¿QUÉ CAMBIÓ EL 2023 EN LINFOMAS?

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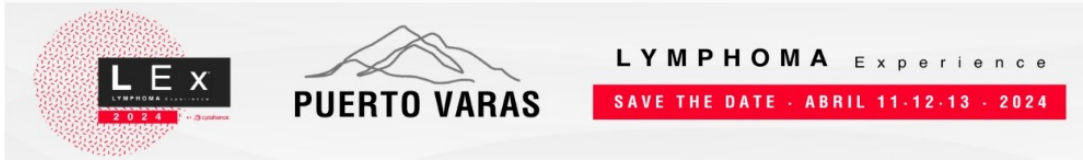


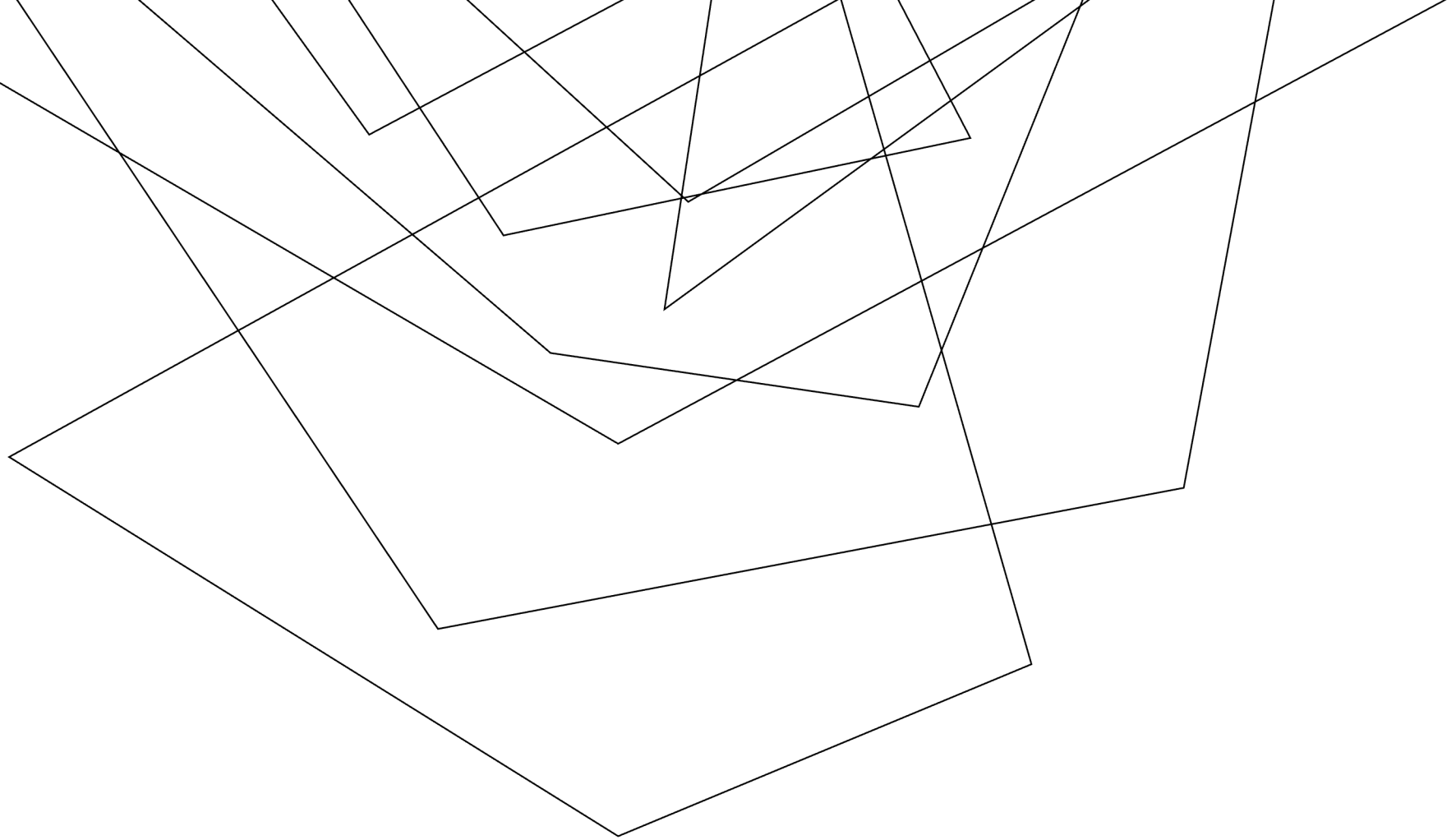
MUCHAS COSAS CAMBIANARON EN 2023!

Como vemos los linfomas

CARs en todas partes

The BTKids on the Block – New and Old

Linfoma de Hodgkin – La consagración de los CPI



COMO VEMOS LOS LINFOMAS?

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

Elias Campo, Elaine S. Jaffe, James R. Cook, Leticia Quintanilla-Martinez, Steven H. Swerdlow, Kenneth C. Anderson, Pierre Brousset, Lorenzo Cerroni, Laurence de Leval, Stefan Dirnhofer, Ahmet Dogan, Andrew L. Feldman, Falko Fend, Jonathan W. Friedberg, Philippe Gaulard, Paolo Ghia, Steven M. Horwitz, Rebecca L. King, Gilles Salles, Jesus San-Miguel, John F. Seymour, Steven P. Treon, Julie M. Vose, Emanuele Zucca, Ranjana Advani, Stephen Ansell, Wing-Yan Au, Carlos Barrionuevo, Leif Bergsagel, Wing C. Chan, Jeffrey I. Cohen, Francesco d'Amore, Andrew Davies, Brunangelo Falini, Irene M. Ghobrial, John R. Goodlad, John G. Gribben, Eric D. Hsi, Brad S. Kahl, Won-Seog Kim, Shaji Kumar, Ann S. LaCasce, Camille Laurent, Georg Lenz, John P. Leonard, Michael P. Link, Armando Lopez-Guillermo, Maria Victoria Mateos, Elizabeth Macintyre, Ari M. Melnick, Franck Morschhauser, Shigeo Nakamura, Marina Narbaitz, Astrid Pavlovsky, Stefano A. Pileri, Miguel Piris, Barbara Pro, Vincent Rajkumar, Steven T. Rosen, Birgitta Sander, Laurie Sehn, Margaret A. Shipp, Sonali M. Smith, Louis M. Staudt, Catherine Thieblemont, Thomas Tousseyn, Wyndham H. Wilson, Tadashi Yoshino, Pier-Luigi Zinzani, Martin Dreyling, David W. Scott, Jane N. Winter, Andrew D. Zelenetz

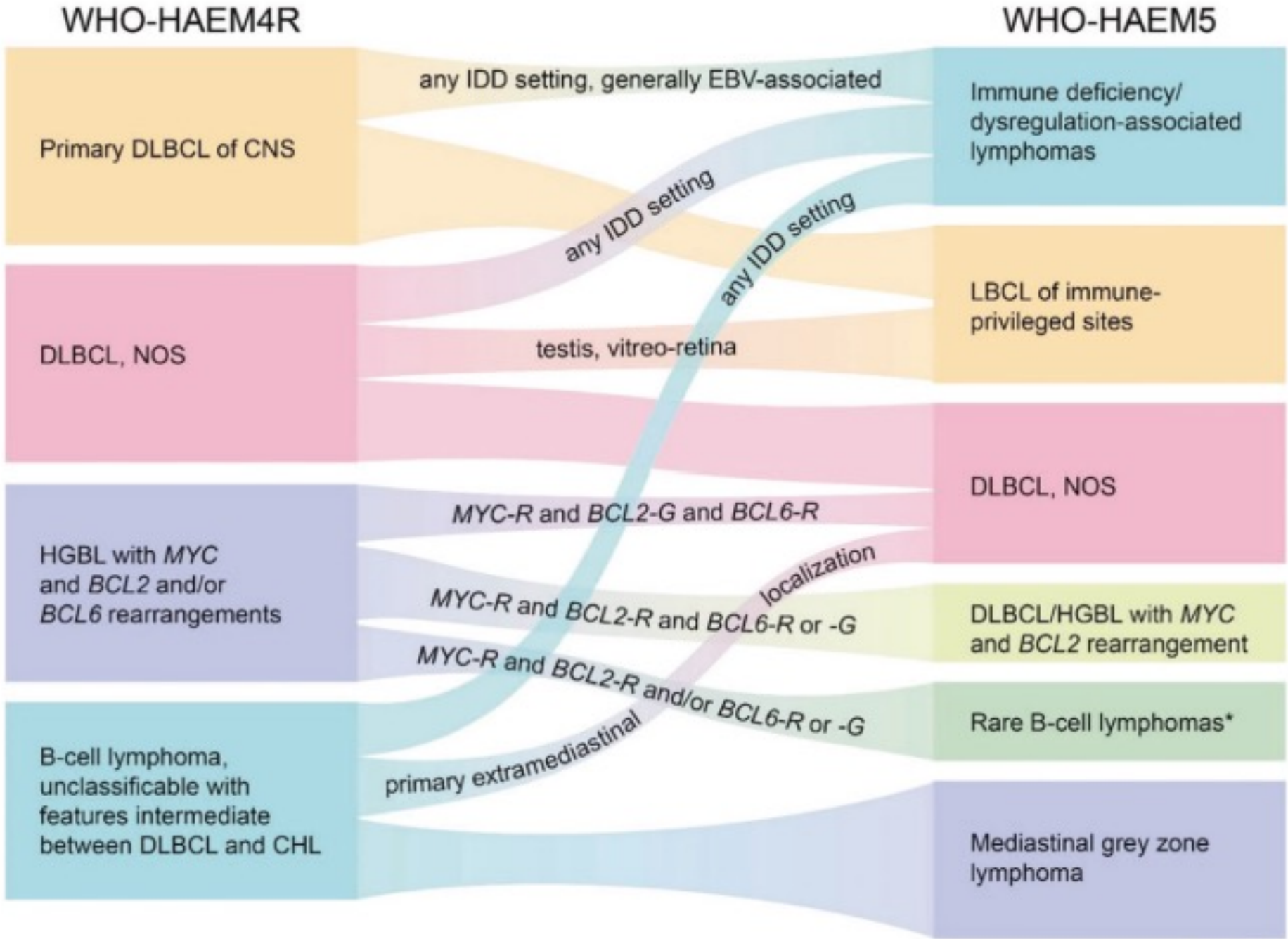
REVIEW ARTICLE OPEN

Check for updates

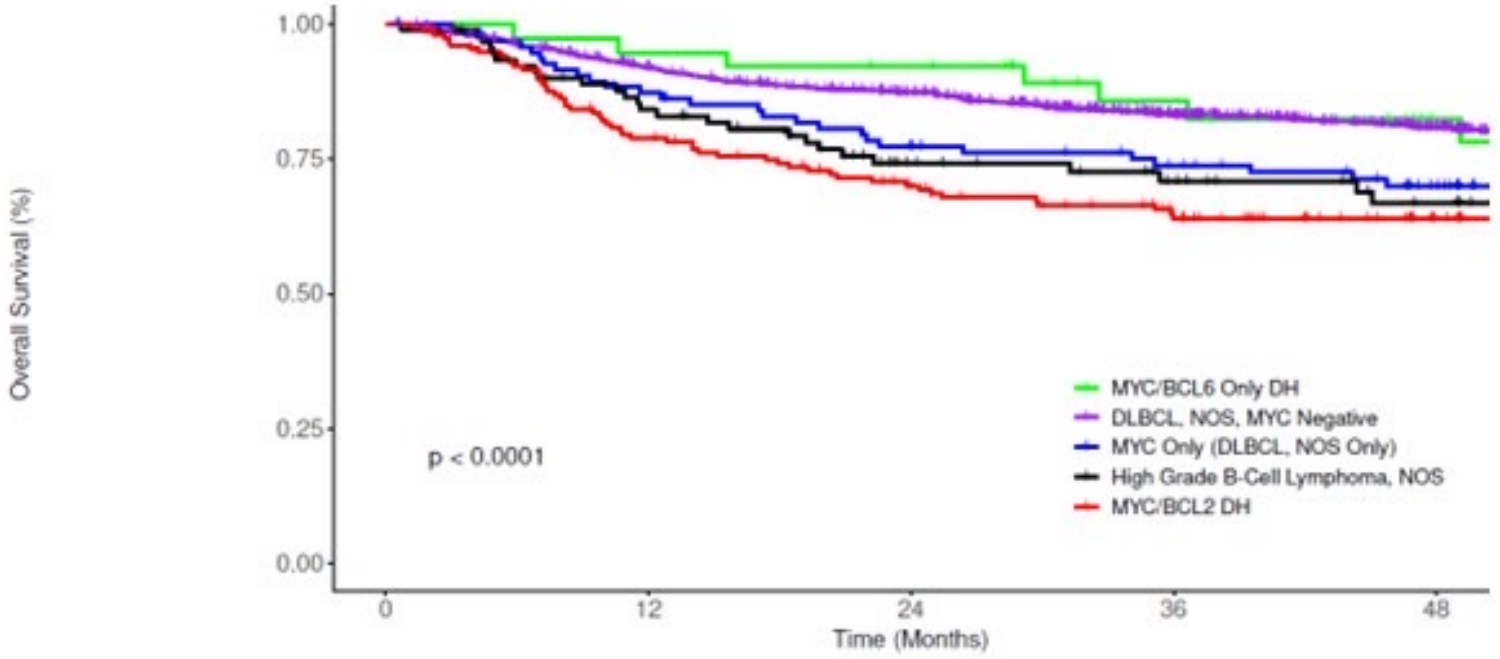
LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

Rita Alaggio[1], Catalina Amador[2], Ioannis Anagnostopoulos[3], Ayoma D. Attygalle[4], Iguaracyra Barreto de Oliveira Araujo[5], Emilio Berti[6], Govind Bhagat[7], Anita Maria Borges[8], Daniel Boyer[9], Mariarita Calaminici[10], Amy Chadburn[11], John K. C. Chan[12], Wah Cheuk[12], Wee-Joo Chng[13], John K. Choi[14], Shih-Sung Chuang[15], Sarah E. Coupland[16], Magdalena Czader[17], Sandeep S. Dave[18], Daphne de Jong[19], Ming-Qing Du[20]✉, Kojo S. Elenitoba-Johnson[21], Judith Ferry[22]✉, Julia Geyer[11], Dita Gratzinger[23], Joan Guitart[24], Sumeet Gujral[25], Marian Harris[26], Christine J. Harrison[27], Sylvia Hartmann[28], Andreas Hochhaus[29], Patty M. Jansen[30], Kennosuke Karube[31], Werner Kempf[32], Joseph Khoury[33], Hiroshi Kimura[34], Wolfram Klapper[35], Alexandra E. Kovach[36], Shaji Kumar[37], Alexander J. Lazar[38], Stefano Lazzi[39], Lorenzo Leoncini[39], Nelson Leung[40], Vasiliki Leventaki[41], Xiao-Qiu Li[42], Megan S. Lim[21], Wei-Ping Liu[43], Abner Louissaint Jr.[22], Andrea Marcogliese[44], L. Jeffrey Medeiros[33], Michael Michal[45], Roberto N. Miranda[33], Christina Mitteldorf[46], Santiago Montes-Moreno[47], William Morice[48], Valentina Nardi[22], Kikkeri N. Naresh[49], Yasodha Natkunam[23], Siok-Bian Ng[50], Ilske Oschlies[35], German Ott[51]✉, Marie Parrens[52], Melissa Pulitzer[53], S. Vincent Rajkumar[54], Andrew C. Rawstron[55], Karen Rech[48], Andreas Rosenwald[3], Jonathan Said[56], Clémentine Sarkozy[57], Shahin Sayed[58], Caner Saygin[59], Anna Schuh[60], William Sewell[61], Reiner Siebert[62]✉, Aliyah R. Sohani[22], Reuben Tooze[63], Alexandra Traverse-Glehen[64], Francisco Vega[33], Beatrice Vergier[65], Ashutosh D. Wechalekar[66], Brent Wood[36], Luc Xerri[67] and Wenbin Xiao[53]


WHO-HAEM4R
WHO-HAEM5
Primary DLBCL of CNS
DLBCL, NOS
HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements
B-cell lymphoma, unclassifiable with features intermediate between DLBCL and CHL
any IDD setting, generally EBV-associated
any IDD setting
any IDD setting
testis, vitreo-retina
MYC-R and *BCL2-G* and *BCL6-R*
MYC-R and *BCL2-R* and *BCL6-R* or *-G*
MYC-R and *BCL2-R* and/or *BCL6-R* or *-G*
primary extramediastinal
localization
Immune deficiency/ dysregulation-associated lymphomas
LBCL of immune-privileged sites
DLBCL, NOS
DLBCL/HGBL with *MYC* and *BCL2* rearrangement
Rare B-cell lymphomas*
Mediastinal grey zone lymphoma

