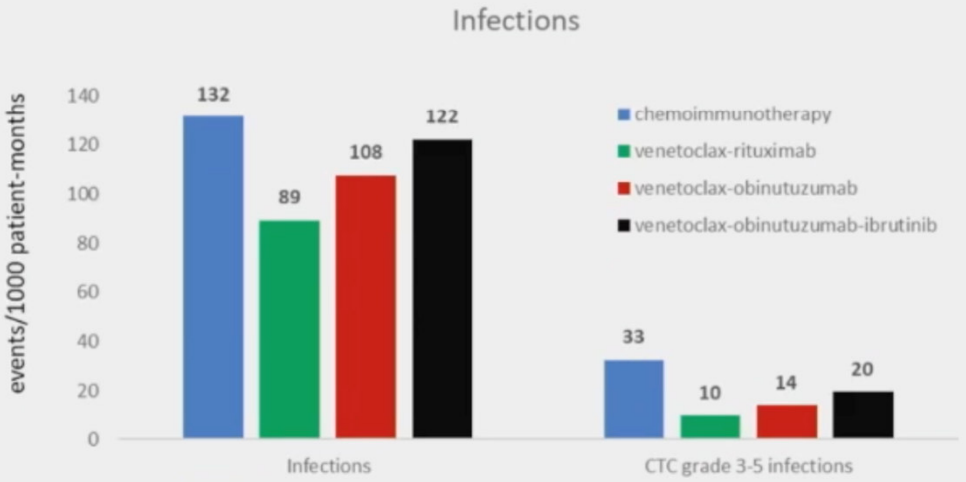
GV *vs* CIT: HR 0.34, 97.5%CI: 0.20-0.60, ***p<0.001***
GV *vs* RV: HR 0.54, 97.5%CI: 0.30-0.97, ***p=0.017***

RV *vs* CIT: HR 0.62, 97.5%CI: 0.39-1.00, ***p=0.023***

CIT = FCR < 65, BR ≥ 65
RV = Venetoclax + Rituximab
GV = Venetoclax + Obinutuzumab
GIV = Venetoclax + Ibrutinib + Obinutuzumab

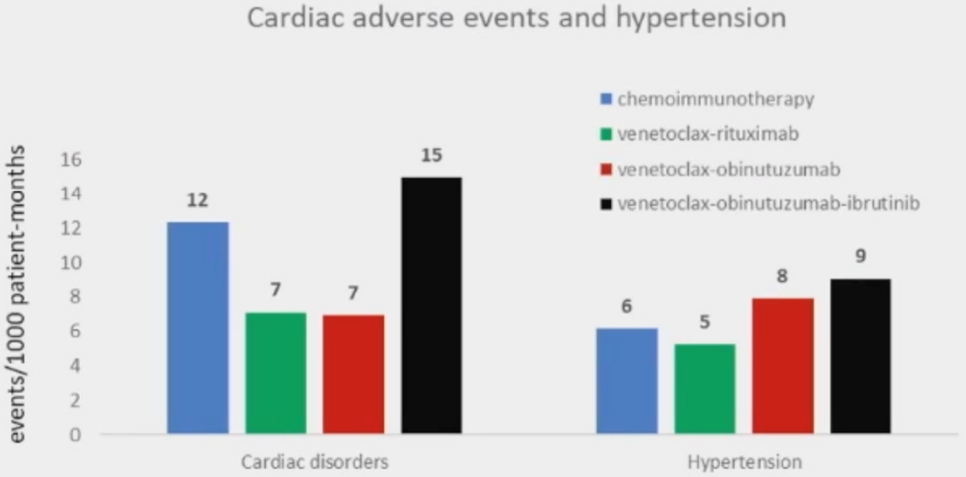
Safety





Exposure-adjusted incidence rates

- Events per 1000 patient-months **based on the treatment period**
- Treatment period = **start of treatment until the end of treatment + 84 days** or until start of first subsequent treatment whichever occurred first



Presentation #636

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of ELEVATE-TN

Jeff P. Sharman,[1] Miklos Egyed,[2] Wojciech Jurczak,[3] Alan Skarbnik,[4] Krish Patel,[5] Ian W. Flinn,[6] Manali Kamdar,[7] Talha Munir,[8] Renata Walewska,[9] Marie Hughes,[10] Laura Maria Fogliatto,[11] Yair Herishanu,[12] Versha Banerji,[13] George Follows,[14] Patricia Walker,[15] Karin Karlsson,[16] Paolo Ghia,[17] Ann Janssens,[18] Florence Cymbalista,[19] John C. Byrd,[20] Emmanuelle Ferrant,[21] Alessandra Ferrajoli,[22] William G. Wierda,[23] Veerendra Munugalavadla,[21] Catherine Wangui Wachira,[24] Chuan-Chuan Wun,[21] Jennifer A. Woyach[20]

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Presented at the American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023

ELEVATE-TN study design

TN CLL (N=535)

Key inclusion criteria

- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria[6]
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- del(17p), yes vs no
- ECOG PS 0–1 vs 2
- Geographic region

RANDOMIZE 1:1:1

- $A^a + O^b$
- A^a
- $O^b + Clb^b$

Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

***Crossover** from O+Clb to A was allowed after IRC-confirmed progression*

Note: After interim analysis, PFS assessments were by investigator only.[3] All analyses are ad-hoc and *P*-values are descriptive.

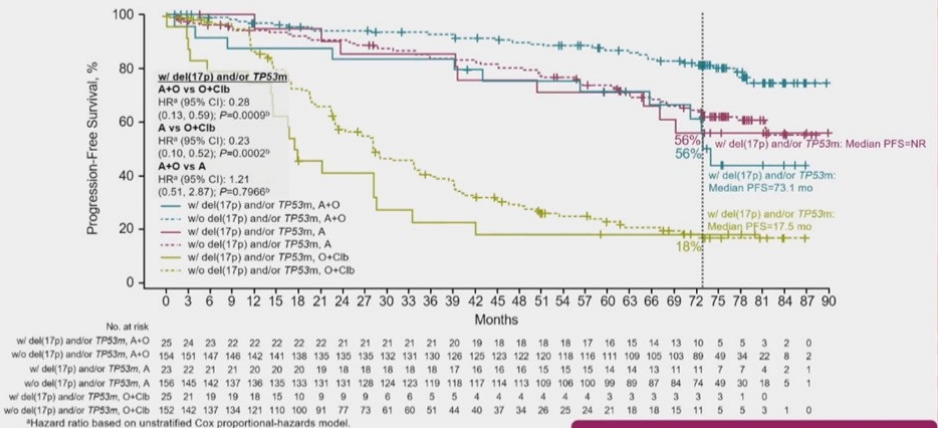
NCT02475681. Data cutoff: March 3, 2023. Patients were enrolled between September 2015 and February 2017.

[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID.

[b]Treatments were fixed duration and administered for 6 cycles.

ELEVATE TN

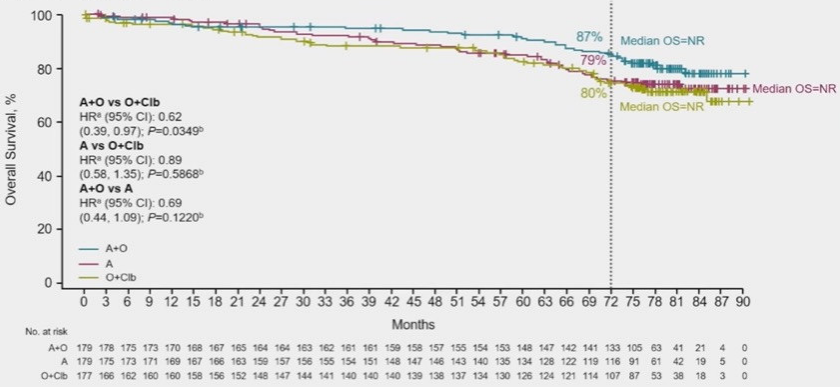
Impact of del(17p) and/or TP53m by treatment arm



[a]Hazard ratio based on unstratified Cox proportional-hazards model.
[b]*P*-value based on unstratified log-rank test.

ELEVATE-TN 6 Year Update

OS was not reached in any treatment arm and was longer with A+O vs O+Clb



[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

ELEVATE-TN 6 Year Update

EXTENDED FOLLOW-UP OF ALPINE RANDOMIZED PHASE 3 STUDY CONFIRMS SUSTAINED SUPERIOR PROGRESSION-FREE SURVIVAL OF ZANUBRUTINIB VERSUS IBRUTINIB FOR TREATMENT OF RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA (R/R CLL/SLL)

Brown, JR et al. Oral Presentation at ASH 2023; abstract number 202

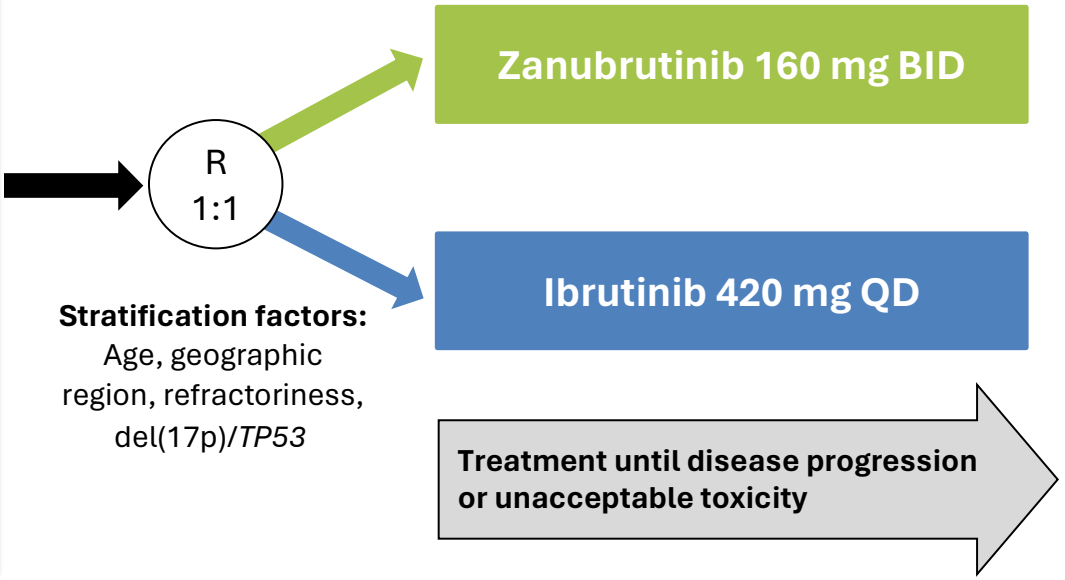
R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