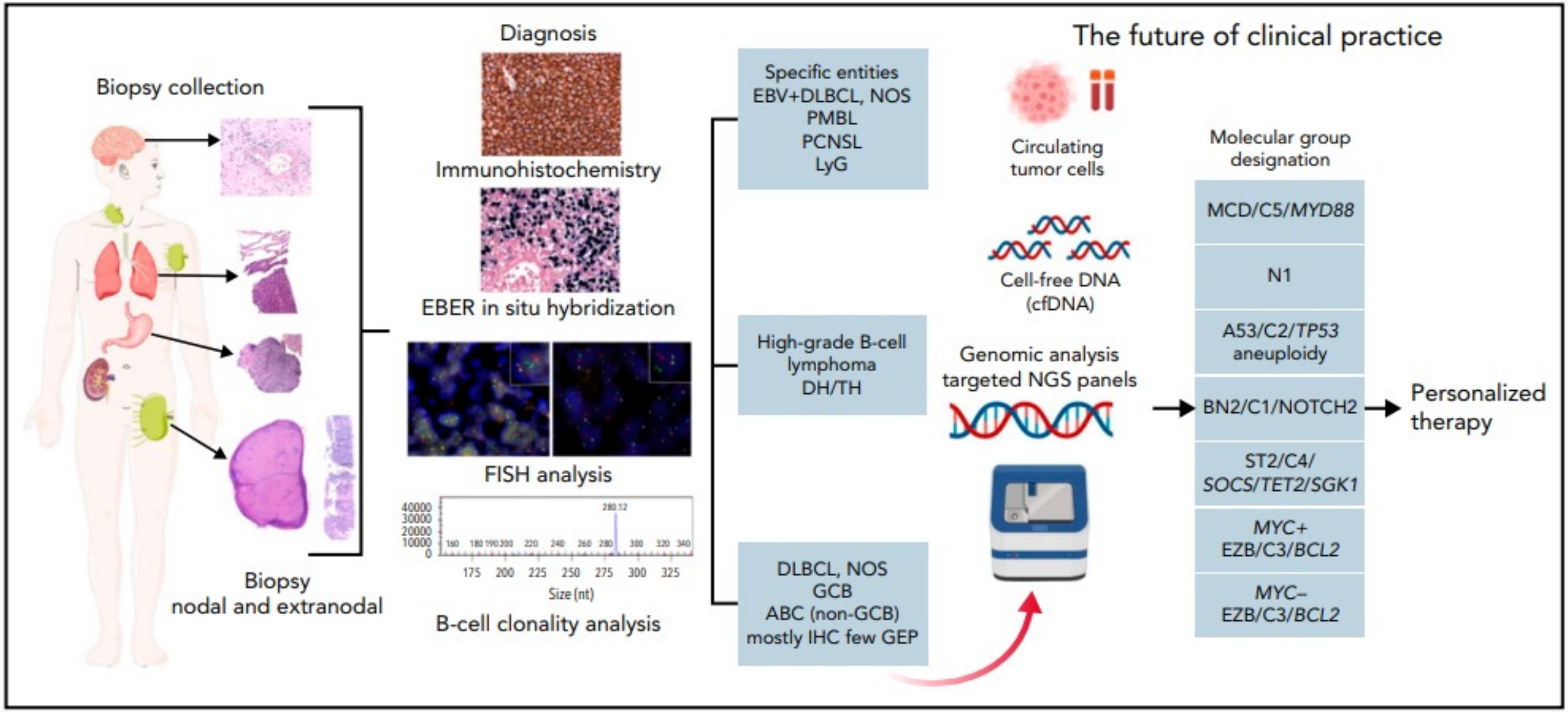
NO MORE DHL WITH BCL6 OR THL



Number at risk

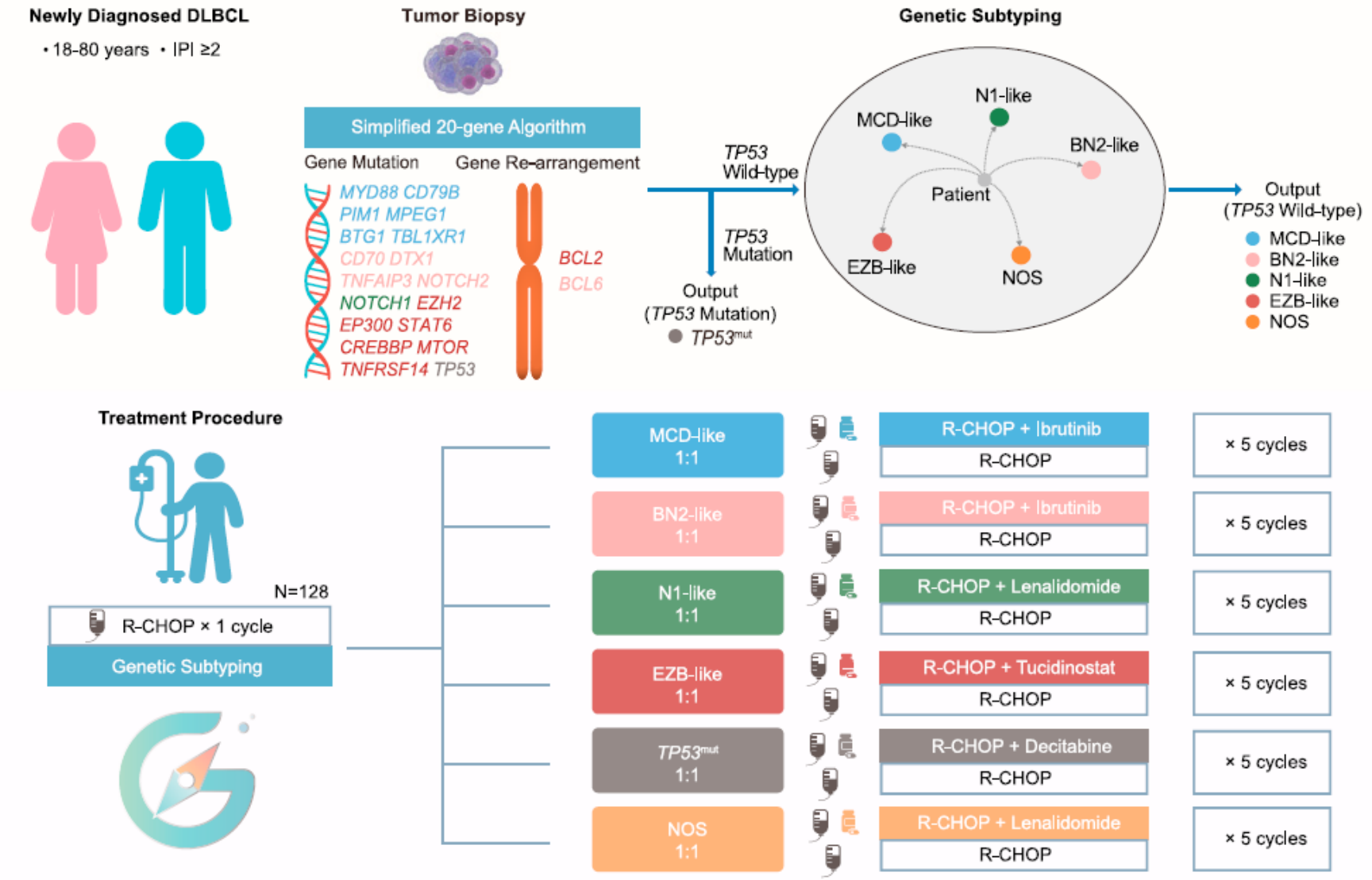
MYC/BCL6 Only DH	38	36	34	26	19
DLBCL, NOS, MYC Negative	1146	1022	928	754	548
MYC Only (DLBCL, NOS Only)	96	81	69	61	48
High Grade B-Cell Lymphoma, NOS	92	72	50	41	31
MYC/BCL2 DH	154	119	98	80	52

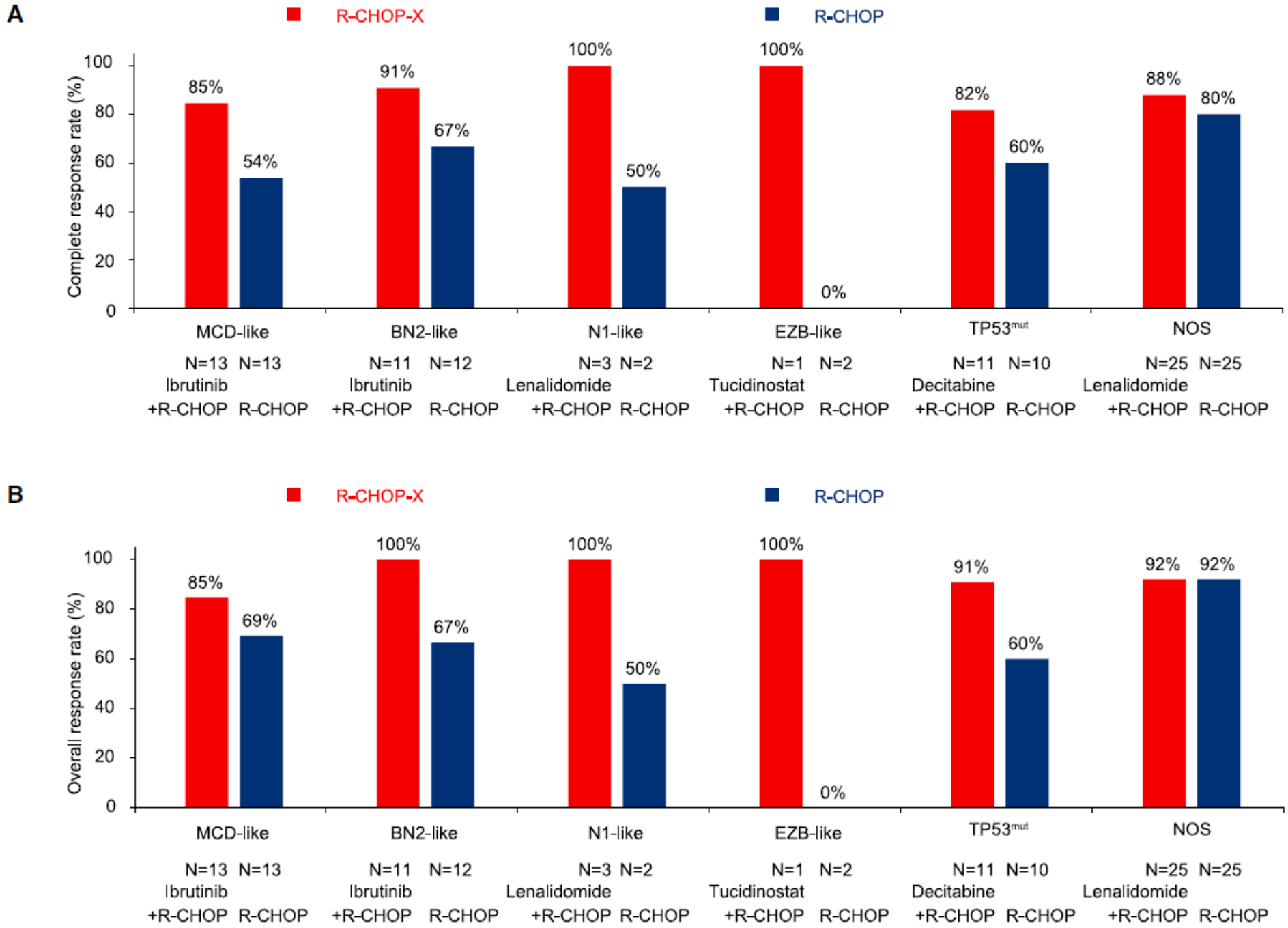
Khurana A, ASH 2023


Biopsy collection
Biopsy
nodal and extranodal
Diagnosis
Immunohistochemistry
EBER in situ hybridization
FISH analysis
B-cell clonality analysis
Specific entities
EBV+DLBCL, NOS
PMBL
PCNSL
LyG
High-grade B-cell lymphoma
DH/TH
DLBCL, NOS
GCB
ABC (non-GCB)
mostly IHC few GEP
The future of clinical practice
Circulating tumor cells
Cell-free DNA (cfDNA)
Genomic analysis targeted NGS panels
Molecular group designation
MCD/C5/MYD88
N1
A53/C2/TP53 aneuploidy
BN2/C1/NOTCH2
ST2/C4/SOCS/TET2/SGK1
MYC+ EZB/C3/BCL2
MYC– EZB/C3/BCL2
Personalized therapy

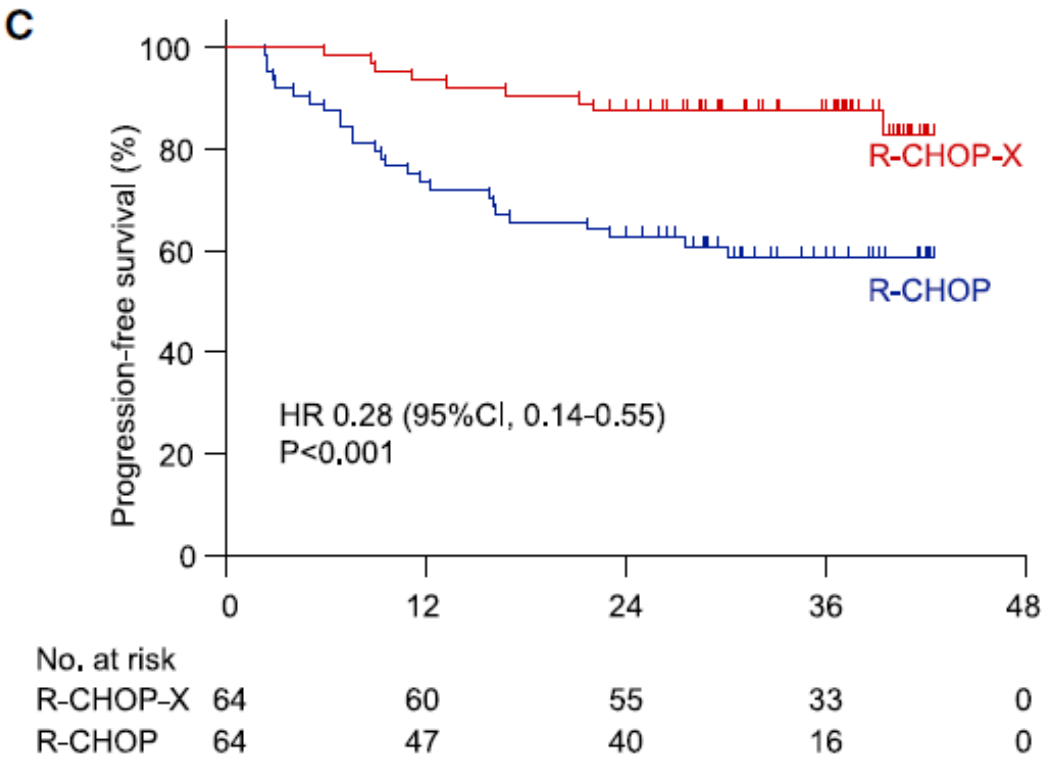
Mu-Cheng, Z et al, Cell 2023

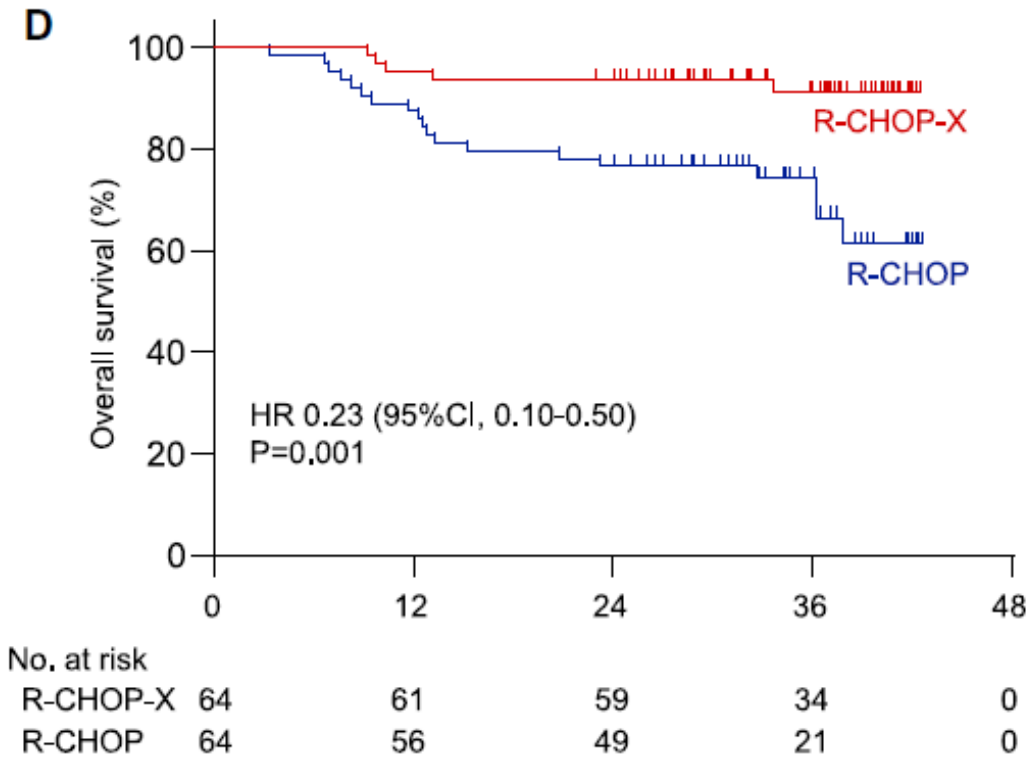
EL FUTURO?




A
R-CHOP-X
R-CHOP
Complete response rate (%)
100
80
60
40
20
0
85%
54%
91%
67%
100%
50%
100%
0%
82%
60%
88%
80%
MCD-like
BN2-like
N1-like
EZB-like
TP53mut
NOS
N=13 N=13
Ibrutinib +R-CHOP R-CHOP
N=11 N=12
Ibrutinib +R-CHOP R-CHOP
N=3 N=2
Lenalidomide +R-CHOP R-CHOP
N=1 N=2
Tucidinostat +R-CHOP R-CHOP
N=11 N=10
Decitabine +R-CHOP R-CHOP
N=25 N=25
Lenalidomide +R-CHOP R-CHOP
B
R-CHOP-X
R-CHOP
Overall response rate (%)
100
80
60
40
20
0
85%
69%
100%
67%
100%
50%
100%
0%
91%
60%
92%
92%
MCD-like
BN2-like
N1-like
EZB-like
TP53mut
NOS
N=13 N=13
Ibrutinib +R-CHOP R-CHOP
N=11 N=12
Ibrutinib +R-CHOP R-CHOP
N=3 N=2
Lenalidomide +R-CHOP R-CHOP
N=1 N=2
Tucidinostat +R-CHOP R-CHOP
N=11 N=10
Decitabine +R-CHOP R-CHOP
N=25 N=25
Lenalidomide +R-CHOP R-CHOP

EL FUTURO?

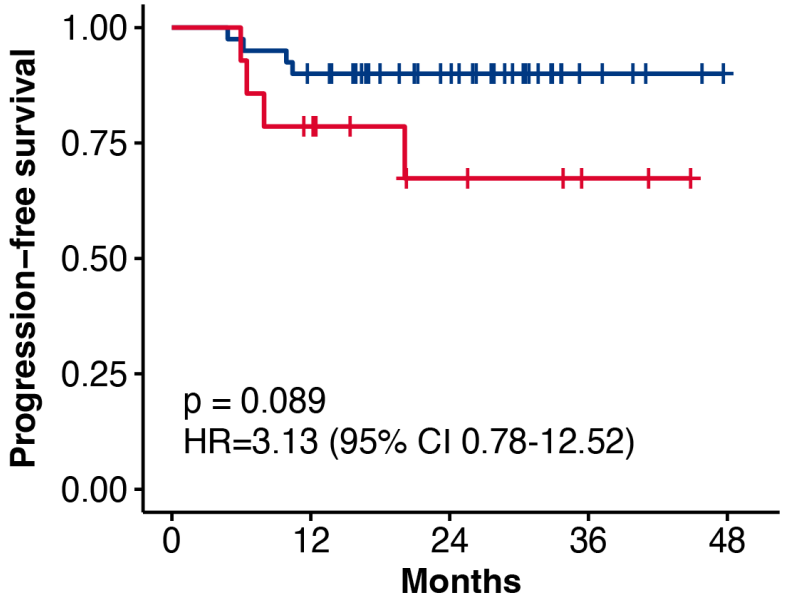




Mu-Cheng, Z et al, Cell 2023

CAMBIANDO COMO EVALUAR RESPOSTA?

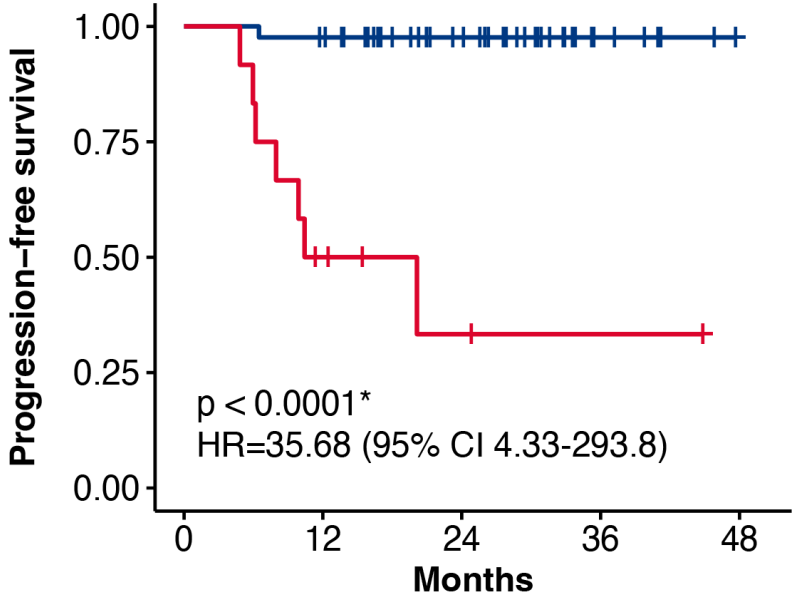
A.