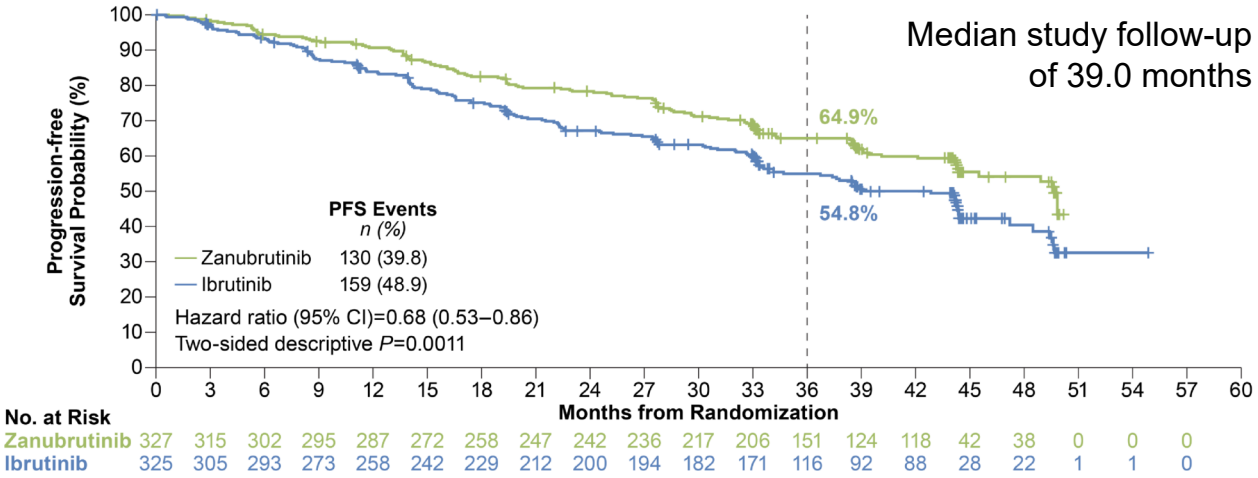
- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- Requires treatment per iwCLL

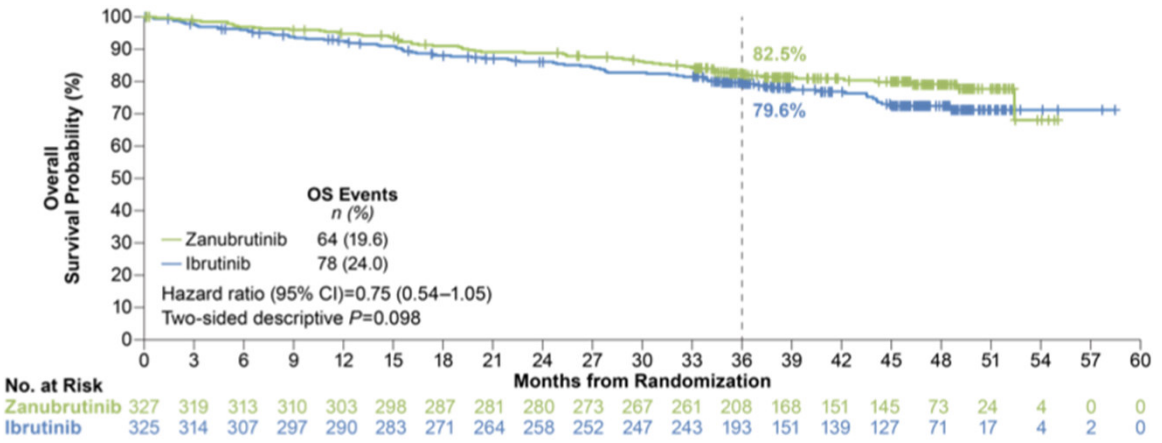
Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



ALPINE: PFS and OS At Extended Follow-up





Data cutoff: 15 Sep 2023.

CI=confidence interval, PFS=progression-free survival.

Brown, JR et al. Oral Presentation at ASH 2023; abstract number 202.

Adverse Events of Special Interest[a] Occurring in ≥2 Patients

ALPINE – ePFS

	Zanubrutinib (n=324)		Ibrutinib (n=324)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infection	264 (81.5)	115 (35.5)	260 (80.2)	111 (34.3)
Opportunistic Infections	8 (2.5)	6 (1.9)	13 (4.0)	5 (1.5)
COVID-19 Related[b]	**145 (44.8)**	**56 (17.3)**	**105 (32.4)**	**38 (11.7)**
Bleeding	142 (43.8)	12 (3.7)	144 (44.4)	13 (4.0)
Major Hemorrhage	13 (4.0)	12 (3.7)	16 (4.9)	13 (4.0)
Hypertension	**86 (26.5)**	**53 (16.4)**	**80 (24.7)**	**47 (14.5)**
Atrial fibrillation/flutter	**22 (6.8)**	**10 (3.1)**	**53 (16.4)**	**16 (4.9)**
Anemia	53 (16.4)	7 (2.2)	59 (18.2)	11 (3.4)
Neutropenia	**100 (30.9)**	**72 (22.2)**	**94 (29.0)**	**72 (22.2)**
Thrombocytopenia	43 (13.3)	12 (3.7)	53 (16.4)	19 (5.9)
Second primary malignancies	46 (14.2)	26 (8.0)	52 (16.0)	19 (5.9)

Data cutoff: 15 Sep 2023
aPooled MedDRA preferred terms. bIncludes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.
Brown, JR et al. Oral Presentation at ASH 2023; abstract number 202.

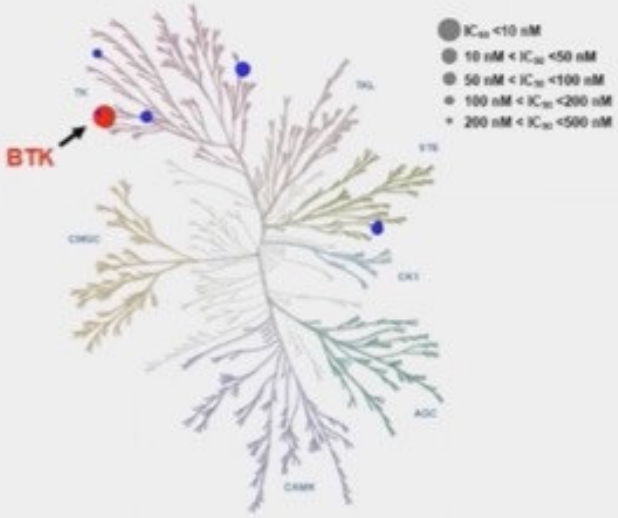
Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-Up and Subgroup Analysis with/without Prior BCL2i from the Phase 1/2 BRUIN Study

Jennifer A. Woyach[1], Jennifer R. Brown[2], Paolo Ghia[3], Lindsey E. Roeker[4], Krish Patel[5], Toby A. Eyre[6], Talha Munir[7], Ewa Lech-Maranda[8], Nicole Lamanna[9], Constantine S. Tam[10], John F. Seymour[11], Benoit Tessoulin[12], Nirav N. Shah[13], Chaitra Ujjani[14], Bita Fahkri[15], Catherine C. Coombs[16], Ian Flinn[17], Manish R. Patel[18], Sunita D. Nasta[19], Jonathon B. Cohen[20], Alvaro J. Alencar[21], Chan Y. Cheah[22], Shuo Ma[23], Joanna M. Rhodes[24], Deepa Jagadeesh[25], Pier Luigi Zinzani[26], Anders Osterborg[27], Koji Izutsu[28], Donald E. Tsai[29], Paolo Abada[29], Minna Balbas[29], Jian Li[29], Amy S. Ruppert[30], Wojciech Jurczak[31], William G. Wierda[32]

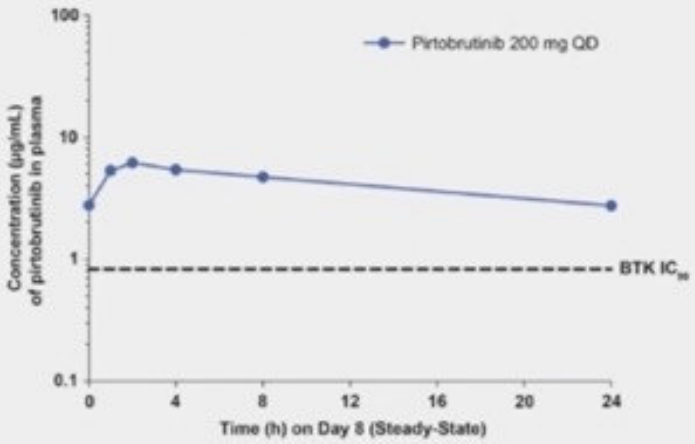
[1]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [2]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; [3]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [4]Memorial Sloan Kettering Cancer Center NY; [5]Swedish Cancer Institute, Seattle, WA; [6]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, UK; [7]Department of Haematology, St. James's University Hospital, Leeds, UK; [8]Institute of Hematology and Transfusion Medicine, Poland; [9]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; [10]Alfred Health and Monash University, Melbourne, Victoria, Australia; [11]Royal Melbourne Hospital, Peter MacCallum Cancer Centre and University of Melbourne, Victoria, Australia; [12]Haematology Department, University Hospital, Nantes, France; [13]Medical College of Wisconsin, Milwaukee, WI; [14]Fred Hutchinson Cancer Research Center, Seattle, WA; [15]Division of Hematology at Stanford University School of Medicine, Stanford, CA; [16]University of California Irvine, Irvine, CA; [17]Sarah Cannon Research Institute, Nashville, TN; [18]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; [19]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [20]Winship Cancer Institute, Emory University, Atlanta, GA; [21]Sylvester Comprehensive Cancer, Miami, FL; [22]Linear Clinical Research and Sir Charles Gairdner Hospital, West Australia, Australia; [23]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; [24]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [25]Cleveland Clinic, Cleveland, OH; [26]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [27]Karolinska Institute and Karolinska University Hospital, Stockholm, SE; [28]National Cancer Center Hospital, JP; [29]Loxo@Lilly, Indianapolis, IN; [30]Eli Lilly and Company, Indianapolis, IN; [31]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [32]MD Anderson Cancer Center, Houston, TX.

Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

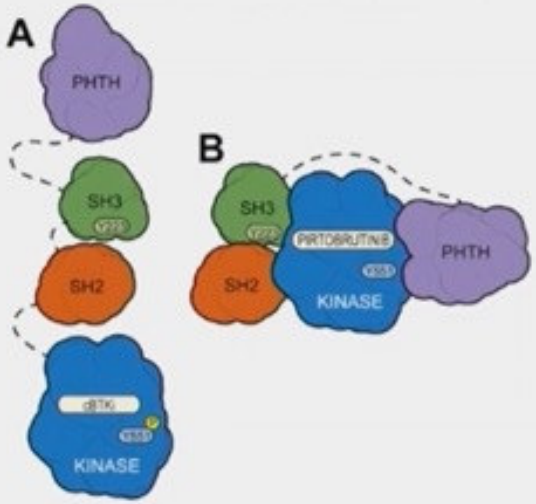
Highly selective for BTK[5,6]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



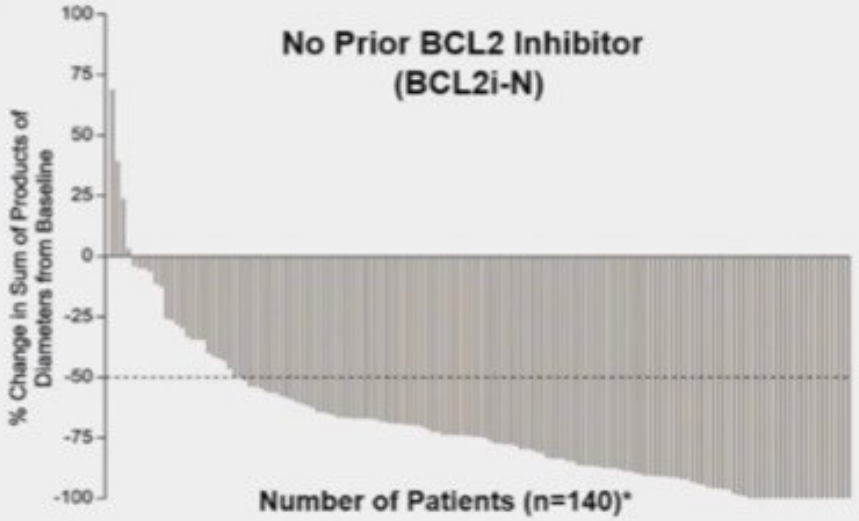
Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[7]

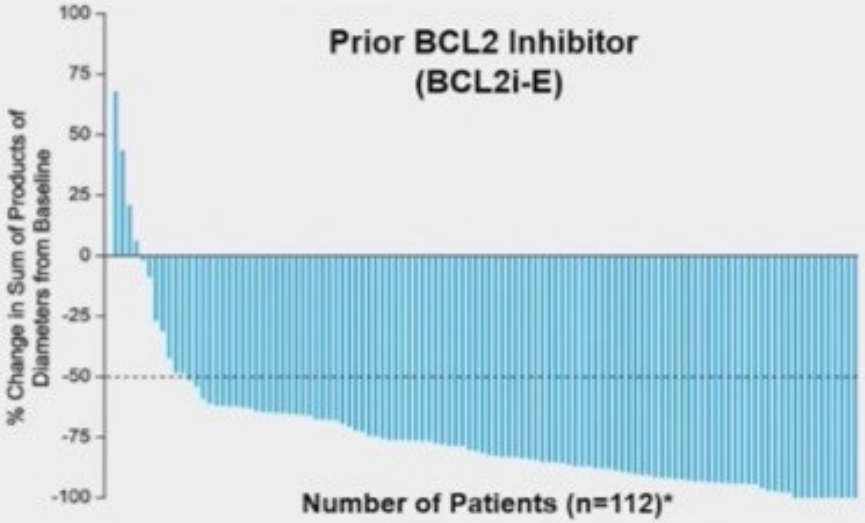


- Inhibits both WT and C481-mutant BTK with equal low nM potency[7]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[7]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[7]

[5]Mato et al, *Lancet* 2021; 397: 892–901. [6]Brandhuber et al. *Clin Lymphoma Myeloma Leuk* 2018; 18(Suppl.1):S216. [7]Gomez et al. *Blood* 2023; 142(1):62-72.

Pirtobrutinib Efficacy in Patients who Received Prior cBTKi, with or without Prior BCL2i





BCL2i-N	(n=154)[b]
ORR[a] incl. PR-L, % (95% CI)	83.1 (76.2-88.7)
Best Response, n (%)	
CR	
nPR	
PR	
PR-L	

BCL2i-E	(n=128)[c]
ORR[a] incl. PR-L, % (95% CI)	79.7 (71.7-86.3)
Best Response, n (%)	
	0 (0)
	0 (0)
	8 (68.8)
	4 (10.9)

Data of patients with baseline and at least one evaluabl
response assessment, or lack of adequate imaging in f
are included in the denominators. Response status per

by CT at baseline, discontinuation prior to first
%) with a best response of not evaluable (NE)

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FDA grants accelerated approval to pirtobrutinib for chronic lymphocytic leukemia and small lymphocytic lymphoma

Follikuläre Lymphome

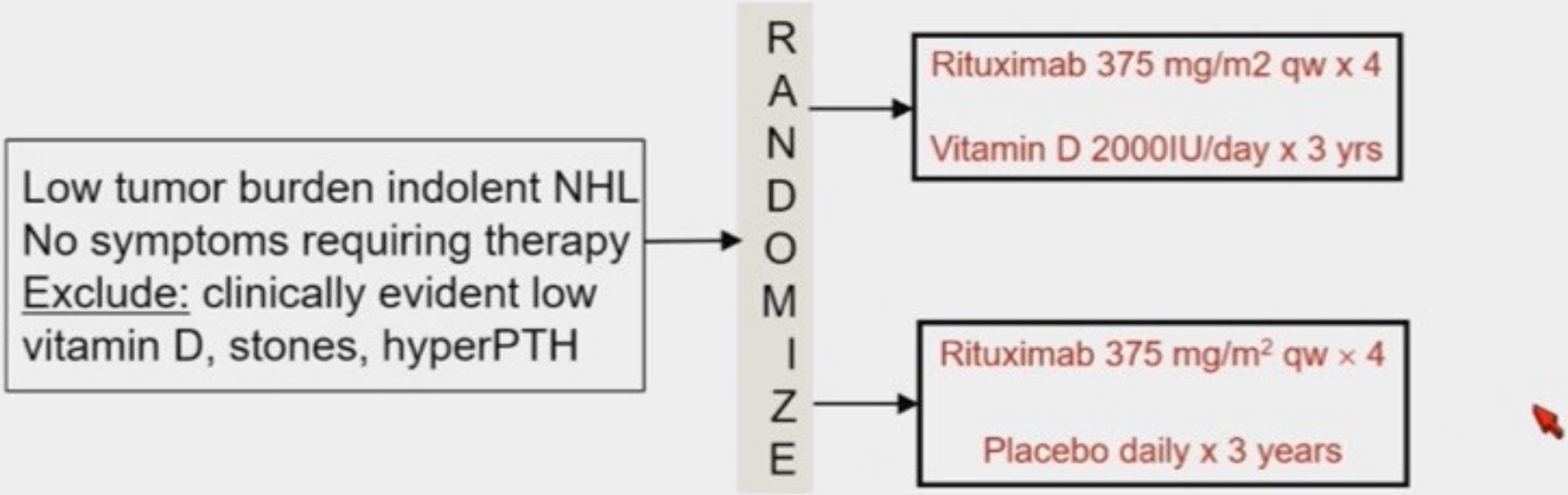
Vitamin D und Rituximab?

Was im Rezidiv?

ILyAD: A Phase III Double Blind, Randomized Trial Evaluating Vitamin D (Cholecalciferol) in Patients with Low Tumor-Burden Indolent Non-Hodgkin Lymphoma Treated with Rituximab Therapy

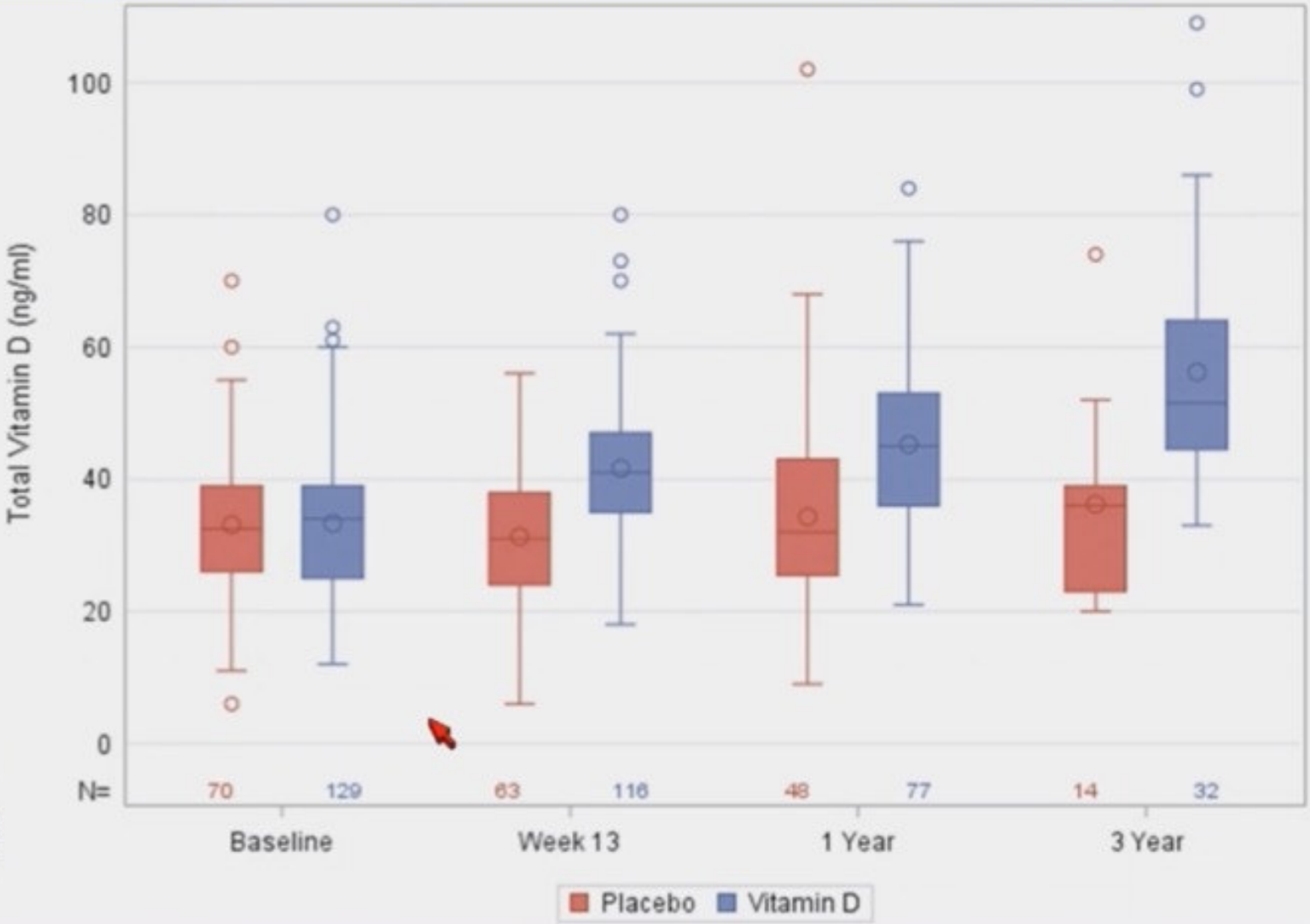
Jonathan W. Friedberg, Michael T. Brady, Myla S. Strawderman, Brad S. Kahl, Izidore S. Lossos, Jonathon B. Cohen, Patrick M. Reagan, Carla Casulo, Barbara L. Averill, Brian K. Link, Paul M. Barr, John P. Leonard, John M. Ashton, Derick R. Peterson, Loretta J. Nastoupil

ILyAD trial: Randomized, placebo controlled, double blind study for patients with indolent NHL



UR MEDICINE
WILMOT

ILyAD Blinded Vitamin D levels over time



UR MEDICINE

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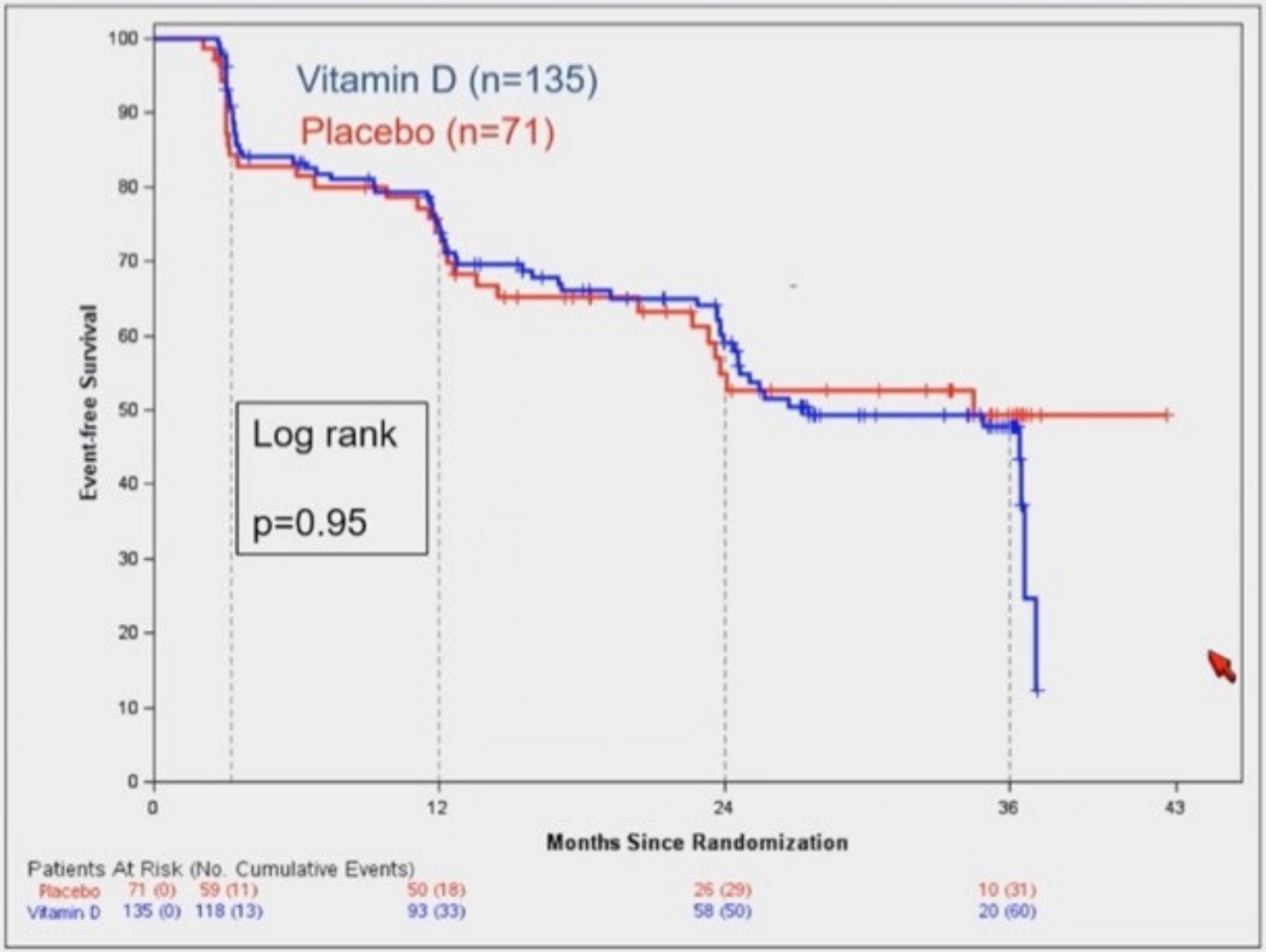
ILyAD Primary Analysis: Event-free survival by arm



UR MEDICINE

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Mosunetuzumab Monotherapy Continues to Demonstrate Durable Responses in Patients with Relapsed and/or Refractory Follicular Lymphoma after ≥2 Prior Therapies: 3-Year Follow-Up from a Pivotal Phase II Study

Stephen J. Schuster,[1] Laurie H. Sehn,[2] Nancy L. Bartlett,[3] Matthew Matasar,[4] Sarit Assouline,[5] Pratyush Giri,[6] John Kuruvilla,[7] Mazyar Shadman,[8] Chan Y. Cheah,[9] Sascha Dietrich,[10] Keith Fay,[11] Matthew Ku,[12] Loretta Nastoupil,[13] Michael C. Wei,[14] Shen Yin,[14] Iris To,[14] Samuel Tracy,[14] Antonia Kwan,[14] Elicia Penuel,[14] L. Elizabeth Budde[15]

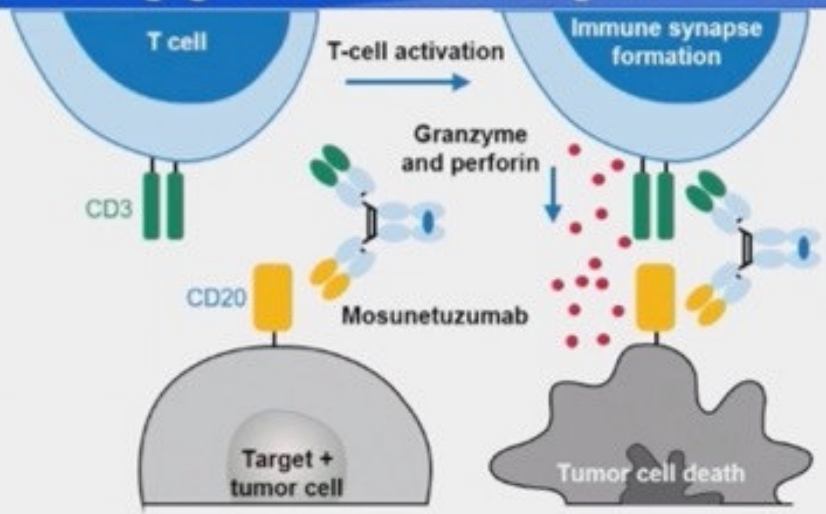
[1]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [2]BC Cancer Centre for Lymphoid Cancer and The University of British Columbia, Vancouver, BC, Canada; [3]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA; [4]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [5]Jewish General Hospital, Montreal, QC, Canada; [6]Royal Adelaide Hospital, Adelaide, Australia; [7]Princess Margaret Cancer Centre, Toronto, ON, Canada; [8]Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA, USA; [9]Linear Clinical Research, Sir Charles Gairdner Hospital, Nedlands, Australia and The University of Western Australia, Perth, Australia; [10]Universitat Heidelberg, Heidelberg, Germany; [11]St Vincent's Hospital and Royal North Shore Hospital, Sydney, Australia; [12]St Vincent's Hospital, University of Melbourne, Melbourne, Australia; [13]MD Anderson Cancer Center, Houston, TX, USA; [14]Genentech, Inc., South San Francisco, CA, USA; [15]City of Hope National Medical Center, Duarte, CA, USA