Number at risk

PET CR	40	35	22	5	0
PET non–CR	14	10	5	2	0

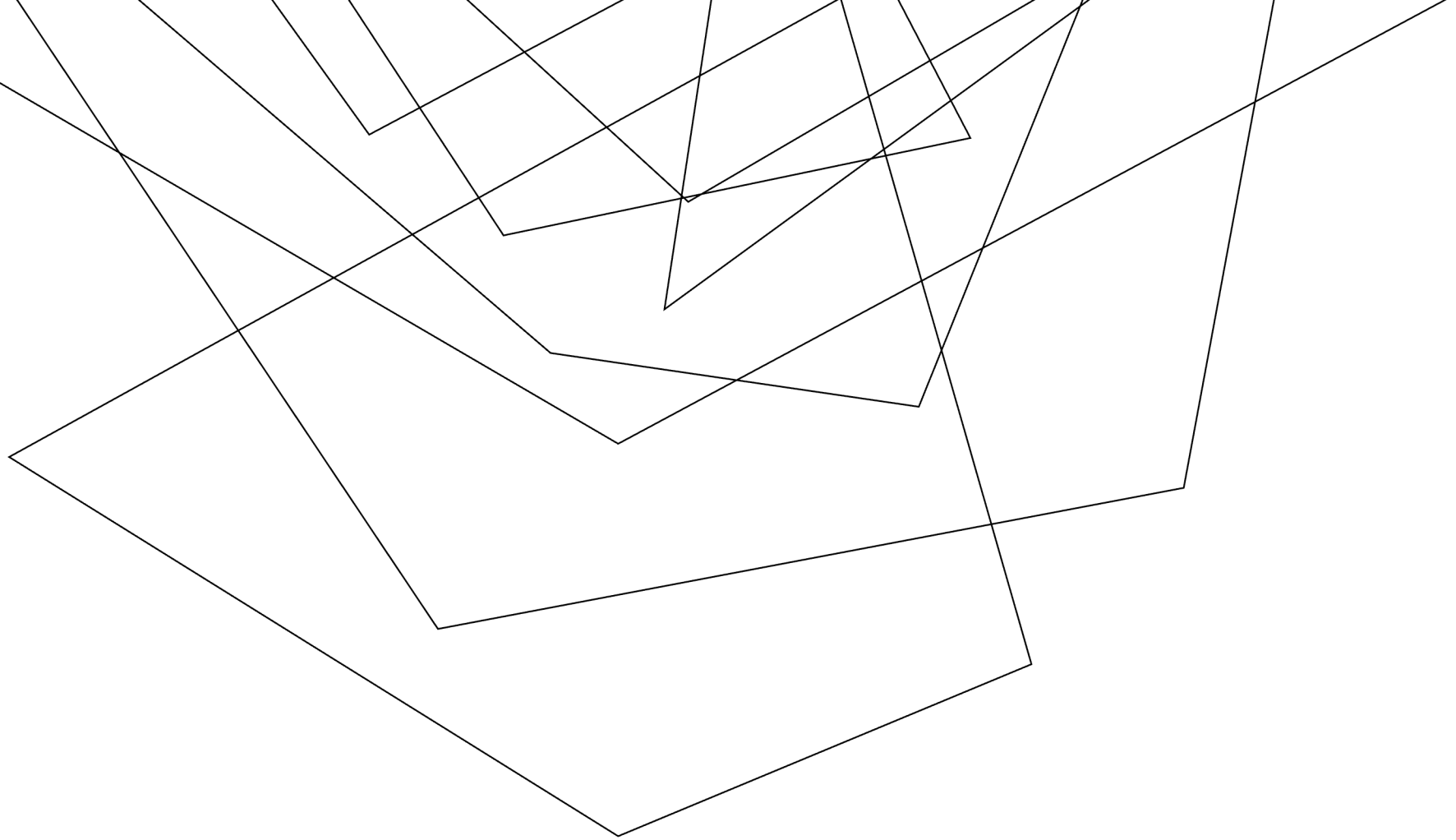
B.



Number at risk

ctDNA Undetected	42	40	25	6	0
ctDNA Detected	12	5	2	1	0

Roschewski M et al, ASH 2023



CARS EN TODOS LOS LUGARES

WITH LONG-TERM FOLLOW-UP, HOW HAS AXICABTAGENE CILOLEUCEL IMPACTED SURVIVAL FOR PATIENTS WITH R/R DLBCL?

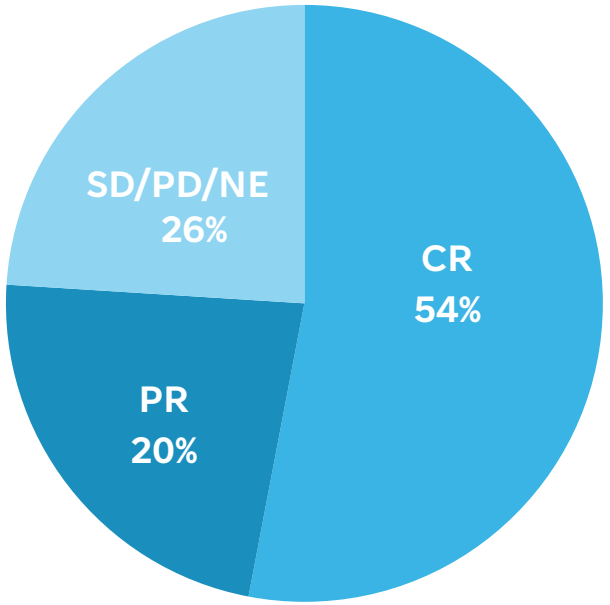
ZUMA-1: Phase 2, single-arm, open-label study of patients with R/R DLBCL treated with axicabtagene ciloleucel (N=101)

Primary endpoint: Response rate

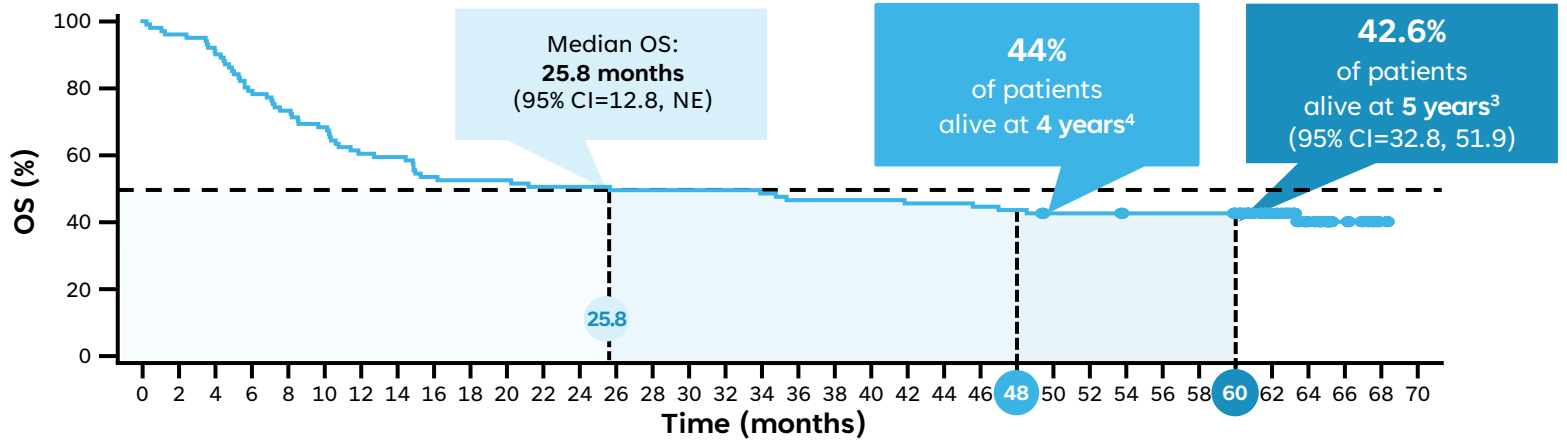
27.1 months' median follow-up (N=101)[1,2]

ORR: 74%[a,b]

CR: 54%



Overall survival: *63.1 months' median follow-up (N=101)*[3]



Safety profile[c]

Median follow-up: 23.5 months (N=108)[1]	
SAEs, %	51
Most common Gr ≥3 non-haematological AEs, %	
Infections	34
Neurological events	31
CRS	11
Median follow-up: 27.1 months (N=108)[2]	
Gr ≥3 AEs, %	98
Most common Gr ≥3 haematological AEs, %	
Neutropenia	80
Anaemia	45
Thrombocytopenia	40

As of the 5-year data cut-off date,[3] no new safety signals have been reported, including:

- No axicabtagene ciloleucel-related secondary malignancies
- No new axicabtagene ciloleucel-related SAEs

With axicabtagene ciloleucel, **42.6%** of patients were alive at **5 years**[3]

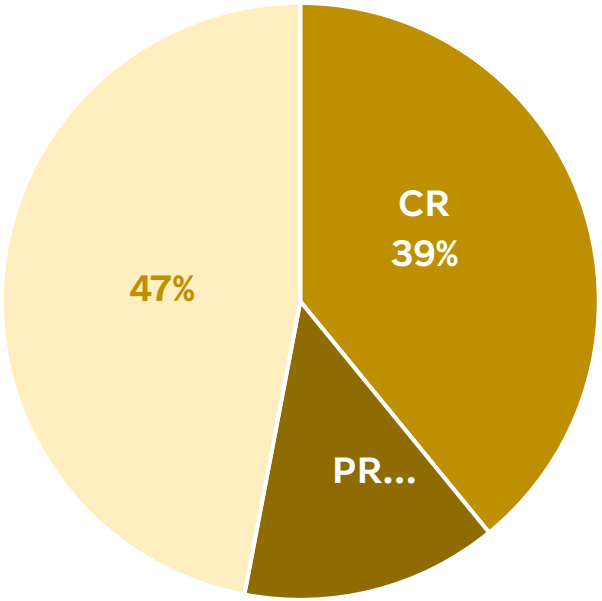
HOW HAS TISAGENLECLEUCEL IMPACTED SURVIVAL FOR PATIENTS WITH R/R DLBCL?

JULIET: Phase 2, single-arm, open-label study of patients with R/R DLBCL treated with tisagenlecleucel (N=115)

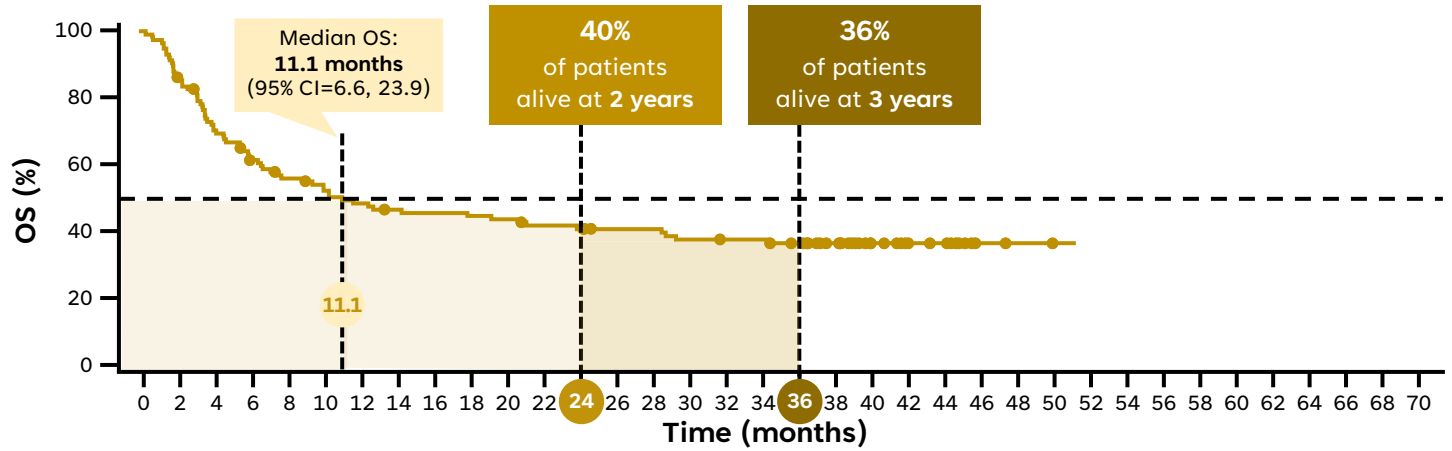
Primary endpoint: Response rate *40.3 months' median follow-up (N=115)*[1,2]

ORR: 53%[a]

CR: 39%[b]



Overall survival: *40.3 months' median follow-up (N=115)*[1,2]



Safety profile[c]

Median follow-up: 40.3 months (N=115)[2–4]	
SAEs,[d] %	65
Gr ≥3 AEs, %	88
Most common Gr ≥3 non-haematological AEs, %	
Infections	34
Neurological events	11
CRS	23
Most common Gr ≥3 haematological AEs, %	
Lymphocyte count decrease	95
Neutrophil count decrease	82
White blood cell count decrease	78

As of the 3-year data cut-off date,[2] no new safety signals have been reported

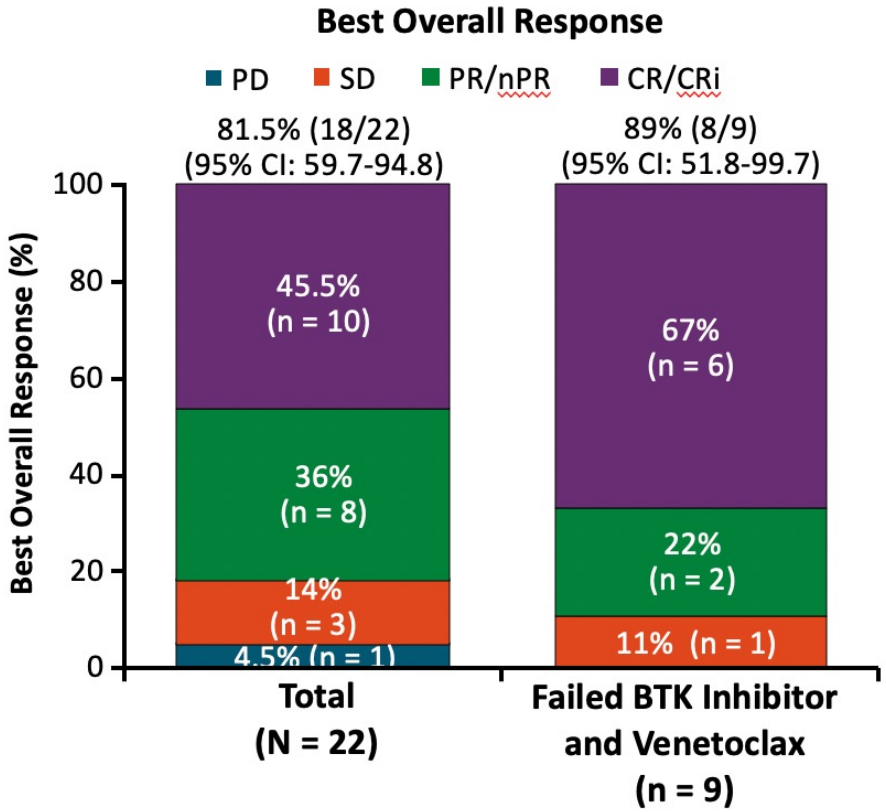
With tisagenlecleucel, **36%** of patients were alive at **3 years**[1]

TRANSCEND CLL 004: Phase I/II clinical trial using Lisocabtagene Maraleucel (liso-cel) for CLL R/R

- Phase I/I, multicenter
- R/R LLC or ineligible for the BTK inhibitor; high-risk disease with ≥ 2 lines of treatment or standard risk with more than ≥ 3 lines of treatment

Characteristic	Patients (N = 23)
High risk, n (%) ▪ del(17p) ▪ TP53 mutation ▪ Complex kariotype*	19 (83) 8 (35) 14 (61) 11 (48)
Median of previous treatments	5 (2-11)
Prior ibrutinib, n (%)	23 (100)
Progression after BTK inhibitor and venetoclax, n (%)	9 (39)

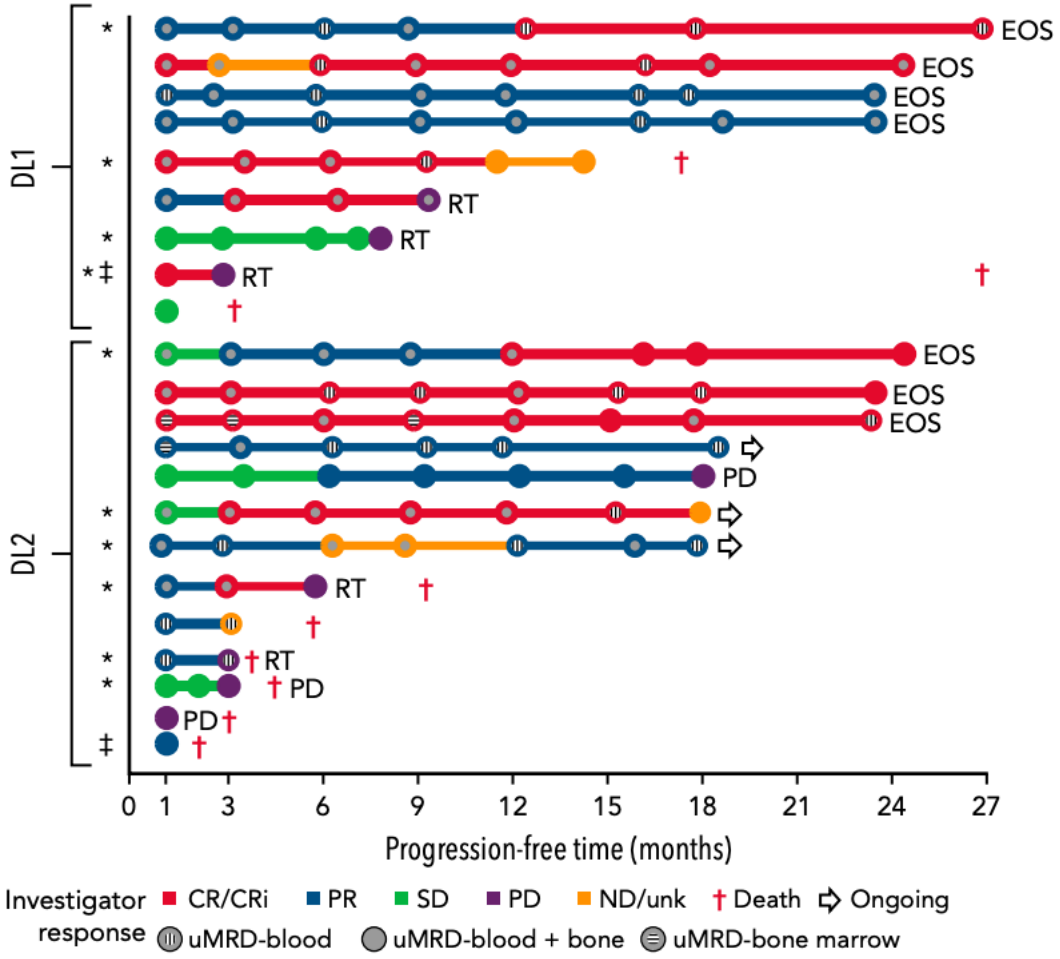
CRS grade ≥ 3 : 9%
ICANS grade ≥ 3: 22%

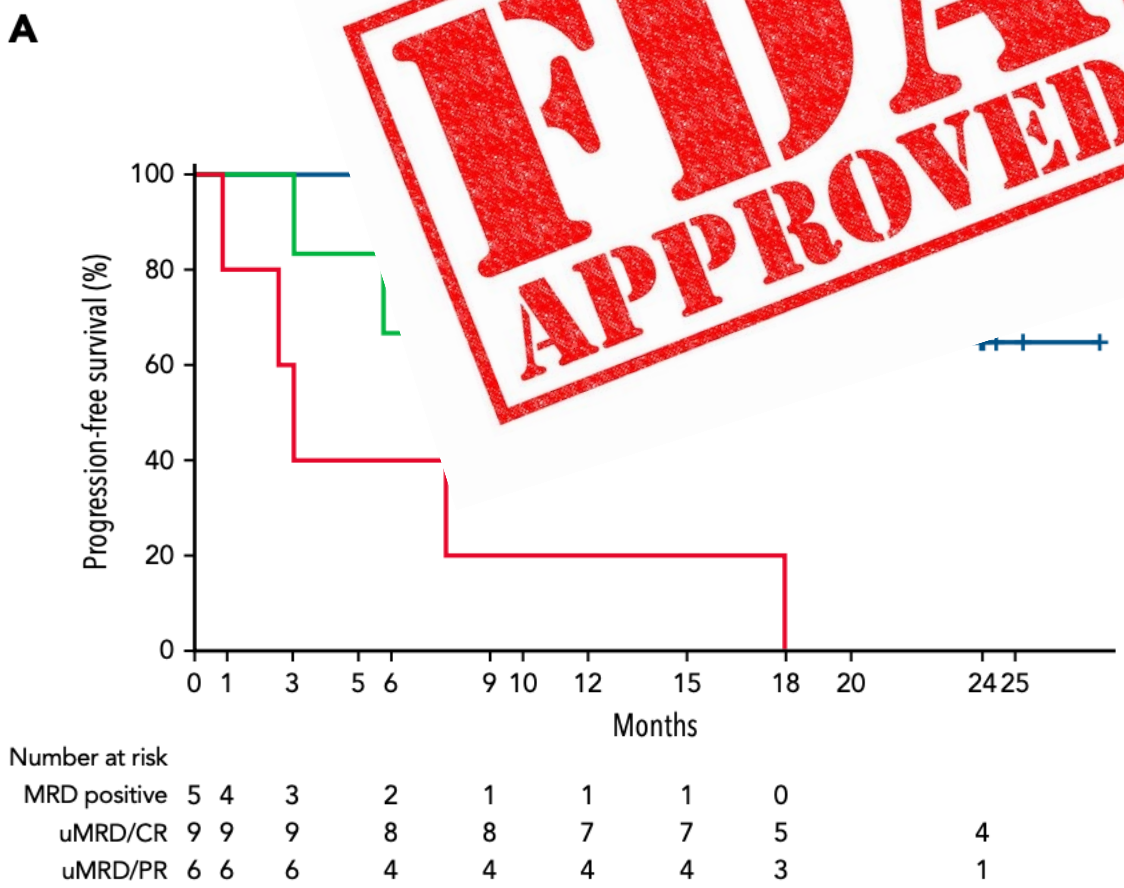


Mediana follow-up: 11 months

Siddiqi T et al. Blood. 2022

Response after 24 months of follow-up





Siddiqi T et al. Blood. 2022

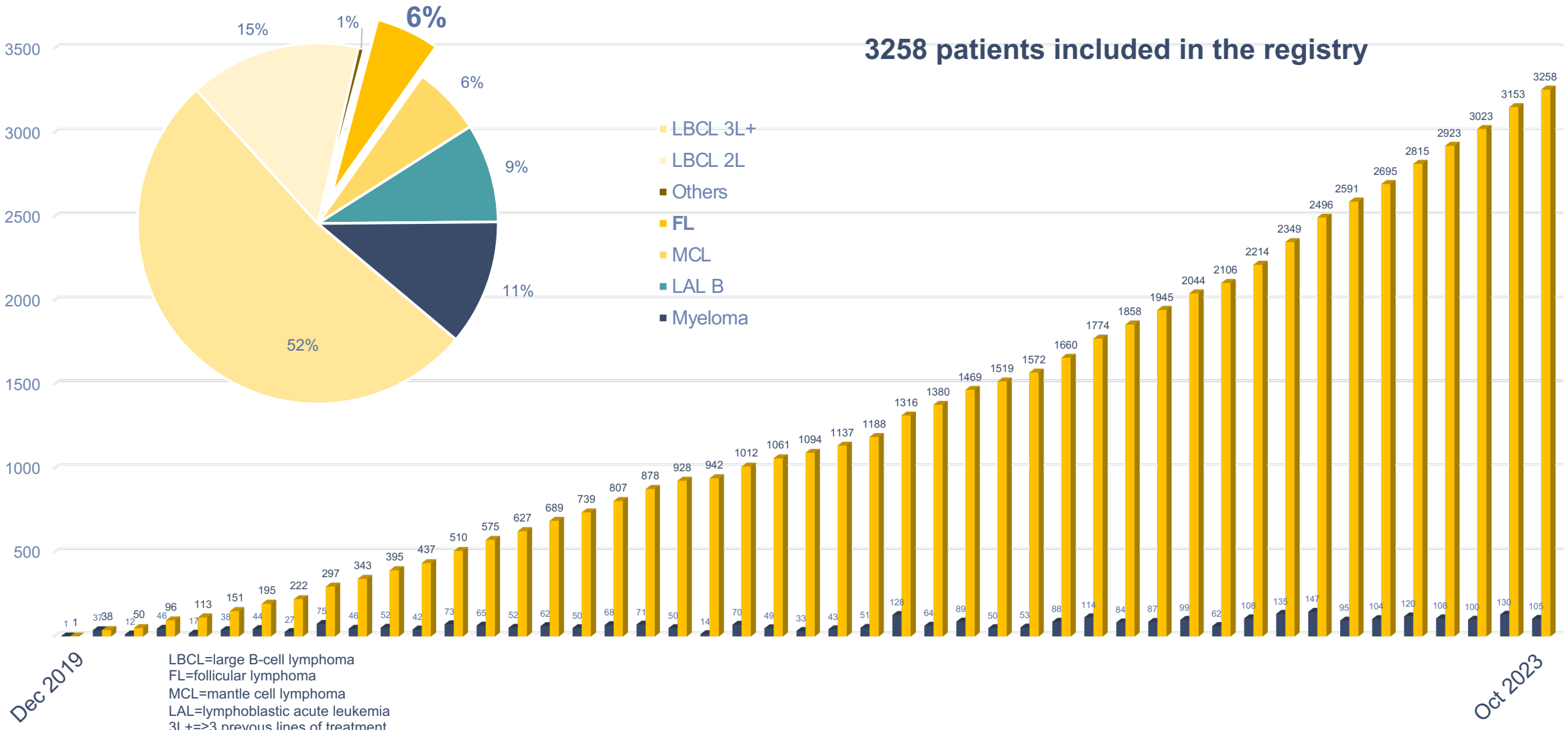
Real world experience of CAR T cells in patients with relapsed/refractory follicular lymphoma : a DESCAR-T registry analysis from the LYSA

Loïc Ysebaert[1], Roch Houot[2], Olivier Casasnovas[3], Sylvain Choquet[4], Fabrice Jardin[5], Michaël Loschi[6], Gabriel Brisou[7], Catherine Thieblemont[8], Jacques Olivier Bay[9], Cristina Castilla Llorente[10], Tom Fradon[11], Steven Le Gouill[12], Franck Morschhauser[13], Guillaume Cartron[14], **Emmanuel Bachy**[15]

[1]Hematology Department, Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France, [2]Clinical Hematology, Hopital Pontchaillou, Rennes University Hospital, Rennes, France, [3]Clinical Hematology, François Mitterand Hospital, Dijon, FRA, [4]Hopital de la Pitié Salpetrière, APHP, Paris, FRA, [5]Centre Henri-Becquerel and University of Rouen, Rouen, France, [6]Service d'hématologie, CHU de Nice, Nice, France, [7]Institut Paoli-Calmettes, Department of Hematology, Marseille Cedex 09, France, [8]Assistance Publique Des Hopitaux De Paris, Paris, FRA, [9]Service d'hématologie, CHU Clermont-Ferrand, Clermont-Ferrand, France, [10]Department of Hematology, Gustave Roussy Cancer Campus, Villejuif, France, [11]LYSARC, Lyon, France, [12]Hematology Department, Institut Curie, Paris, France, [13]Hôpital Claude Huriez, Lille, France, [14]CHU Montpellier, France, [15]Lyon-Sud Hospital Center, Pierre-Bénite, France

Abstract #296

Recruitment

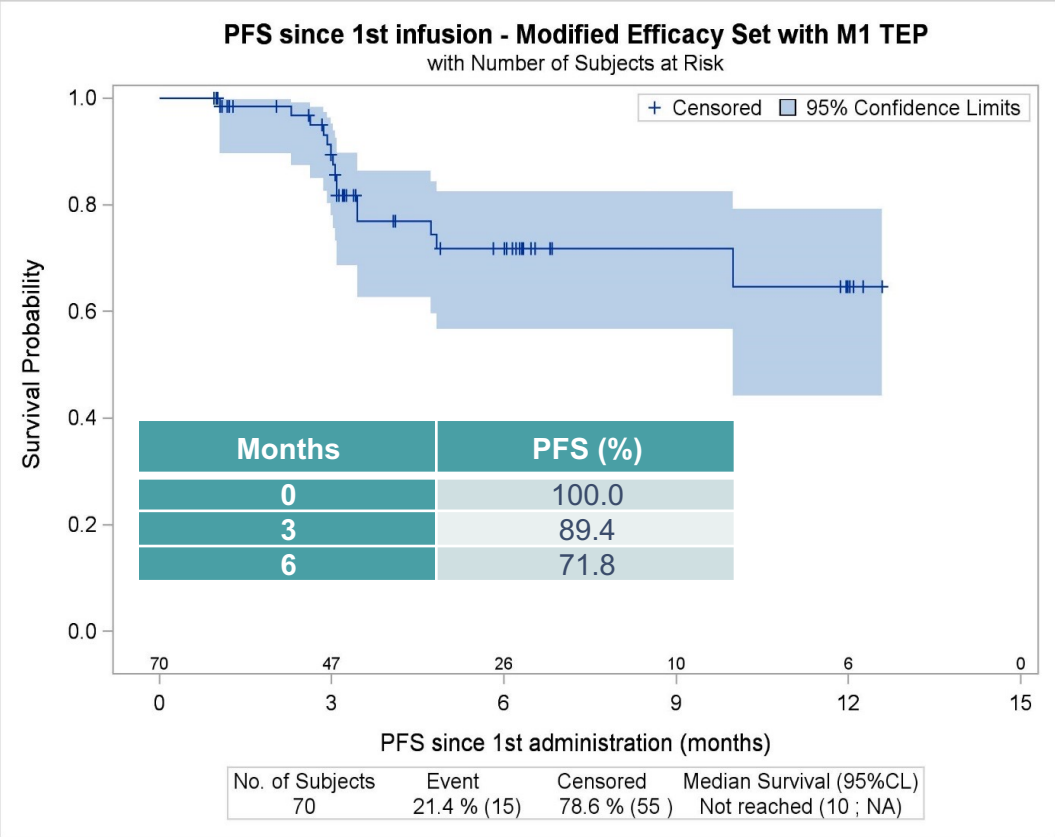


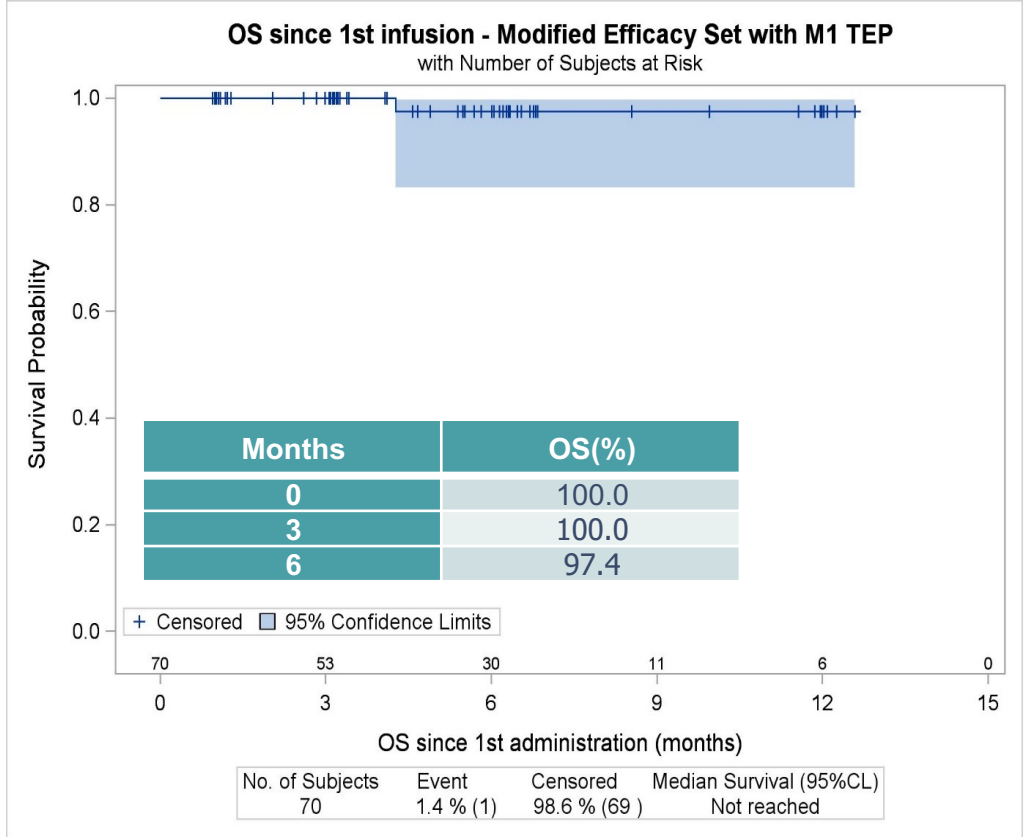
LBCL=large B-cell lymphoma
FL=follicular lymphoma
MCL=mantle cell lymphoma
LAL=lymphoblastic acute leukemia
3L+=≥3 prevous lines of treatment
2L=2 prevous lines of treatment

Bachy et al. ASH 2023, Abstract #296

Survival

	Median	Min	Max
FU (mos.)	5.4	1.0	12.6



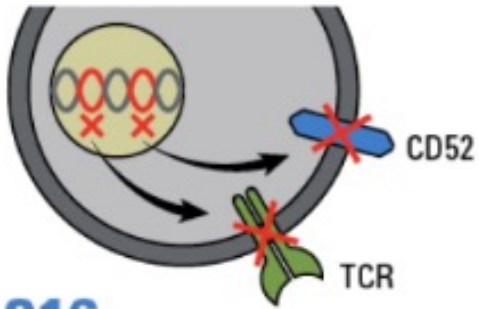


Bachy et al. ASH 2023, Abstract #296

Novel allogeneic CAR T cell therapy delivers promising early results in patients with metastatic clear cell renal cell carcinoma

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Phase I TRAVERSE clinical trial



ALLO-316

Anti-CD70 allogeneic CAR T cell product

Genetically edited to disrupt:

- TRAC to reduce GvHD risk
- CD52 gene to allow lymphodepletion with ALLO-647

Cutoff data as of November 2022

Methods

6 Sites

17 Patients treated

65 Median age

3 Median prior therapies

Treatment course

Conditioning (Days minus 5-3):
Fludarabine + cyclophosphamide with/without ALLO-647

Day 0:
40 – 120 X 10^6 CAR T cells

Results

In patients with CD70+ tumors:

33%
Overall response rate

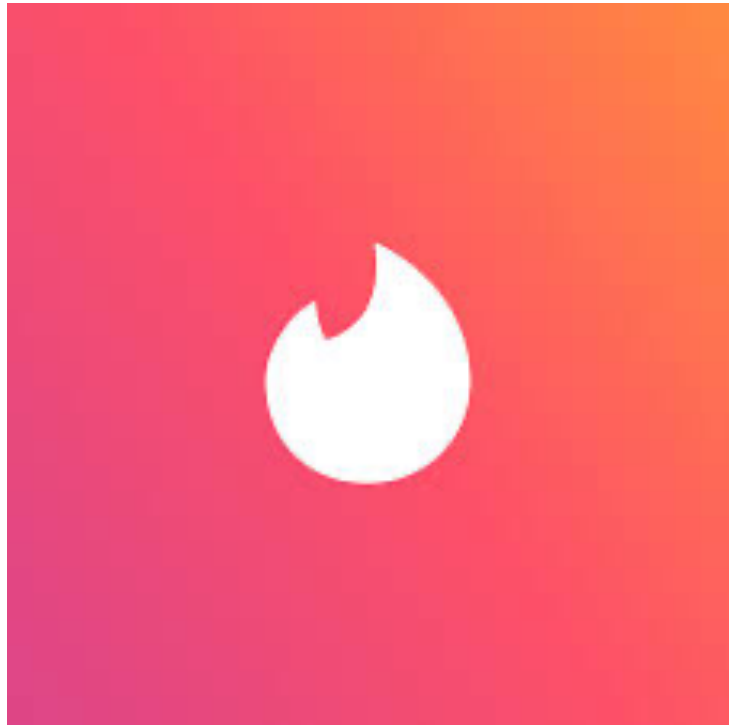
100%
Disease control rate

Side effects

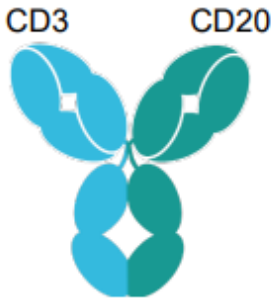
- CRS in 65%, all low grade except 1
- **No** ICANS
- **No** GvHD

Srour, et al. Abstract CT011. 2023 American Association for Cancer Research Annual Meeting.

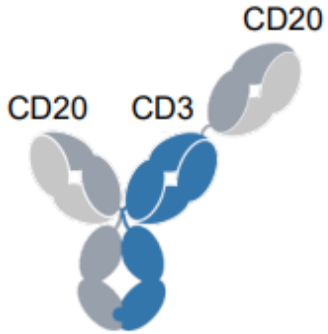
THESE CARS ARE NOT RIDING ALONE...



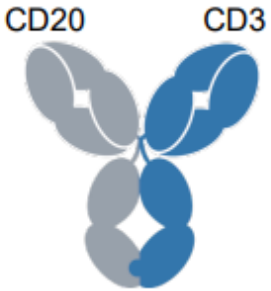
Overview of Select CD3×CD20 bispecific Abs for B-NHL[1-3]



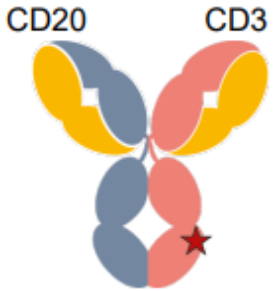
Epcoritamab
DuoBody-CD3×CD20
IgG1



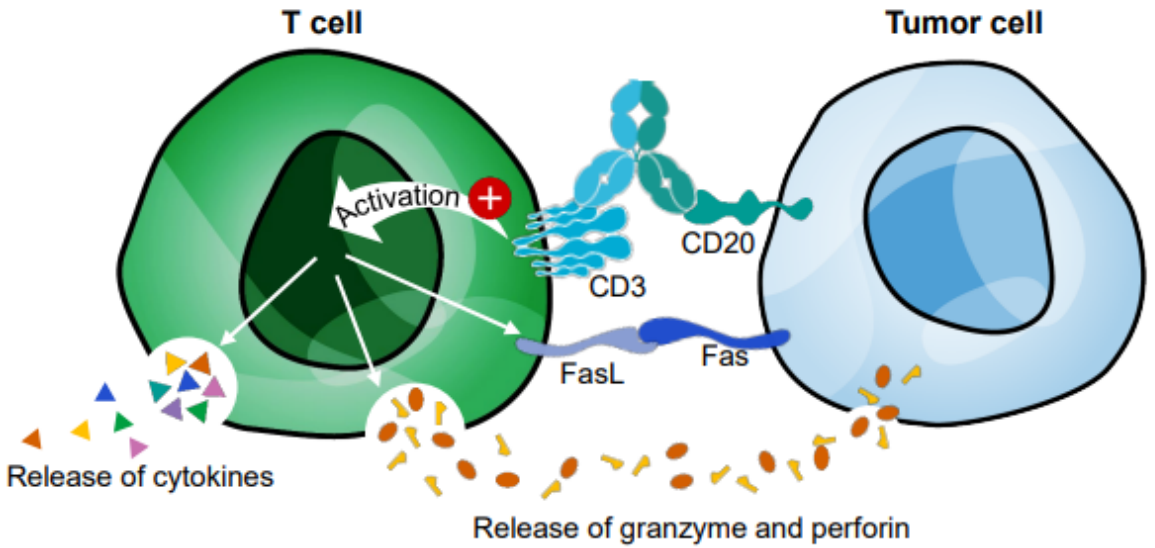
Glofitamab
2+1 CrossMab
IgG1



Mosunetuzumab
Knob-in-hole
IgG1



Odronextamab
VELOCI-Bi
IgG4



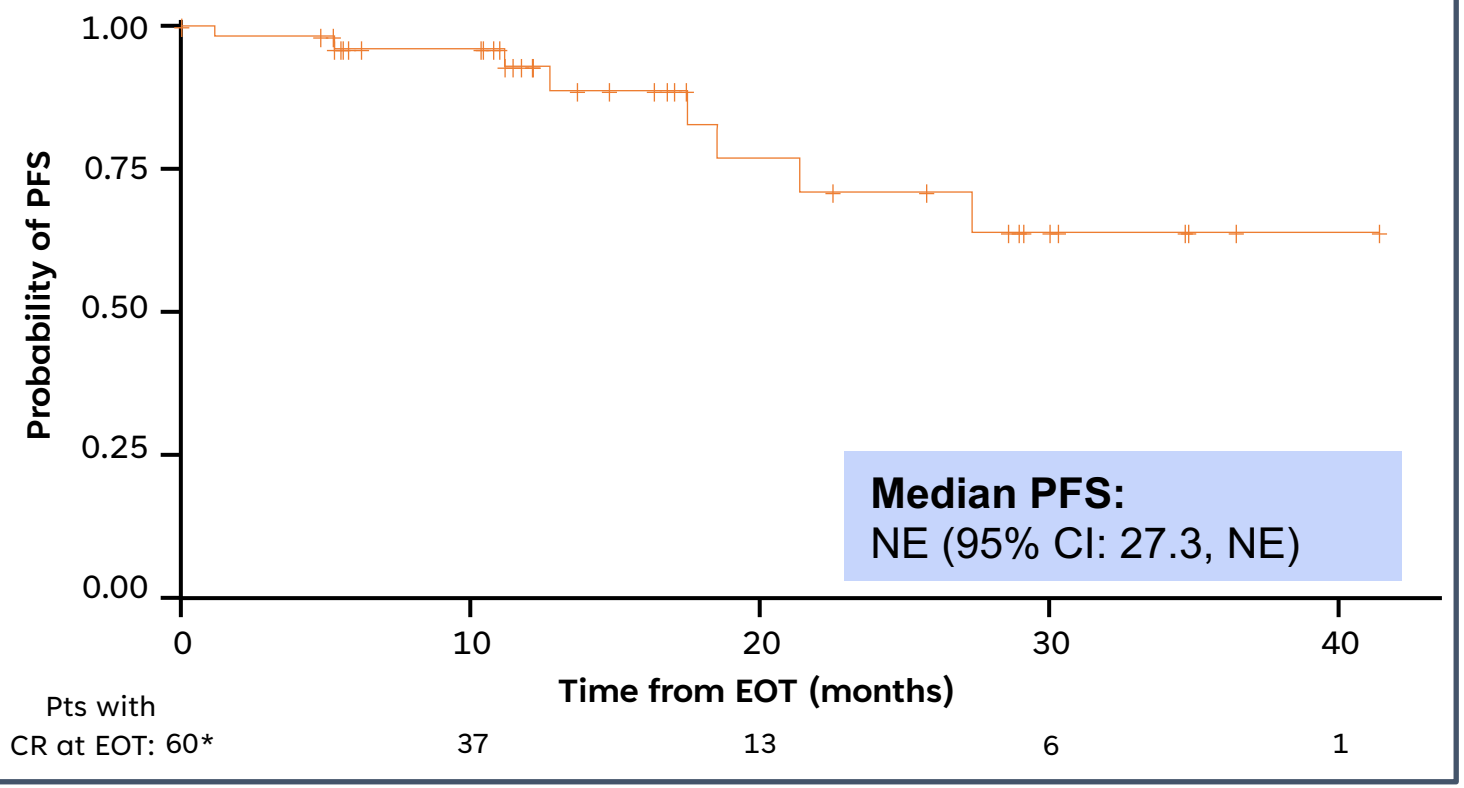
- CD3 ×CD20 bsAbs bring together T cells and CD20+ tumor cells to induce T cell-mediated killing of the tumor cell[2]
- Able to induce effector T cell binding without requiring MHC-mediated antigen presentation[2]

B-NHL, B-cell non-Hodgkin lymphoma; bsAb, bispecific antibody; MHC, major histocompatibility complex; TCR, T-cell receptor.

1. Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625. 2. Schuster SJ. *Hematological Oncology*. 2021;39(S1):113–116. 3. You G, et al. *Vaccines*. 2021;9:724.

GLOFITAMAB: PFS IN PATIENTS WITH CR AT EOT

Progression-free survival with landmark at EOT (N=61)*



	N=61
Median PFS follow-up from EOT, months (95% CI)	11.5 (10.5–16.4)
Median PFS, months (95% CI)	NE (27.3–NE)
12-month PFS, % (95% CI)	92.6 (84.3–100.0)

High proportion of patients (93%) remain progression free 12 months post-EOT

*One patient had pseudoprogression prior to CR at EOT visit and is by definition excluded from PFS analysis.

DESENHO DO ESTUDO EPCORE LNH-1[1]

EPCORITAMABE EM PACIENTES COM LDGCB R/R 3L+

Epcoritamabe foi avaliado com base nos resultados do EPCORE NHL-1, um estudo aberto, multicêntrico, multicoorte, de braço único com pacientes de LDGCB R/R após duas ou mais linhas de terapia sistêmica (N = 139).

População de Eficácia (N = 139)

Desfecho primário:[2]* **TRG, RC + RP**
Desfechos secundários selecionados:[2] **Taxa de RC, DOR, DOCR, tempo para resposta**

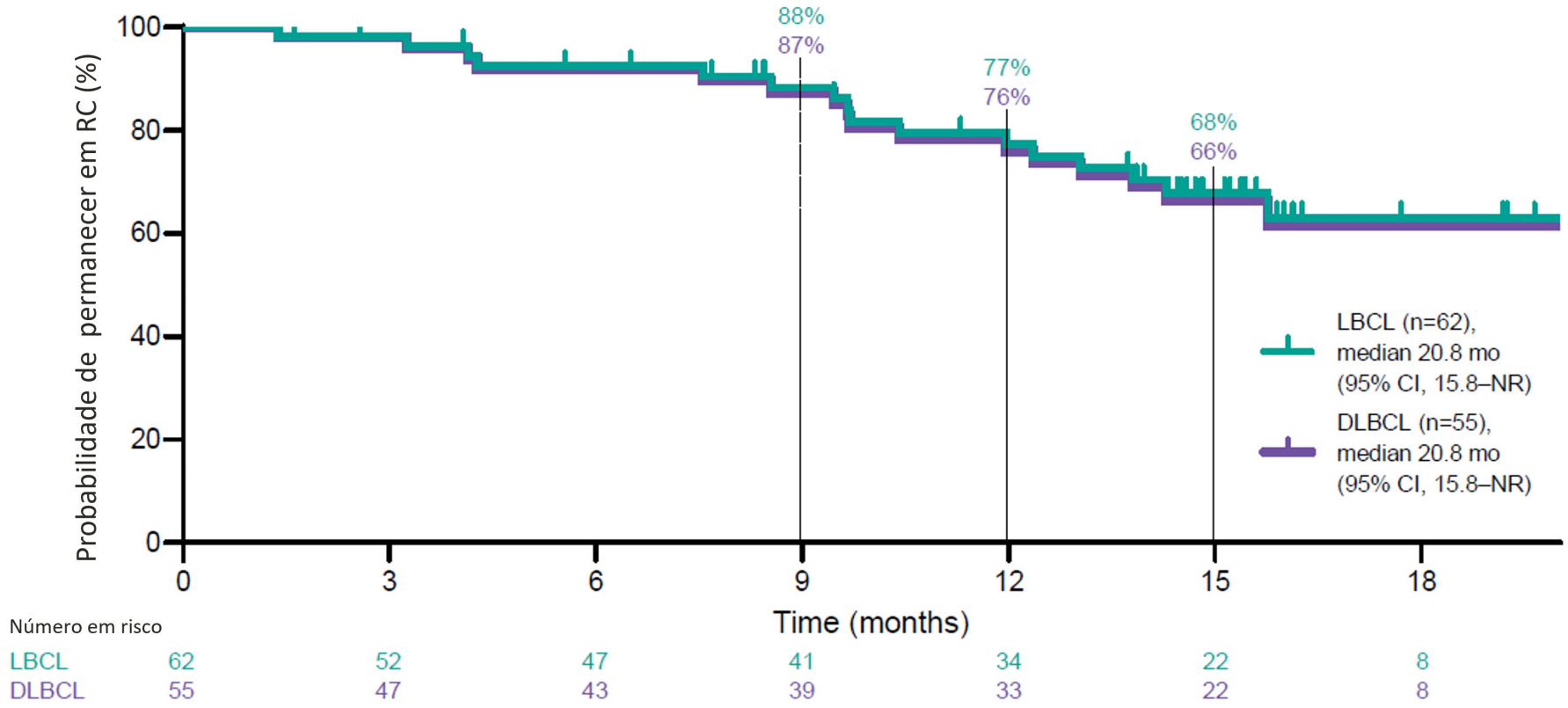
Principais critérios de inclusão:[2]
- ECOG PS 0-2;
- CAR T prévio permitido;
- ≥ 2 linhas prévias de terapia antineoplásica;
- ≥ 1 mAb anti-CD20.

Principais critérios de exclusão:
- Envolvimento do linfoma no SNC;
- TCTH alogênico ou transplante de órgãos sólidos;
- Infecção ativa contínua;
- Quaisquer pacientes com imunidade de células T reconhecidamente prejudicada.

A população total do estudo foi de 157 pacientes, dos quais: **139 apresentavam LDGCB**; nove, Linfoma de célula B de alto grau e cinco, de linfomas folicular G3B e quatro apresentavam LBPM.

*Determinado pelos critérios de Lugano (2014) conforme avaliado por um IRC.
LNH: linfoma não-Hodgkin; **TRG:** taxa de resposta global; **RC:** resposta completa; **RP:** resposta parcial; **DOCR:** duração da resposta completa; **DOR:** duração da resposta; **ECOG PS**: Status de desempenho do Grupo de Oncologia Cooperativa Oriental; **CD20:** *cluster* de diferenciação 20; **SNC:** sistema nervoso central; **TCTH:** transplante de células-tronco hematopoéticas; **IRC:** Comitê de Revisão Independente; **mAb:** anticorpo monoclonal; **LBPM:** linfoma de grandes células B primário do mediastino.
Referências:1. Thieblemont CT, Ghesquieres H, Cheah CY, Clausen MR, Cunningham D, et al. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. *J Clin Oncol*. 2022;JCO2201725.

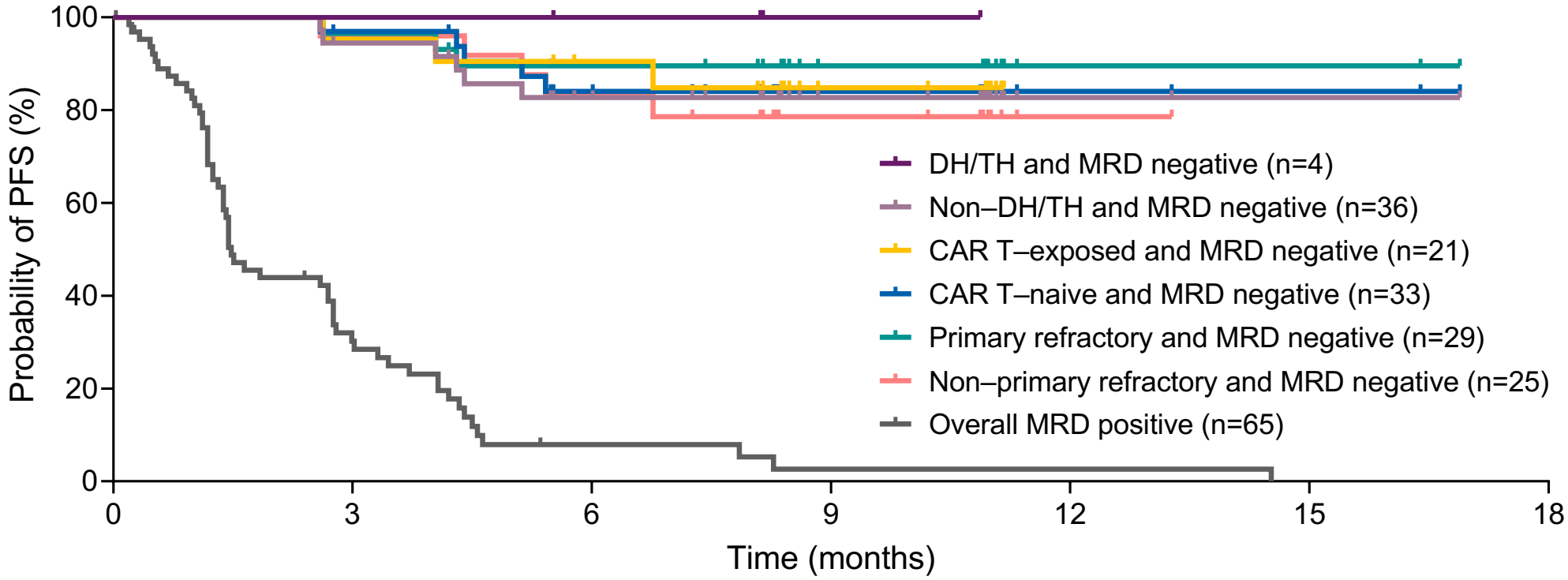
RESPOSTAS COMPLETAS DURÁVEIS[1]



DLBCL: Linfoma difuso de grandes células **B. LBCL:** Linfoma de grandes células B

Referência: 1. Thieblemont C, et al. Abstract 94, Oral Presentation, ICML 2023

MRD Negativity And PFS



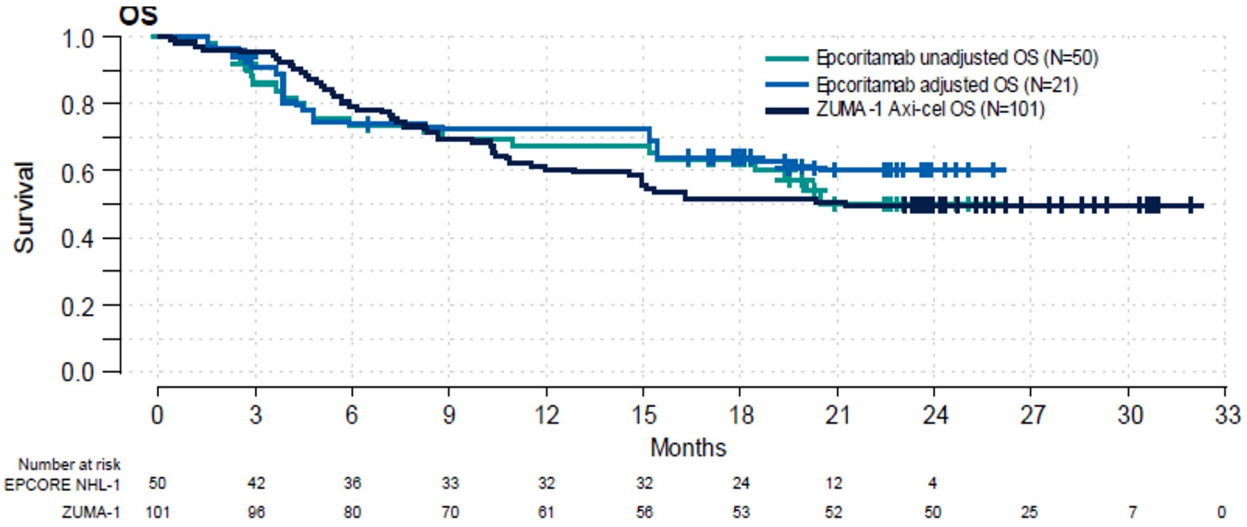
- MRD-negative patients had similar PFS across subgroups

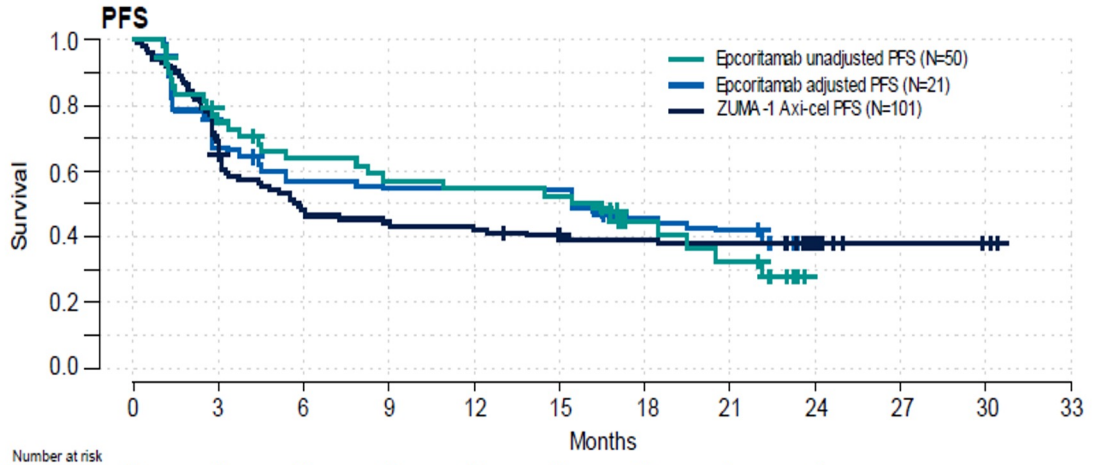
Data cutoff: Jan 31, 2022.

CAR T, chimeric antigen receptor T cell; DH, double-hit; MRD, minimal residual disease; PFS, progression-free survival; TH, triple-hit.

Phillips T, et al. Poster presentation at: American Society of Hematology; December 10–13, 2022; New Orleans, LA, USA/Virtual.

BISPECIFICS X CART: AN INDIRECT COMPARISON



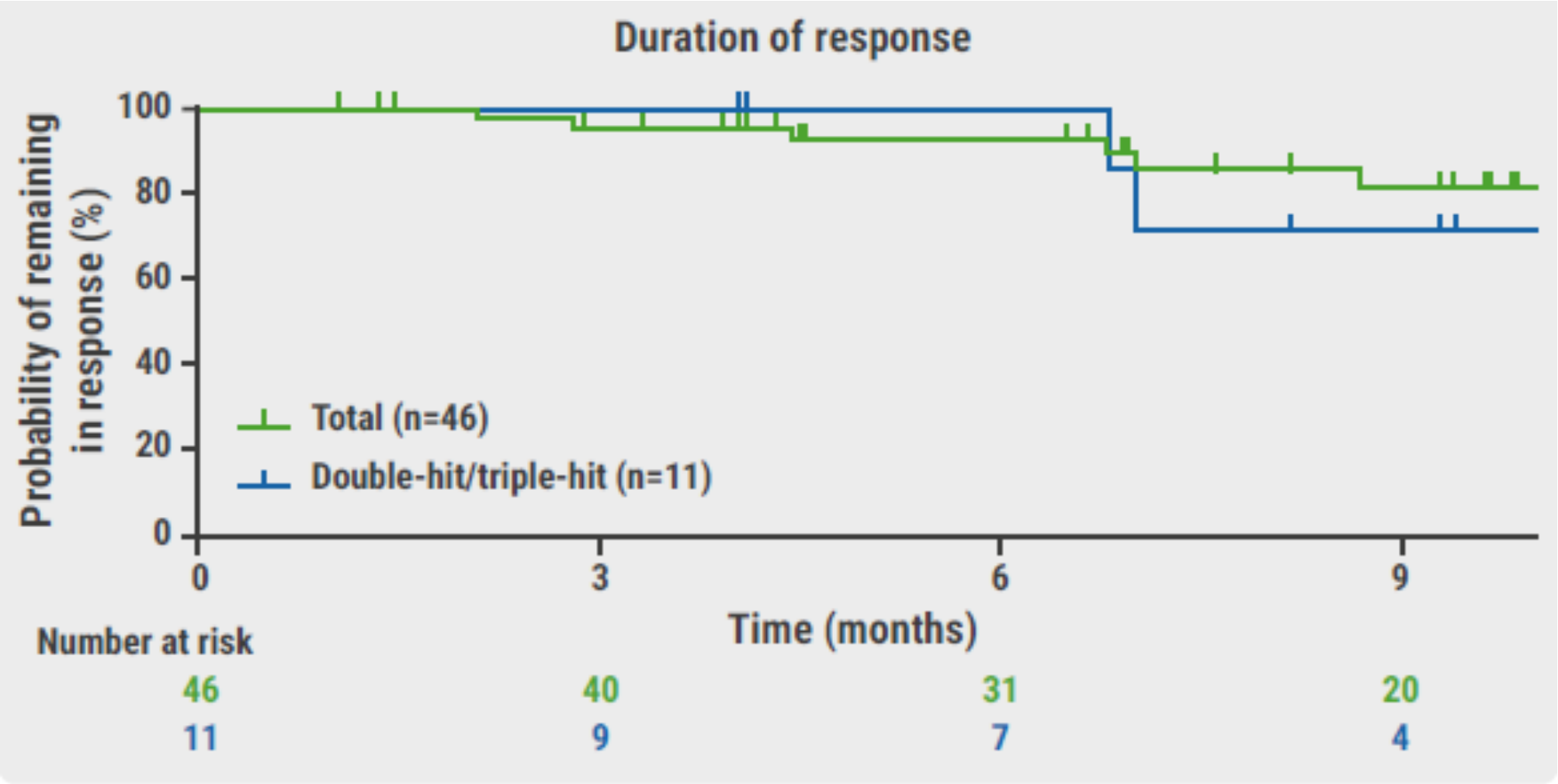


	OS HR (95% CI)	*P*-value
Unadjusted	0.929 (0.560, 1.542)	0.777
Adjusted	0.760 (0.354, 1.634)	0.483

	PFS HR (95% CI)	*P*-value
Unadjusted	0.933 (0.613, 1.420)	0.746
Adjusted	0.931 (0.491, 1.768)	0.828

Thieblemont C, Fox C, Wang et al. P1154: EFFICACY OF SUBCUTANEOUS EPCORITAMAB VS AXI-CEL IN R/R DLBCL CAR T-NAIVE AND CAR T-ELIGIBLE PATIENTS: AN INDIRECT COMPARISON. Hemasphere. 2023 Aug 8;7(Suppl):e006348e.