Presented at the 65th ASH Annual Meeting | December 9–12, 2023

Background

- **Mosunetuzumab** has been granted conditional marketing authorization by the EMA and accelerated approval by the US FDA for the treatment of **R/R FL** after ≥2 prior systemic therapies[1,2]
- Previous analysis of the pivotal Phase II study at a median follow-up of 18.3 months demonstrated:
  - **High response rates with durable responses** in heavily pre-treated patients with R/R FL[3]
  - **Off-the-shelf, fixed-duration** treatment that can be administered in the **outpatient** setting[3]

Mosunetuzumab: CD20×CD3 T-cell-engaging bispecific antibody that redirects T cells to engage and eliminate malignant B cells[4,5]



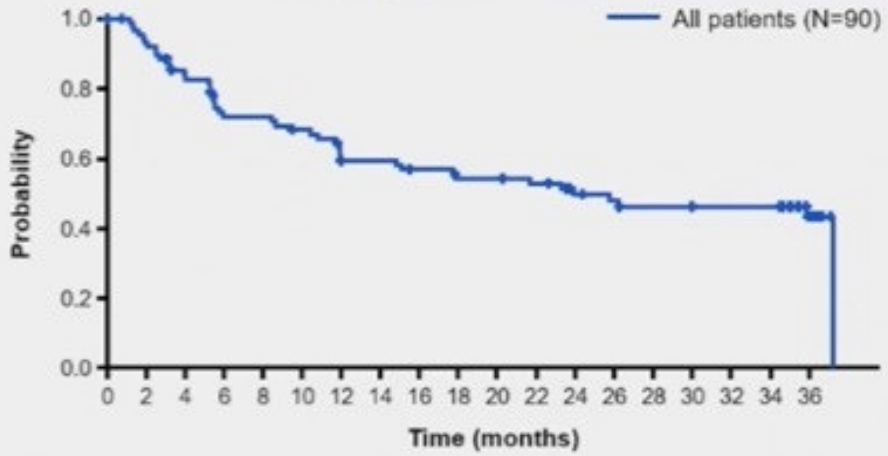
Aim: To present updated results from the Phase II study after a median time on study of 37.4 months (data cut-off: May 2, 2023)

EMA, European Medicines Agency; FDA, Food and Drug Administration; FL, follicular lymphoma; R/R, relapsed and/or refractory; US, United States.

1. Lunsumio SmPC: https://www.ema.europa.eu/en/medicines/human/EPAR/lunsumio;
2. Lunsumio US PI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761263s000lbl.pdf;
3. Budde LE, et al. Lancet Oncol 2022;23:1055–65; 4. Sun LL, et al. Sci Transl Med 2015;7:287ra70;
5. Hernandez G, et al. ASH 2019; poster presentation (P-1585).

PFS and OS; median follow-up >36 months

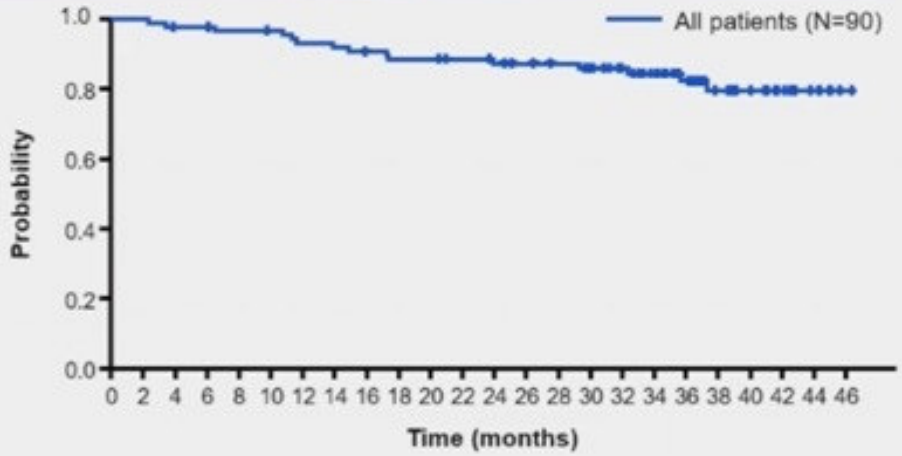
PFS



Patients at risk 90 81 72 60 59 55 47 46 43 40 40 38 30 27 25 25 24 24 13

	N=90
Median PFS, months (95% CI)	**24.0** (12.0–NE)
36-month PFS, months (95% CI)	**43.2%** (31.3–55.2)

OS



Patients at risk 90 89 87 86 85 84 81 80 78 76 76 74 72 70 68 62 56 51 39 26 21 14 8 1

	N=90
Median OS, months (95% CI)	**NR** (NE–NE)
36-month OS, months (95% CI)	**82.4%** (73.8–91.0)

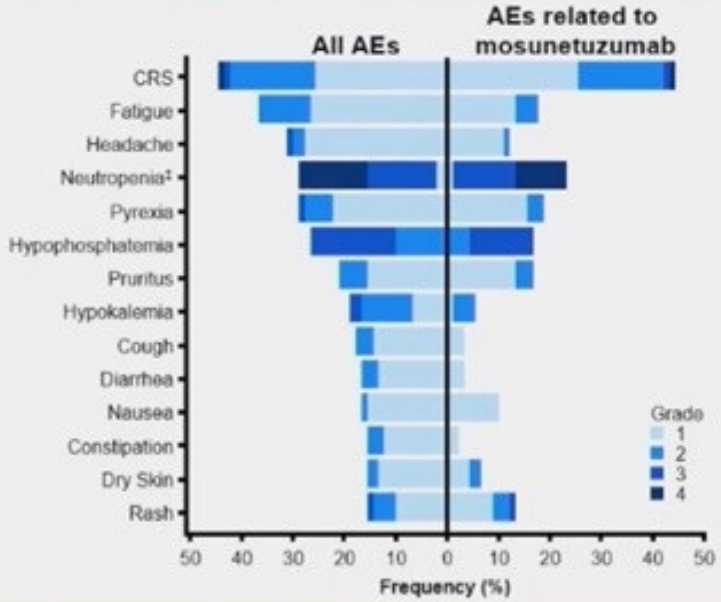
Robust and stable progression-free and overall survival rates at 3 years

OS, overall survival; PFS, progression-free survival.

Safety profile

Adverse events (AEs), n	N=90
AE	90 (100%)
Mosunetuzumab-related	83 (92%)
Grade 3/4 AE	63 (70%)
Mosunetuzumab-related	46 (51%)
Serious AE	42 (47%)
Mosunetuzumab-related	30 (33%)
Grade 5 (fatal) AE	2 (2%)*
Mosunetuzumab-related	0
AE leading to treatment discontinuation	4 (4%)†
Mosunetuzumab-related	2 (2%)

AEs (≥15%) by grade and relationship with mosunetuzumab



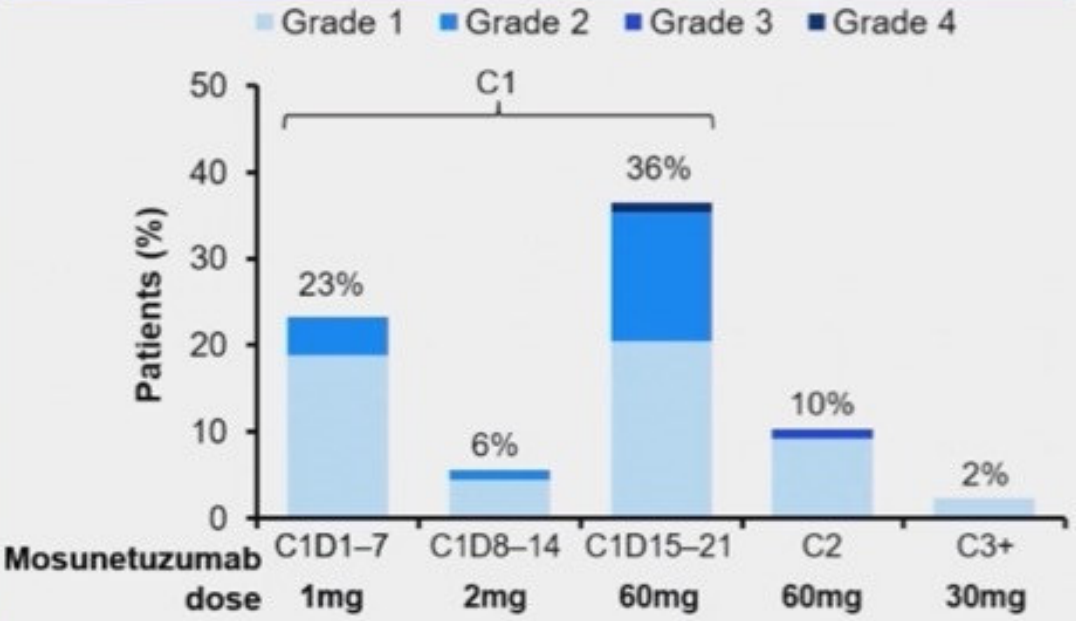
No new AEs were reported since the previous data cut-off§; incidence of AEs and serious AEs remains unchanged with this extended follow-up

*Malignant neoplasm progression (n=1, onset study D94) and unexplained death (n=1, onset study D60). †Mosunetuzumab related: CRS (n=2, onset study D15 and D22 [both recovered]); mosunetuzumab unrelated: Epstein-Barr viremia (n=1, onset study D11, recovered) and Hodgkin's disease (n=1, onset study D193, not recovered). ‡Preferred terms neutropenia and neutrophil count decreased are combined. §One non-serious, unrelated AE was reported outside of the AE-reporting window and was subsequently inactivated.