EPCORITAMAB + R-CHOP IN DLBCL



https://doi.org/10.55788/d4e8de1e

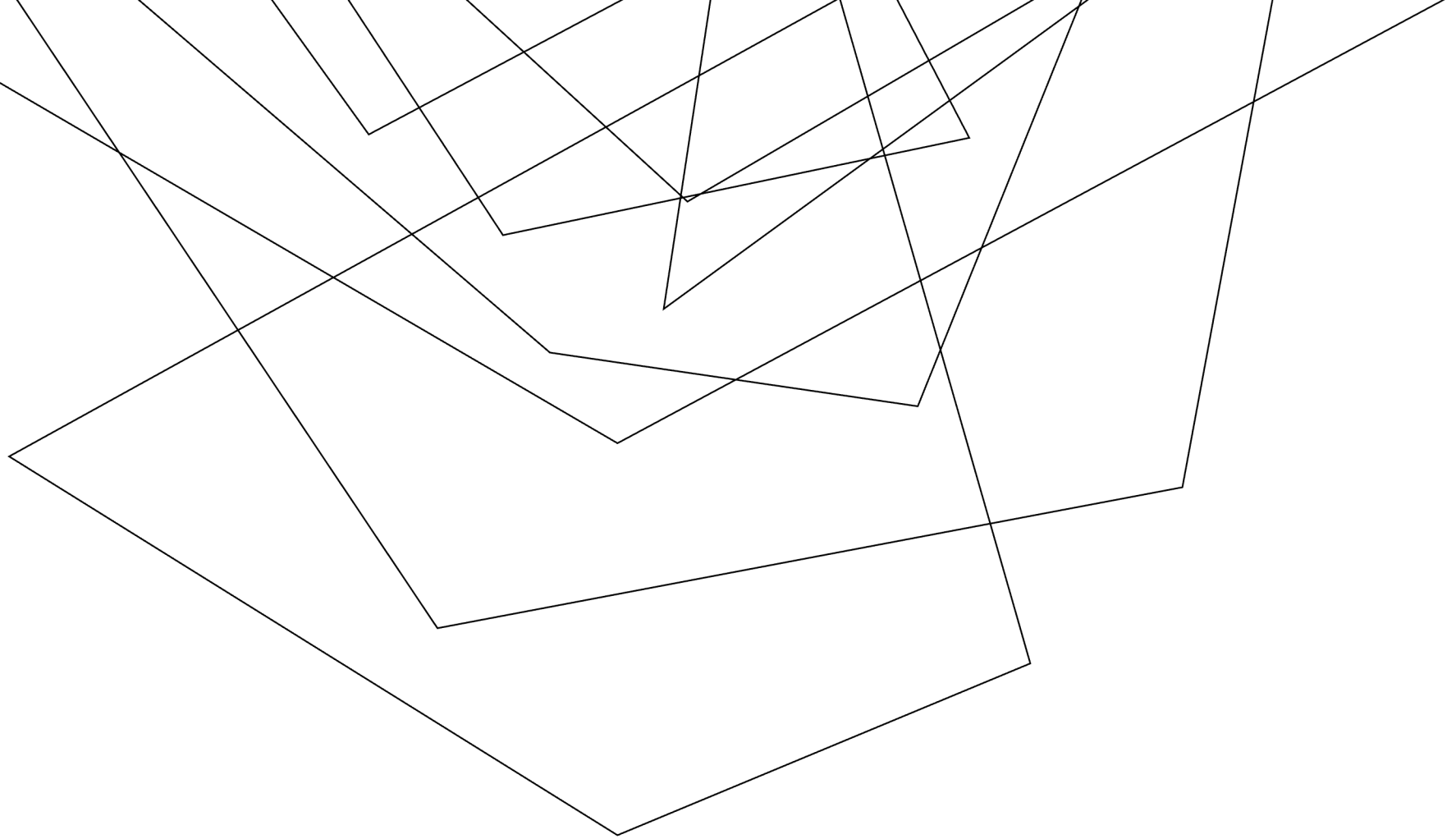
CONCLUSIONS

Vamos ter un embotellamiento de CARs en futuro

Sin embargo, los biespecíficos lo ven como una opción razonable en Latinoamérica.

Aprobaciones nuevas de CART en FL e LLC

CARTs/NKs en tumores sólidos – Estamos listos?



THE BTKIDS ON THE BLOCK SHOW CONTINUES

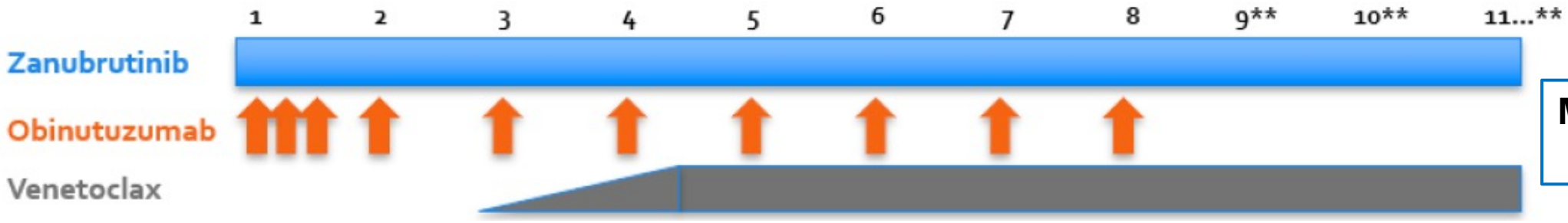

lymphoma_experience
Sheraton Miramar Hotel & Convention Center
te uno?
TP53 mutated
(N = 20)
N
%
P
Eskelland et al, Blood 2016
LEX

Memorial Sloan Kettering Cancer Center

A multicenter, phase 2 trial with zanubrutinib, obinutuzumab, and venetoclax (BOVen) in patients with treatment-naïve, *TP53*-mutant mantle cell lymphoma

Anita Kumar, MD, Jacob Soumerai, MD, Jeremy S. Abramson, MD, Jeffrey A. Barnes, MD, PhD, Philip Caron, MD, Maria Chabowska, BSc, Mary Devlin, Ahmet Dogan, MD, PhD, Lorenzo Falchi, MD, Rayna N. Garcia, Clare Grieve, MPH, Emma Haskell, Julie E. Haydu, MD PhD, Patrick Connor Johnson, MD, Ashlee Joseph, Hailey E. Kelly, Alyssa Labarre, Emerald D Littlejohn, MPH, Jennifer Kimberly Lue, Joanna Mi, Rosalba Martignetti, Grace McCambridge, Alison Moskowitz, MD, Colette Owens, MD, Sean F. Plummer, Madeline G. Puccio, Gilles Salles, MD, PhD, Venkatraman Seshan, PhD, Natalie Slupe, and Andrew D. Zelenetz, MD, PhD

Phase II Multicenter Study of BOVen



Minimum of 24 cycles

Dosing:

Zanubrutinib 160 mg oral twice daily

Obinutuzumab 1000 mg IVPB
Cycle 1: day 1, 8, 15
Cycle 2-8: day 1

Venetoclax 400mg oral daily
5-week ramp-up: 1 week each of 20mg; 50mg; 100mg; 200mg; 400 mg oral daily

After 24 cycles, MRD-driven approach to limit treatment duration in selected patients:

CR and uMRD	→	Stop treatment
<CR and/or dMRD	→	Continue ZANU and VEN

Key Eligibility Criteria:

- Previously untreated MCL (except localized RT prior)
- *TP53* mutation (of any variant allele frequency)
- ECOG ≤2, adequate organ and hematologic function (ANC >1, PLT >75, HGB ≥9 (unless due to MCL))

Primary Endpoint:

- 2-year progression-free survival.
- A promising 2-yr PFS rate ≥55% and an unacceptable rate ≤30%
- If ≥11 patients were progression-free at 2 years, the treatment regimen would be declared effective

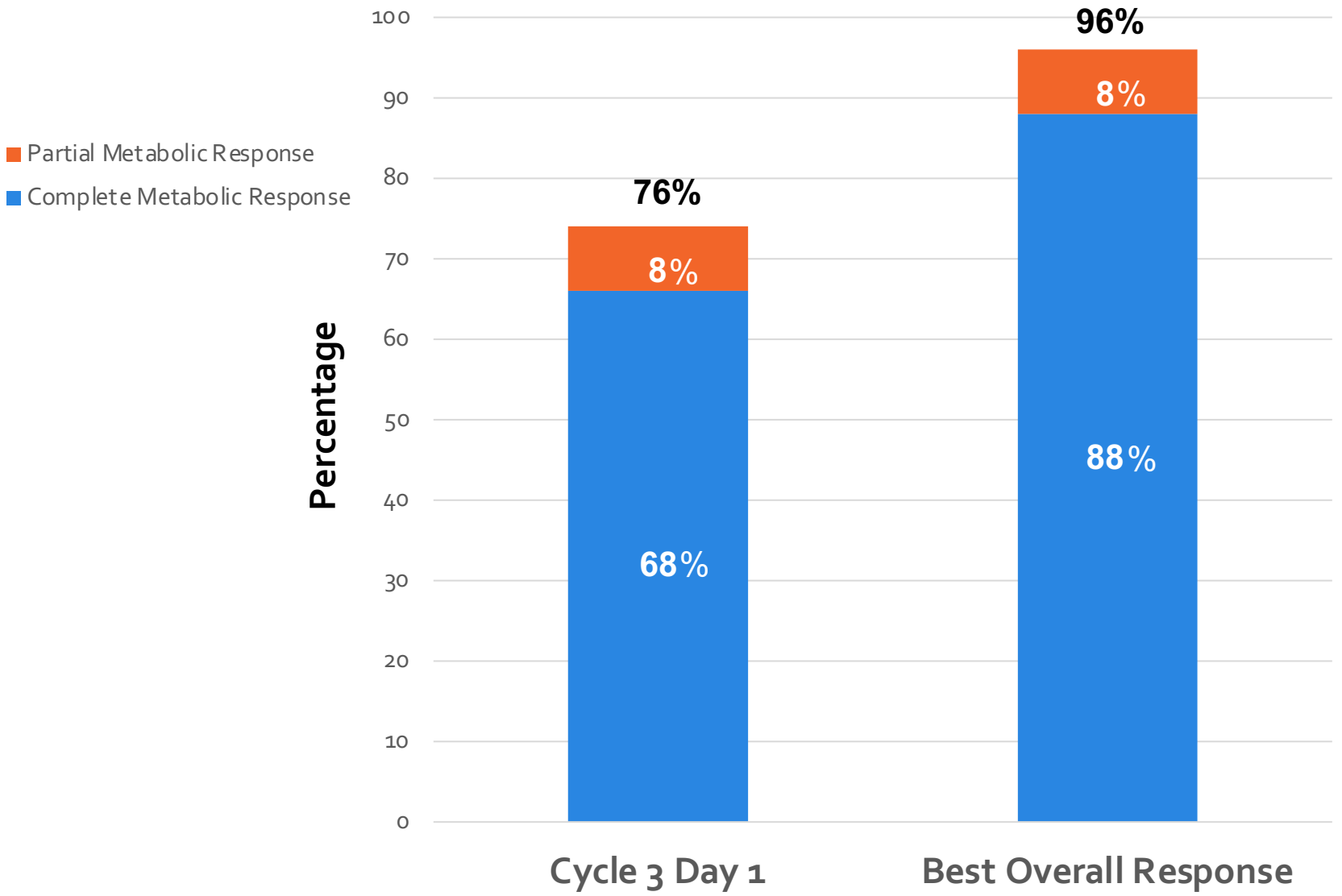
Baseline Patient Characteristics (n=25)

Characteristic	N(%)
Enrollment Site	
Memorial Sloan Kettering	13 (52%)
Massachusetts General Hospital	12 (48%)
Age in years, median (range)	68 (60-73)
Male, n (%)	19 (76%)
MCL Histology	
Classical	15 (60%)
Non-nodal leukemic	5 (20%)
Blastic/Blastoid	2 (8%)
Pleomorphic	3 (12%)
Stage IV	25 (100%)
Ki-67 Proliferation Rate	
<30%	8 (38%)
≥30% and <50%	6 (29%)
≥50%	7 (33%)
Unknown	4
MIPI Classification	
Low	1 (4.0%)
Intermediate	7 (28%)
High	17 (68%)

Characteristic	N(%)
Bone marrow involvement	
Yes	22 (88%)
No	3 (12%)
Peripheral blood involvement*	
Yes	20 (80%)
No	5 (20%)
GI involvement**	
Yes	8 (32%)
No	17 (68%)
TP53 overexpression by IHC***	
Positive	18 (86%)
Negative	3 (14%)
Unknown	4
IGVH mutation	
Mutated	5 (28%)
Unmutated	13 (72%)
Unknown	7
17p deletion by FISH / SNP Array	
Yes	11 (44%)
No	14 (56%)

*Abnormal B-cell population detected by flow cytometry in peripheral blood **Endoscopic evidence of MCL***TP53 expression: ≥30% tumor nuclei staining and strong intensity

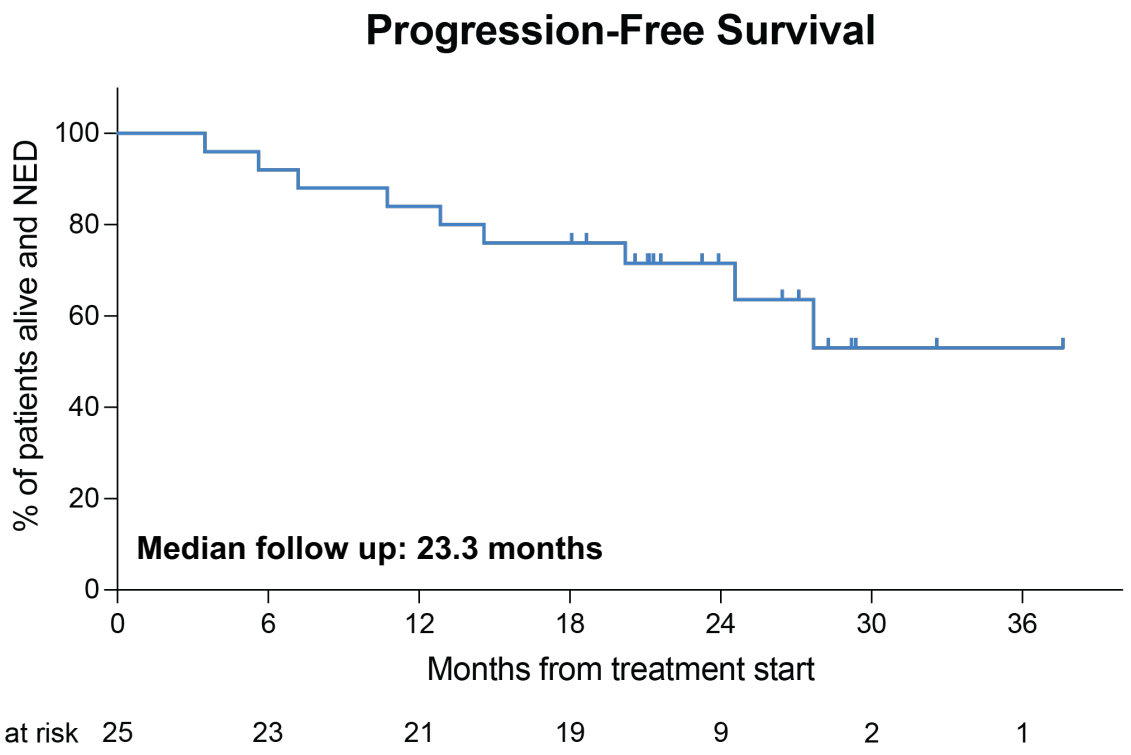
Response Rates By Timepoint



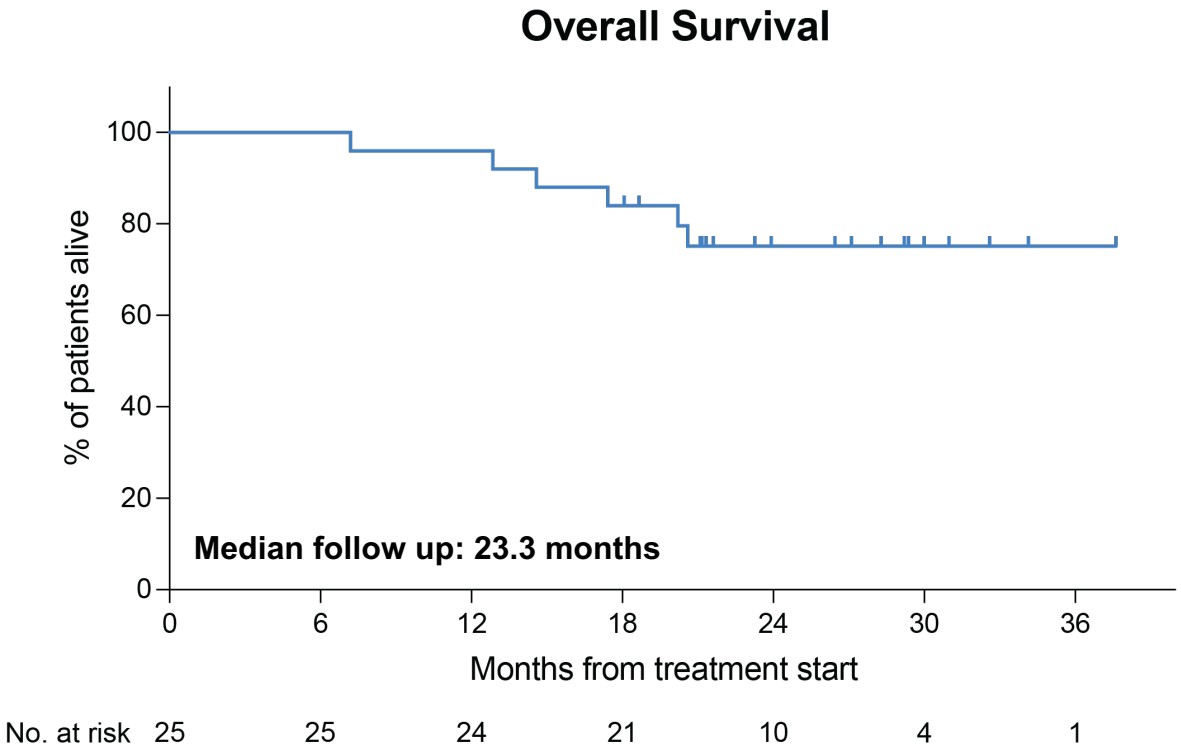
- **High Metabolic Response Rates after 2 cycles of Zanu+Obin**
- **High Overall Metabolic Response Rate with Zanu+Obin+Ven**

Memorial Sloan Kettering Cancer Center

Progression-Free and Overall Survival Outcomes



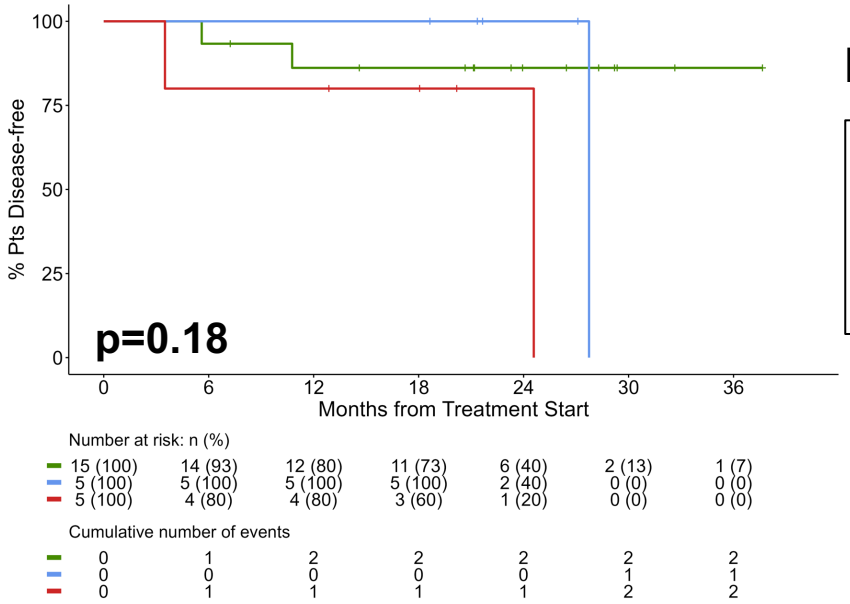
2-year PFS: 72% [95% CI: 56, 92]
Median PFS: not reached



2-year OS: 75% [95% CI: 58, 93]
Median OS: not reached

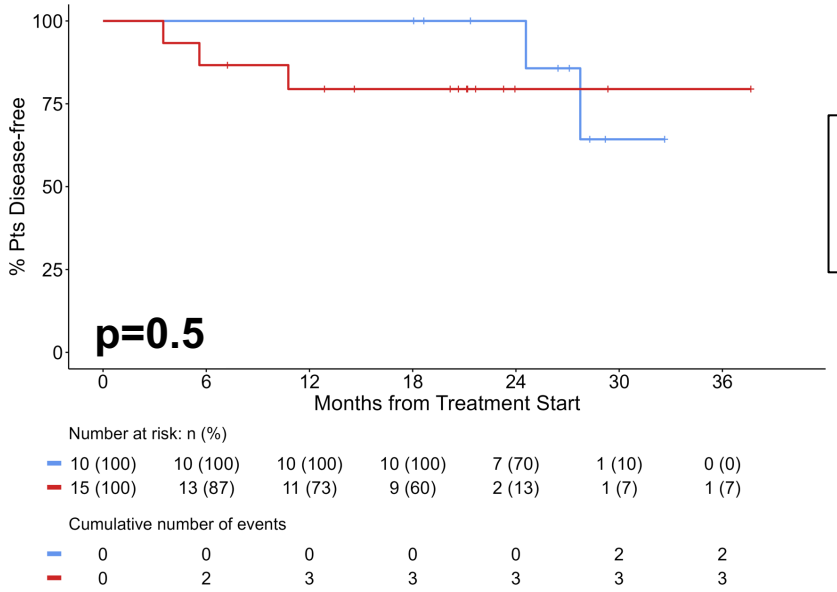
Primary PFS Endpoint is Met:
11 patients progression-free at 2 years

DFS by Baseline Factors



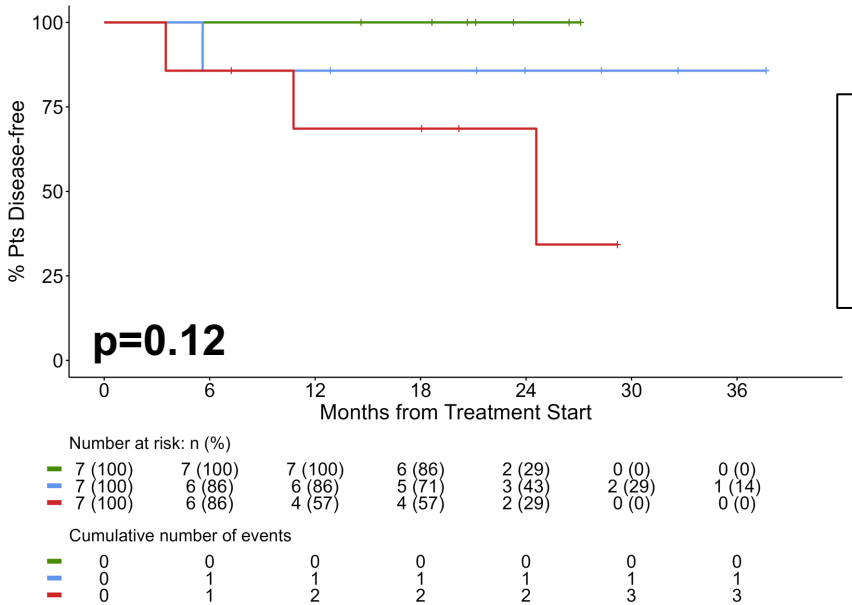
Morphology

- Classic
- Leukemic
- Blastoid



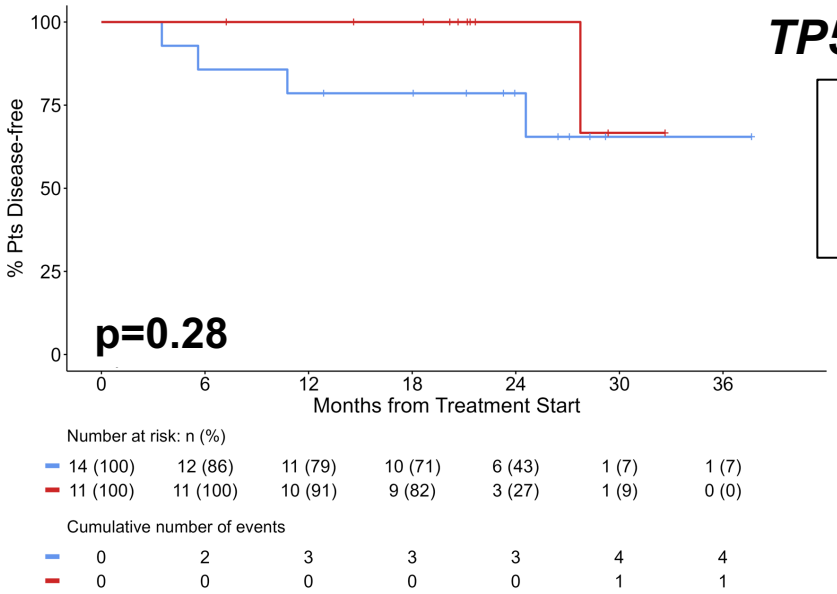
Age

- <65 years
- ≥ 65 years



Ki-67

- < 30%
- ≥30 - <50%
- ≥ 50%



TP53 Mut and Del

- *TP53*mut⁺
- *TP53*mut⁺ / 17pdel⁺

ROSEWOOD study design

Key eligibility criteria

- Age ≥18 years
- Grade 1-3A R/R FL
- Previous treatment with ≥2 lines of therapy, including an anti-CD20 antibody and an alkylating agent
- Measurable disease
- ECOG PS of 0-2
- Adequate organ function
- No prior BTK inhibitor

Arm A
Zanubrutinib[a] + obinutuzumab[b] (N=145)
Until PD or unacceptable toxicity

Randomization 2:1
Stratification factors
- Number of prior lines of treatment
- Rituximab-refractory status
- Geographic region

Arm B
Obinutuzumab[b] (N=72)
Option to cross over to combination if PD is centrally confirmed or if there is no response at 12 months

Primary endpoint
- ORR by IRC according to Lugano 2014 classification[1]

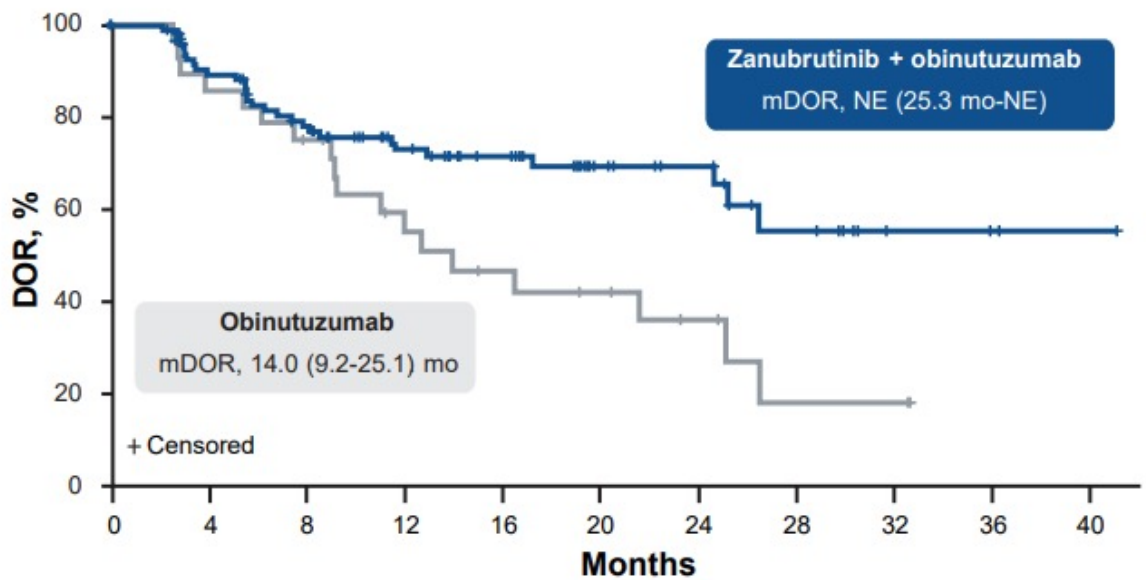
Other endpoints
- DOR by IRC[c]
- PFS by IRC[c]
- OS[c]
- TTNT
- Safety (AEs)[c]

127 sites; 17 countries/regions
Randomized November 2017 to June 2021

AE, adverse event; BTK, Bruton tyrosine kinase; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R/R, relapsed or refractory; TTNT, time to next treatment.
[a] Zanubrutinib was given orally at 160 mg twice daily. [b] Obinutuzumab was given intravenously at 1000 mg in both arms on days 1, 8, and 15 of cycle 1, day 1 of cycles 2-6, and then every 8 weeks up to a maximum of 20 doses. [c] Secondary endpoint.
1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3068.

DOR and PFS were longer with zanubrutinib + obinutuzumab

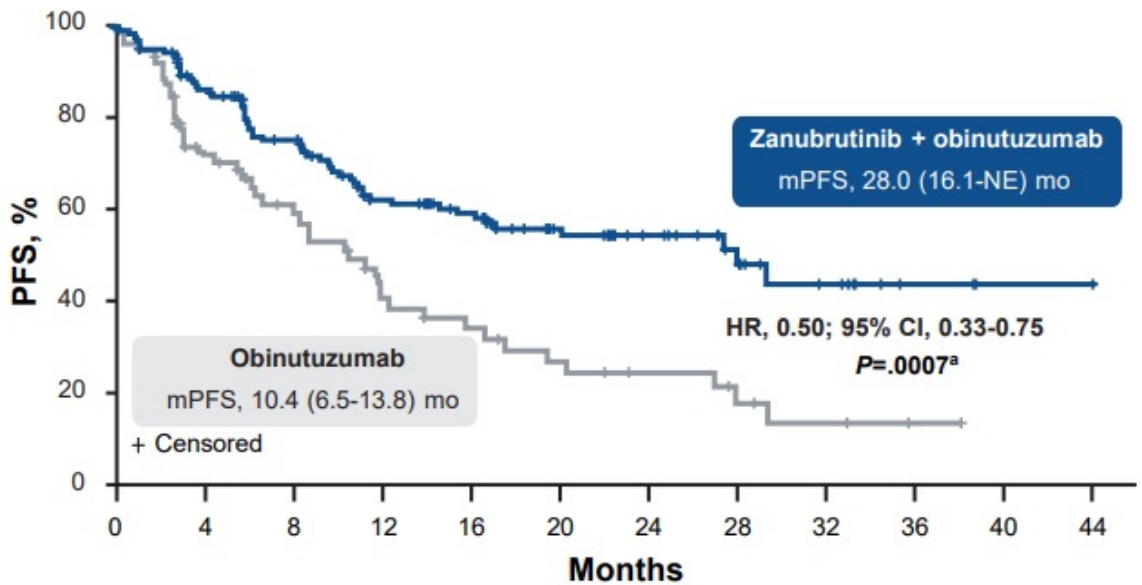
DOR by IRC



No. at risk

Zanubrutinib + obinutuzumab	100	97	82	73	68	59	51	43	40	33	23	21	19	12	10	7	3	3	2	1	1	0
Obinutuzumab	33	29	24	23	20	16	13	11	10	9	8	6	5	3	2	2	2	0				

PFS by IRC

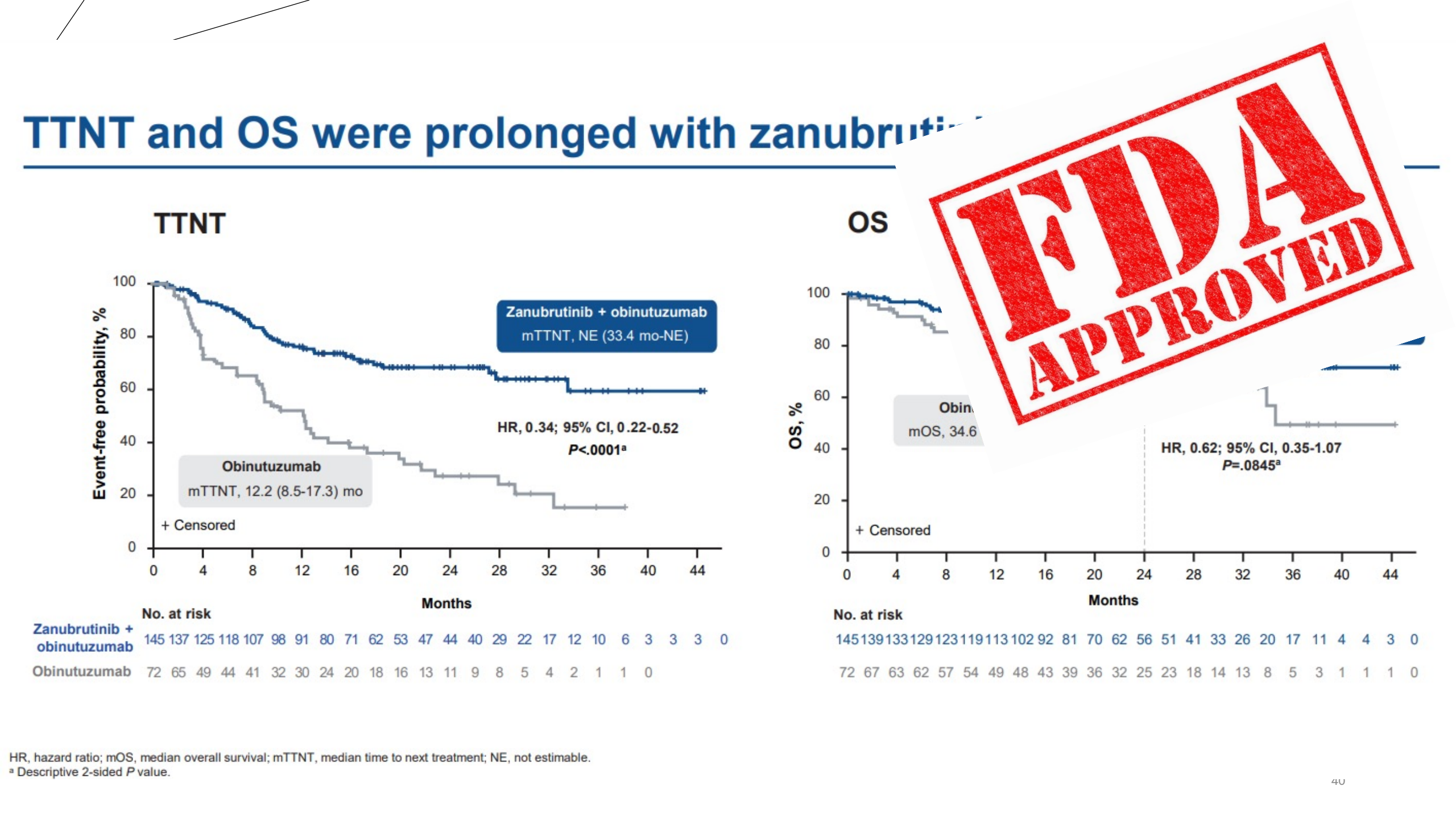


No. at risk

Zanubrutinib + obinutuzumab	145	135	116	96	92	79	67	62	56	45	38	35	25	22	15	10	9	5	3	3	1	1	0
Obinutuzumab	72	63	42	34	30	27	19	16	15	12	11	9	8	8	5	3	3	2	1	1	0		

HR, hazard ratio; IRC, independent review committee; mDOR, median duration of response; mPFS, median progression-free survival; NE, not estimable.
[a] Descriptive 2-sided *P* value.

TTNT and OS were prolonged with zanubruti



TTNT

No. at risk

Zanubrutinib + obinutuzumab	145	137	125	118	107	98	91	80	71	62	53	47	44	40	29	22	17	12	10	6	3	3	3	0
Obinutuzumab	72	65	49	44	41	32	30	24	20	18	16	13	11	9	8	5	4	2	1	1	0			

OS

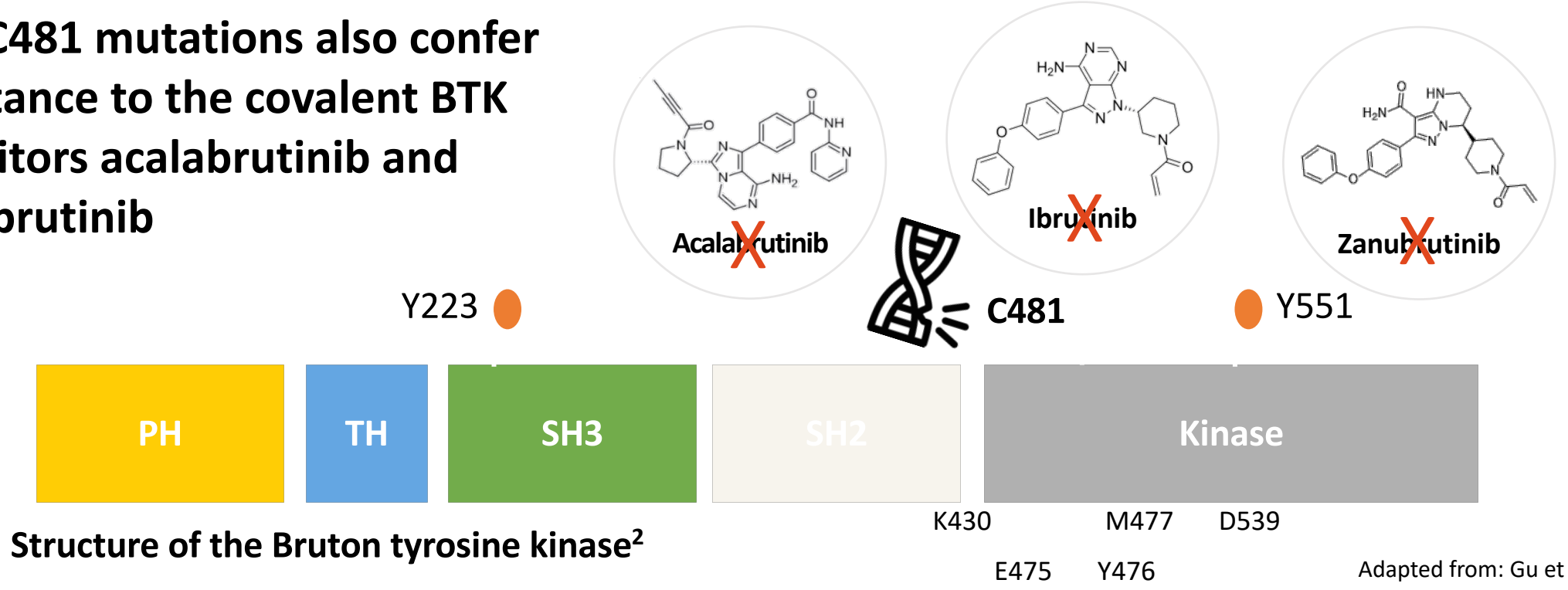
No. at risk

	145	139	133	129	123	119	113	102	92	81	70	62	56	51	41	33	26	20	17	11	4	4	3	0
	72	67	63	62	57	54	49	48	43	39	36	32	25	23	18	14	13	8	5	3	1	1	1	0

HR, hazard ratio; mOS, median overall survival; mTTNT, median time to next treatment; NE, not estimable.
[a] Descriptive 2-sided *P* value.