CRS summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade), n	40 (44%)
Grade 1	23 (26%)
Grade 2	15 (17%)
Grade 3	1 (1%)
Grade 4	1 (1%)
Median time to CRS onset, hours (range)	
C1D1	5 (1–24)
C1D15	27 (0–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management, n	10 (11%)*
Tocilizumab for CRS management, n	7 (8%)*
Events resolved	100%

CRS by cycle and grade



CRS was predominantly low-grade and occurred during C1
All CRS events resolved; no new events have been reported in this extended follow-up

Data cut-off: August 27, 2021, as no new CRS events occurred subsequently.*Four patients received both corticosteroids and tocilizumab for CRS management. ASTCT, American Society for Transplantation and Cellular Therapy.

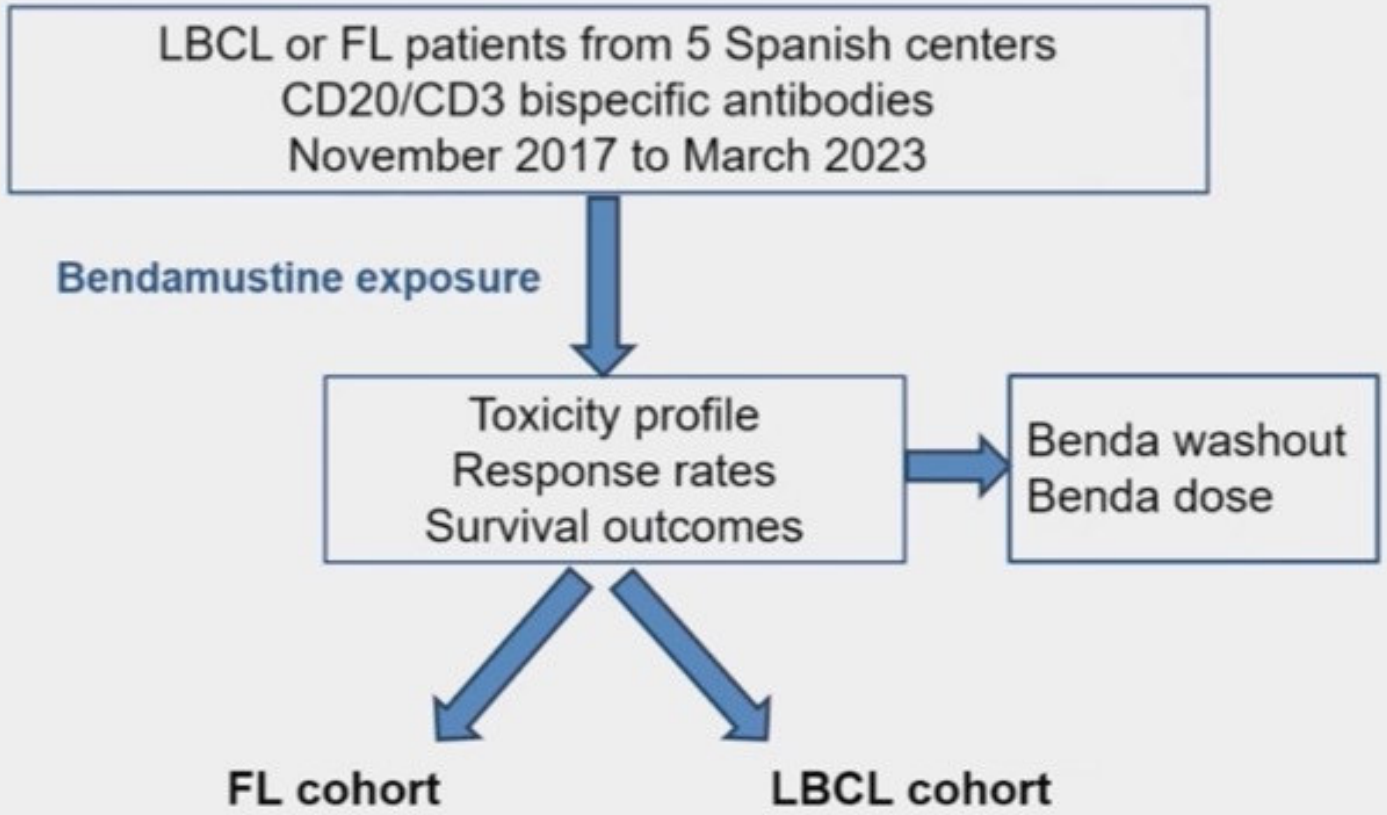
1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

Impact of Prior Bendamustine Exposure on Bispecific Antibody Treatment Outcomes for Patients with B-Cell Lymphoma

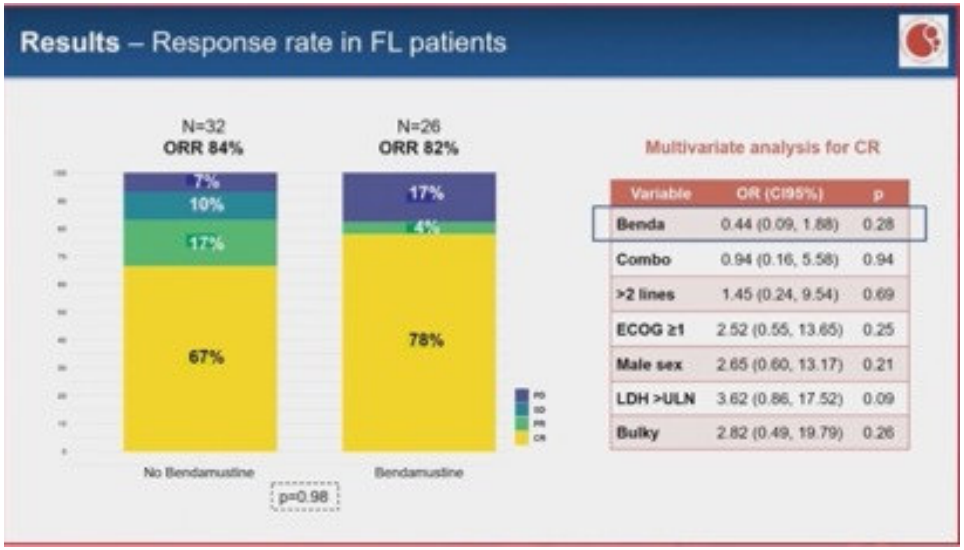
Gloria Iacoboni, Angel Serna, Victor Navarro, Ana Jimenez-Ubieto, Evelyn Valencia, Alberto Lopez-Garcia, Itziar Carro, Sergi Camarillas, Josu Iraola-Truchuelo, Lucia Medina, Gala Vega, Maria Pozas, Anna Sureda, Raúl Córdoba, Miguel Canales, Francesc Bosch, Pere Barba* and Pau Abrisqueta*

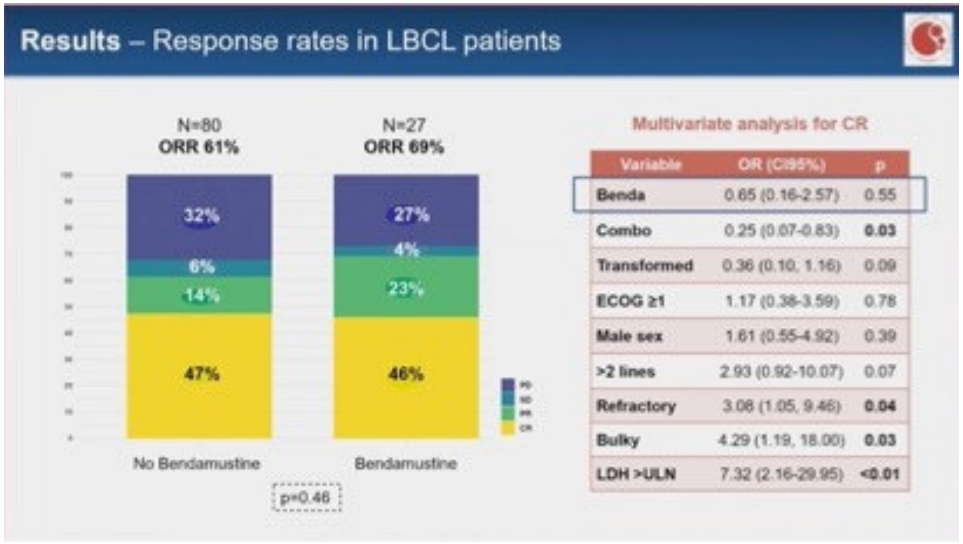
* Contributed equally

Methods


LBCL or FL patients from 5 Spanish centers
CD20/CD3 bispecific antibodies
November 2017 to March 2023
Bendamustine exposure
Toxicity profile
Response rates
Survival outcomes
Benda washout
Benda dose
FL cohort
LBCL cohort

No impact on response





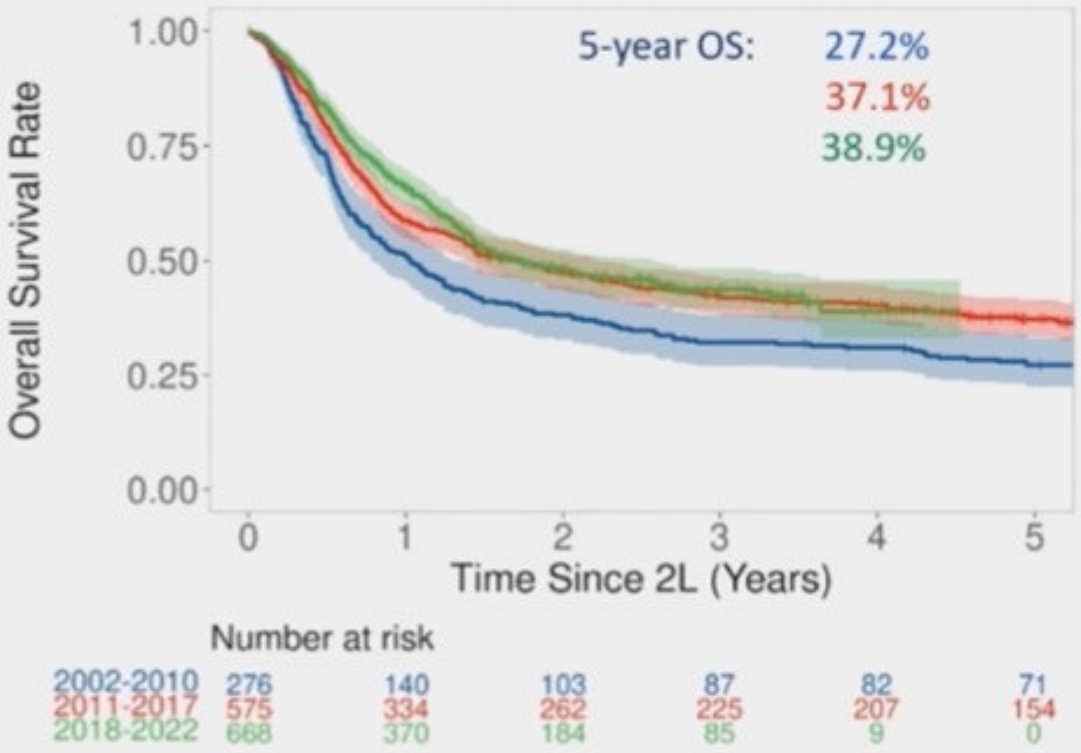
Aggressive B-NHL

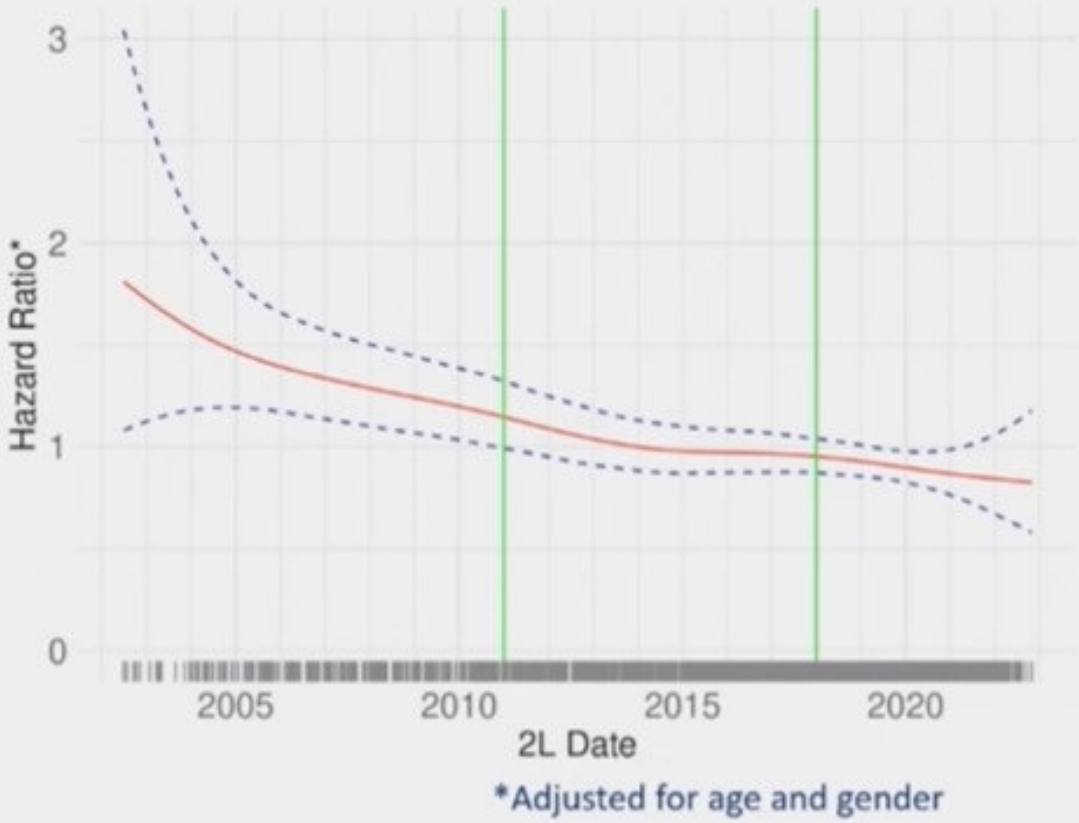
2. Linie: werden wir besser?

LEO Consortium for Real World Evidence (CReWE): Outcomes After Second-Line Therapy in Large B-Cell Lymphoma by Treatment Era

Jean L Koff, Melissa C Larson, Peter Martin, Jonathon B Cohen, Sabarish R Ayyappan, Brian K Link, Thomas M Habermann, Yucai Wang, Arushi Khurana, Grzegorz S Nowakowski, Dai Chihara, Sara Haddadi, Izidore S Lossos, Carla Casulo, Brad S Kahl, Amy A Ayers, Tanner W Reicks, Christopher R Flowers, James R Cerhan, Matthew J Maurer, Loretta J Nastoupil

Overall survival (OS) after 2L by treatment era





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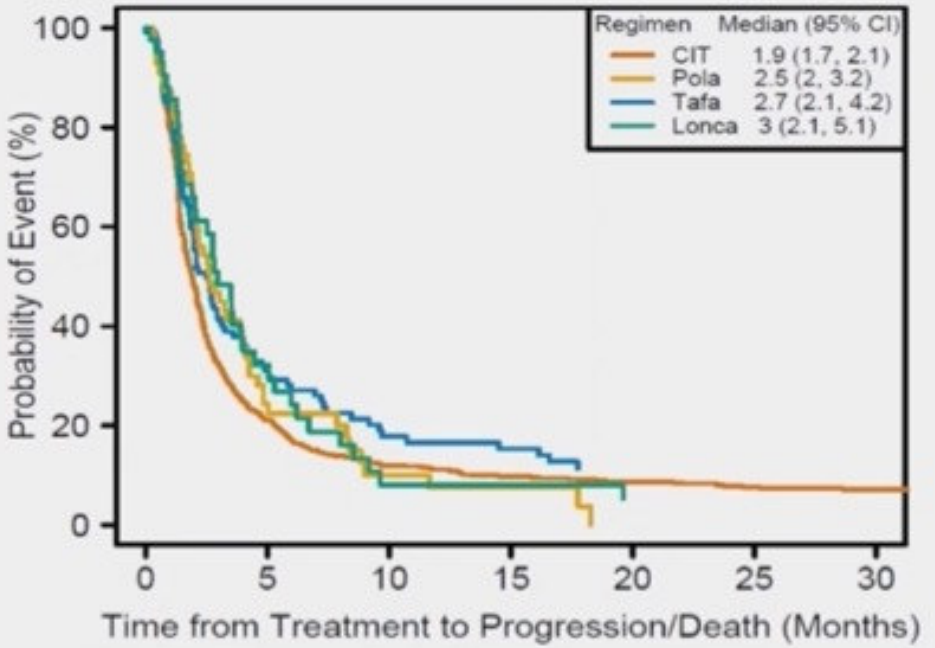
Effectiveness of Chemo-Immunotherapy (CIT) and Novel Therapies in Second or Later Line of Therapy (2L+) for Patients with Relapsed/Refractory (R/R) Aggressive Large B-Cell Lymphoma (LBCL)

LJ Nastoupil, CR Andersen, A Ayers, Y Wang, TM Habermann, D Chihara, BS Kahl, BK Link, JB Cohen, P Martin, IS Lossos, C Casulo, R Lin, Z Li, MC Larson, MJ Maurer, L Huynh, C Gao, R Ramasubramanian, MS Duh, A Mutebi, T Wang, M Jun, A Wang, R Kamalakar, A Kalsekar, JR Cerhan, CR Flowers

Progression Free Survival (PFS)

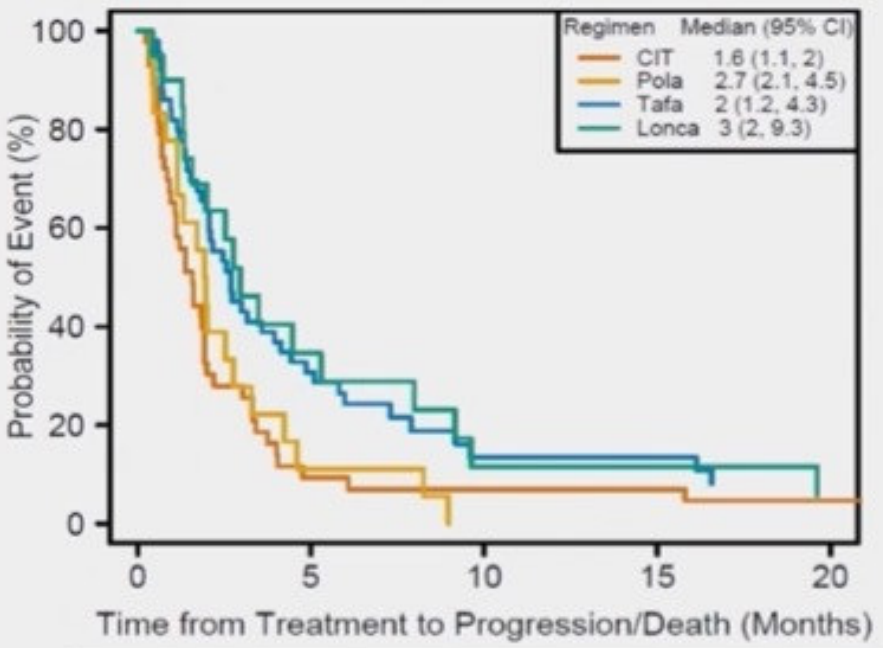
Overall



Number at Risk

CIT	653	137	75	57	49	42	38
Pola	116	33	16	13	NR	NR	NR
Tafa	55	15	5	4	NR	NR	NR
Lonca	42	13	4	4	NR	NR	NR

Prior CAR T



Number at Risk

CIT	43	5	4	4	3
Pola	50	16	6	6	NR
Tafa	18	3	NR	NR	NR
Lonca	20	7	3	3	NR

Abbreviation: CAR, chimeric antigen receptor; CI, confidence interval; CIT, chemo-immunotherapy; NR, not reached

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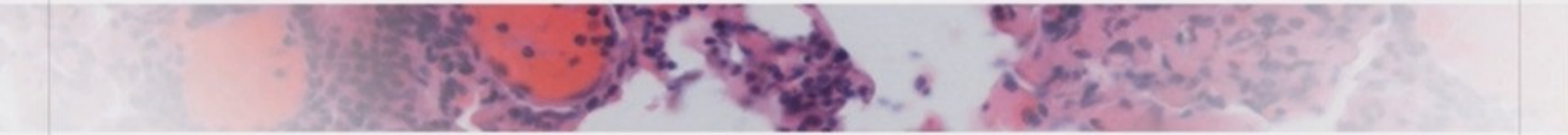
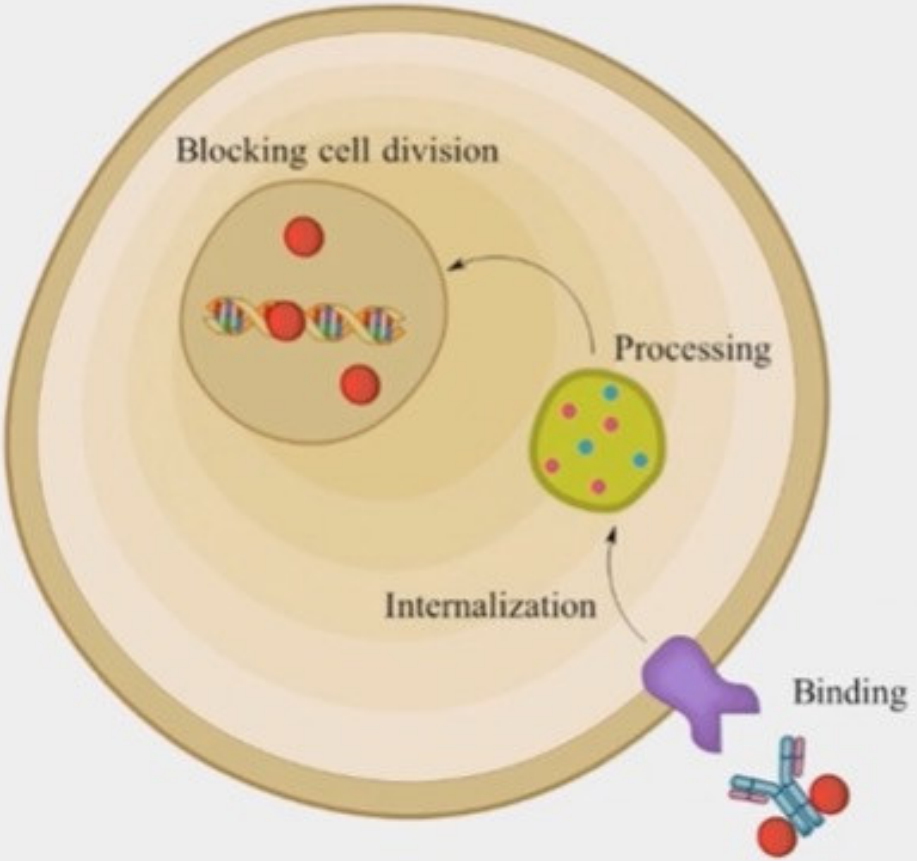


Loncastuximab in High-Risk and Heavily-Pretreated Relapsed/Refractory Diffuse Large B-Cell Lymphoma: A Real World Analysis from 21 US Centers

Emily C Ayers*, Viktoriya Zelikson*, Ashwath Gurumurthi, Yazeed Sawalha, Kaitlin Annunzio, Aditi Saha, Ning Dong, David Qualls, Behzad Amoozgar, Brad Kahl, John Baird, Pavan Challa, Jennifer Santos, Steven Bair, Scott Huntington, Mayur Narkhede, Shuning Li, Zachary Frosch, Carrie Ho, Stephen D Smith, Allison Winter, Daniel Landsburg, Fateeha Furqan, Mehdi Hamadani, Katelin Baird, Jason Romancik, Hanan Alharthy, Jennie Law, Leyla Bojanini, Ranjana Advani, Boyu Hu, Patrick Connor Johnson, Natalie Grover, Mwanasha Merril, Jennifer Crombie, Nazila Shafagati, Cole Sterling, Loretta Nastoupil*, Narendranath Epperla*

Background: Loncastuximab-tesirine

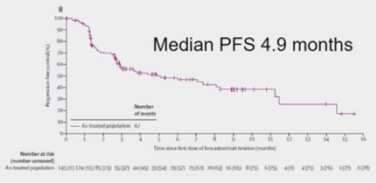
- Loncastuximab (Lonca) is CD19-targeting antibody drug conjugate containing a cytotoxic payload
- FDA approved for relapsed/refractory large B cell lymphoma in 2021 after promising results in the LOTIS-2 trial

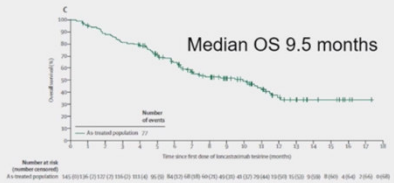


Loncastuximab-tesirine and „real world“

Background: LOTIS-2

- Multicenter open-label single-arm study of patients with R/R LBCL
- Included: 2+ systemic therapies, CD19 + after prior anti CD19 therapy
- Excluded: Bulky disease (>10cm), ECOG >2, GFR <60
- N=145, ORR 48%, CR rate 25%
- Duration of response was longer for CR compared to PR





P. Caimi. Lancet Oncol 2021; 22: 790–800

Study Design

- Multicenter, retrospective chart review from 21 different US centers
- **Hypothesis: Real world (RW) outcomes with Lonca will be inferior compared to those reported in LOTIS-2**
- Primary Endpoint
  - Complete response rate (CRR) to Lonca in RW
- Secondary Endpoint
  - PFS and OS with Lonca in RW
  - CR/ORR based on number of prior lines of therapy and prior CART

Loncastuximab-tesirine and „real world“

Results: Patient Demographics

Factor	N = 187 (%)
Age (yrs)	
<65	72 (39)
65-75	66 (33)
>75	39 (21)
Sex (M)	119 (64)
Advanced stage disease	161 (86)
IPI >3	63 (77)
ECOG >2	13 (7)
eGFR <60	34 (19)
Bulky disease (>10cm)	32 (17)
CNS involvement	12 (7)

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Results: Prior Treatment Characteristics

Factor	N (%)
Loncastuximab Line of therapy	
2nd or 3rd	36 (19)
>3rd	151 (81)
Primary refractory	47 (25)
Prior ASCT	31 (16)
Median time from ASCT (months)	25.9
Prior CAR	112 (60)
CAR as 2nd Line	11 (10)
Median time from CAR (months)	7.7
Last response prior to lonca	
CR	16 (9)
PR	15 (8)
PD	144 (77)

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Loncastuximab-tesirine and „real world“

Background: LOTIS-2

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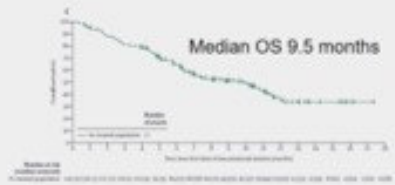

P. Caimi. Lancet Oncol 2021; 22: 790–800

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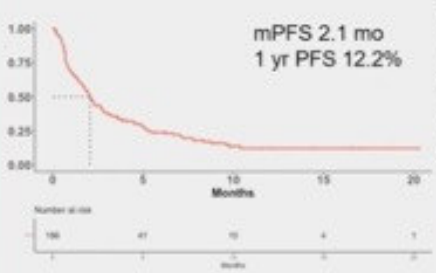
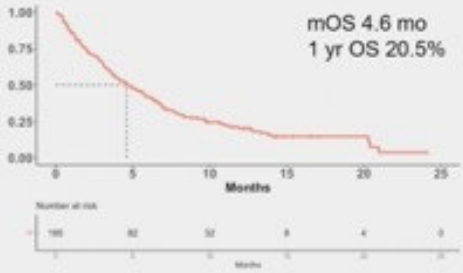
Results: PFS and OS

Progression Free Survival



Overall Survival



Median follow-up of 12.5 months

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- Who is a good candidate for Lonca?
  - Non bulky disease
  - Not refractory to last line of therapy
  - nonGCB