ACQUIRED RESISTANCE TO COVALENT BTK INHIBITORS IS GENERALLY DRIVEN BY MUTATIONS IN *BTK* AT THE C481 SITE[1]

***BTK* C481 mutations also confer resistance to the covalent BTK inhibitors acalabrutinib and zanubrutinib**



Structure of the Bruton tyrosine kinase[2]

Adapted from: Gu et al. 2021.

In sum, BTK resistance contributes to disease progression and diminishes the efficacy of all covalent BTK inhibitors

1. Woyach. NEJM 2014;370:2286. 2. Gu. J Hematol Oncol. 2021;14:40

PIRTOBRUTINIB: A HIGHLY POTENT AND SELECTIVE NON-COVALENT (REVERSIBLE) BTK INHIBITOR

Kinome Selectivity[1]

Highly selective for BTK

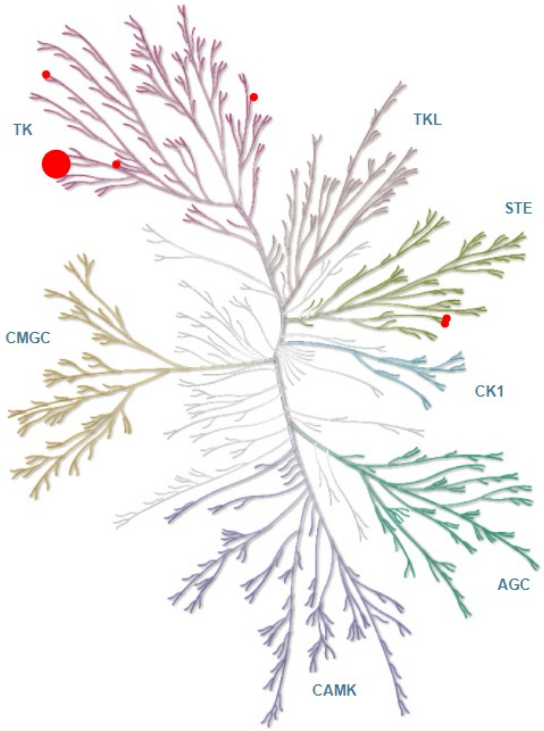
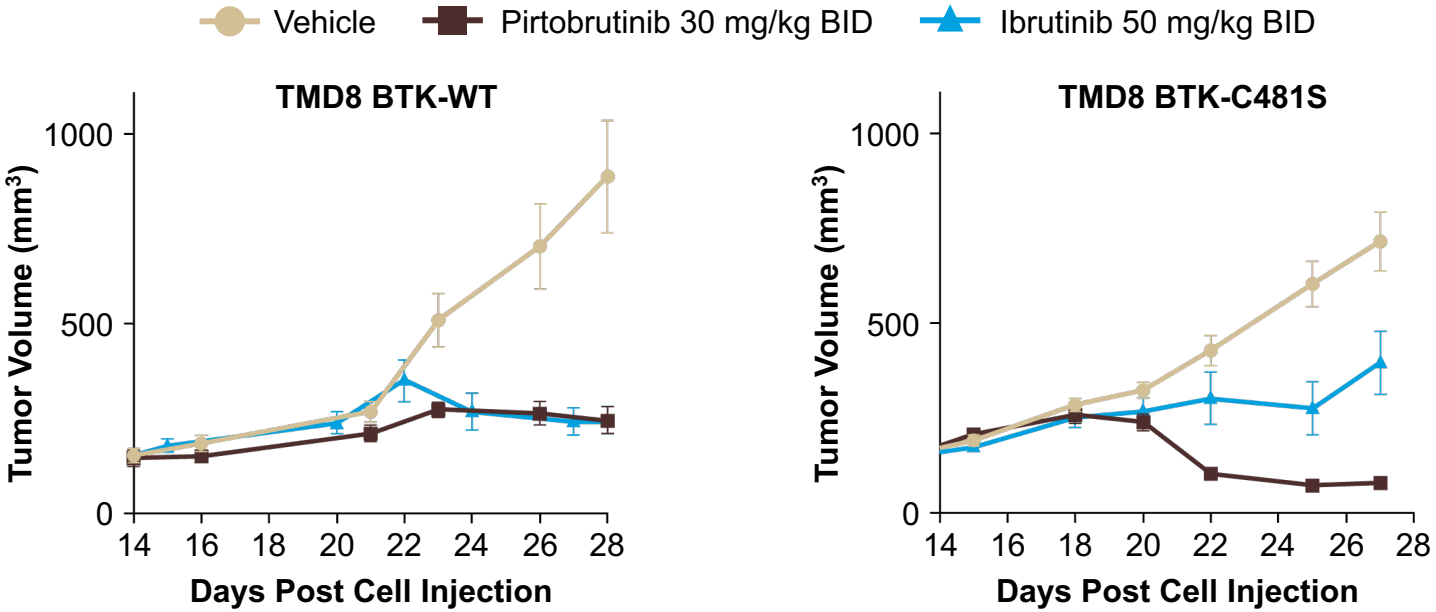


Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

Xenograft Models

In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



Nanomolar potency against WT and C481-mutant BTK in cell and enzyme assays[2]

More than 300-fold selectivity for BTK vs. 370 other kinases[2]

Because of reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[2]

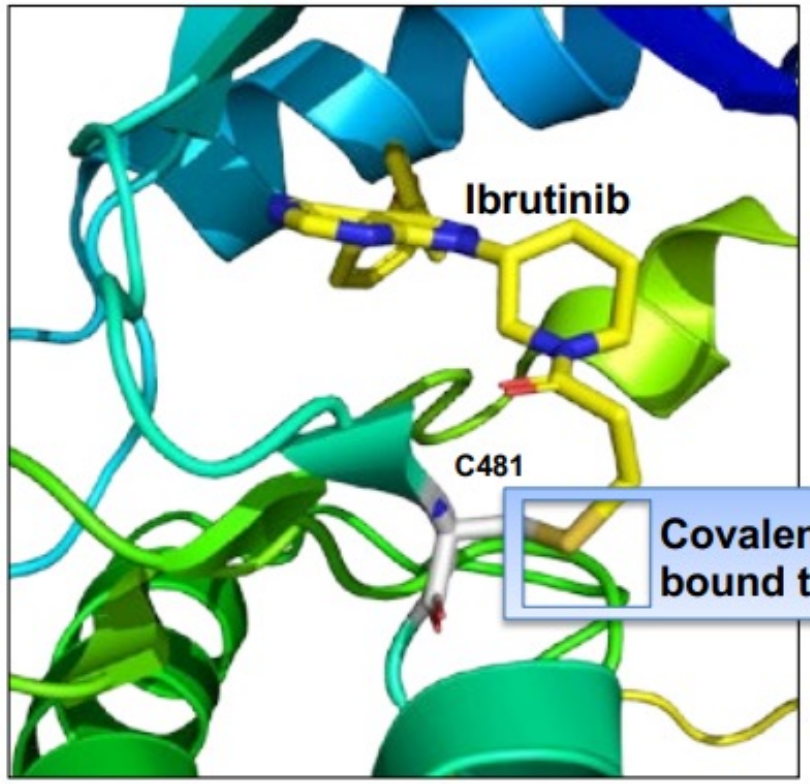
Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]

BID=Twice Daily; BTK=Bruton Tyrosine Kinase; WT=Wild Type.

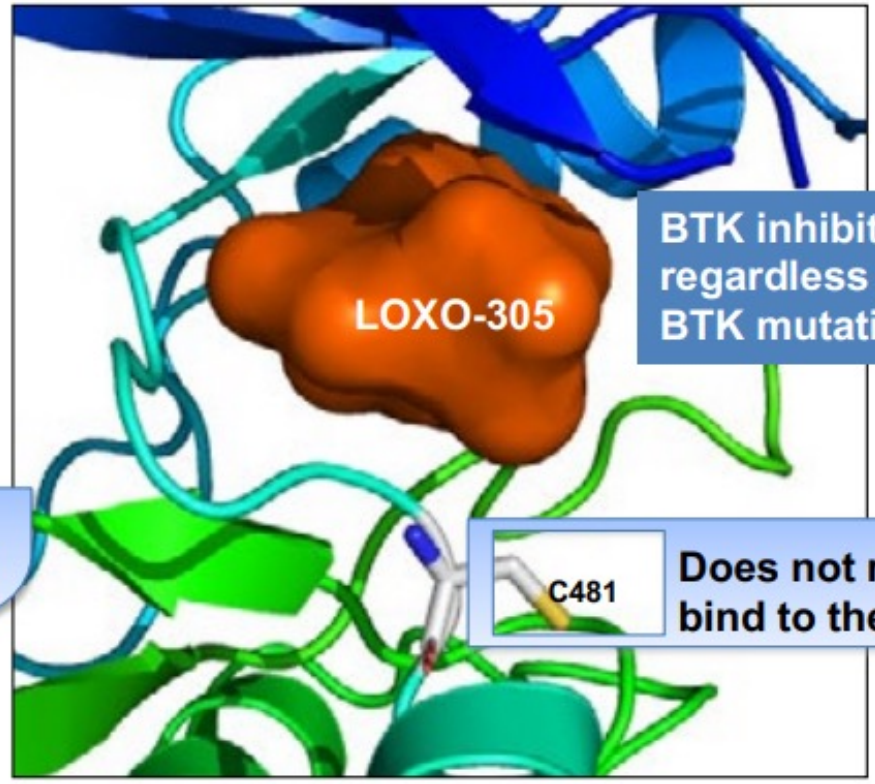
1. Mato AR, et al. *Lancet.* 2021;397(10277):892-901. 2. Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:S216.

LOXO-305 MECHANISM OF ACTION

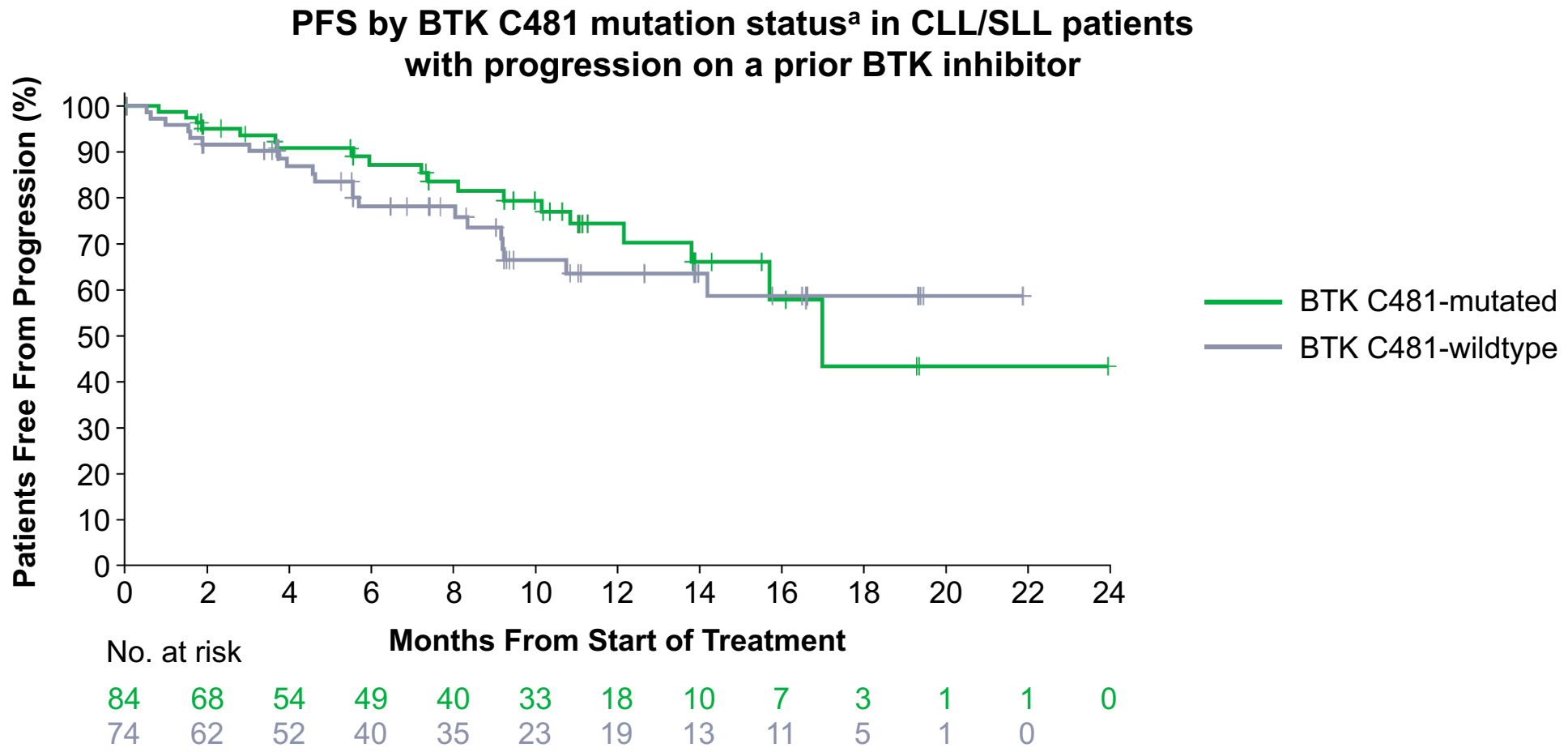
Covalent BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) require WT BTK for activity



LOXO-305 is a non-covalent BTK inhibitor that is potent against both WT and C481-mutant BTK

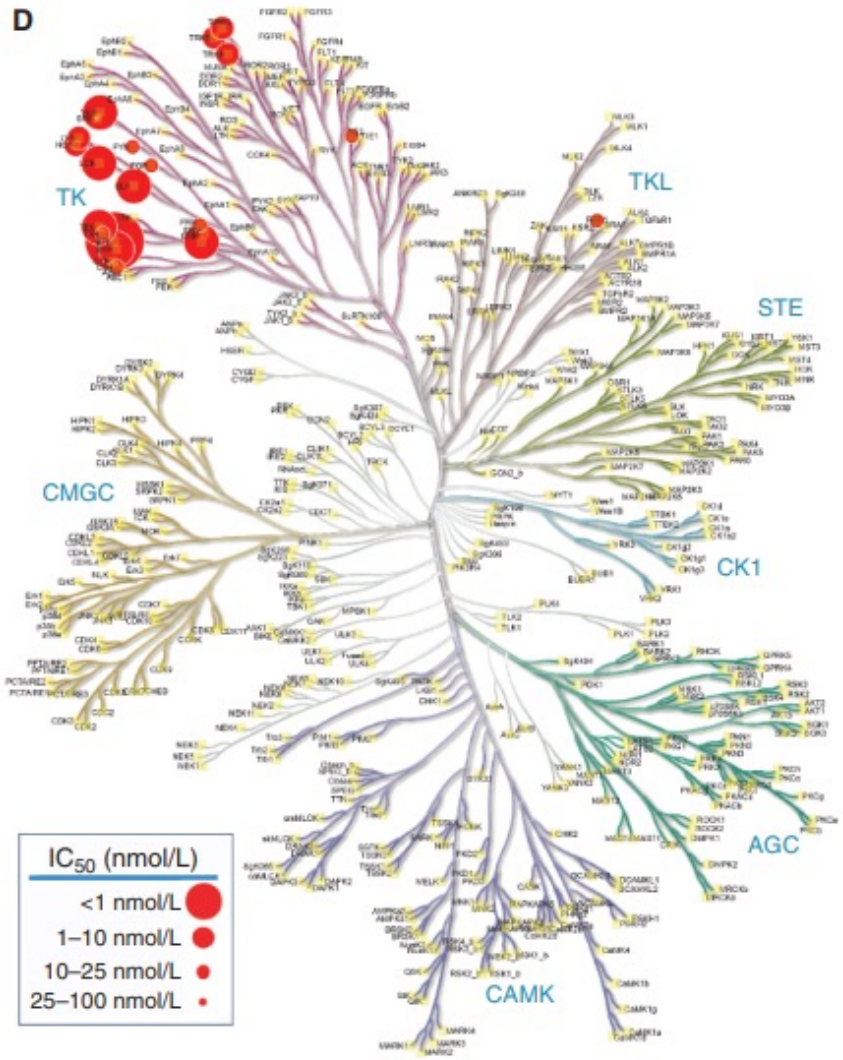


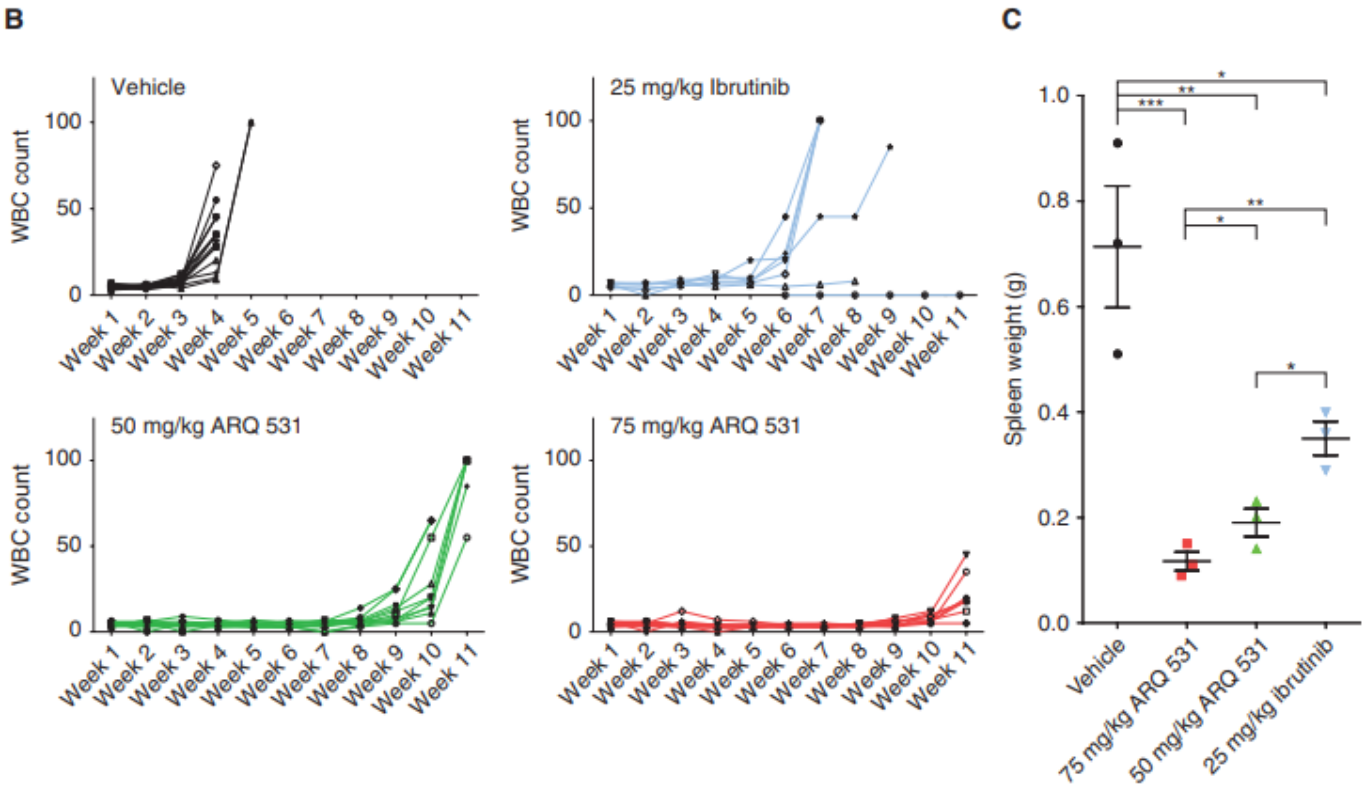
BTK C481 MUTATION STATUS NOT PREDICTIVE OF PIRTOBRUTINIB BENEFIT



Data cutoff date: July 16, 2021.
Response status per iwCLL 2018 according to investigator assessment. [a]BTK C481 mutation status was centrally determined and based on pretreatment samples.
BTK=Bruton's tyrosine kinase; iwCLL=International Workshop on Chronic Lymphocytic Leukemia; CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma.

NEMTABRUTINIB, FORMERLY ARQ531

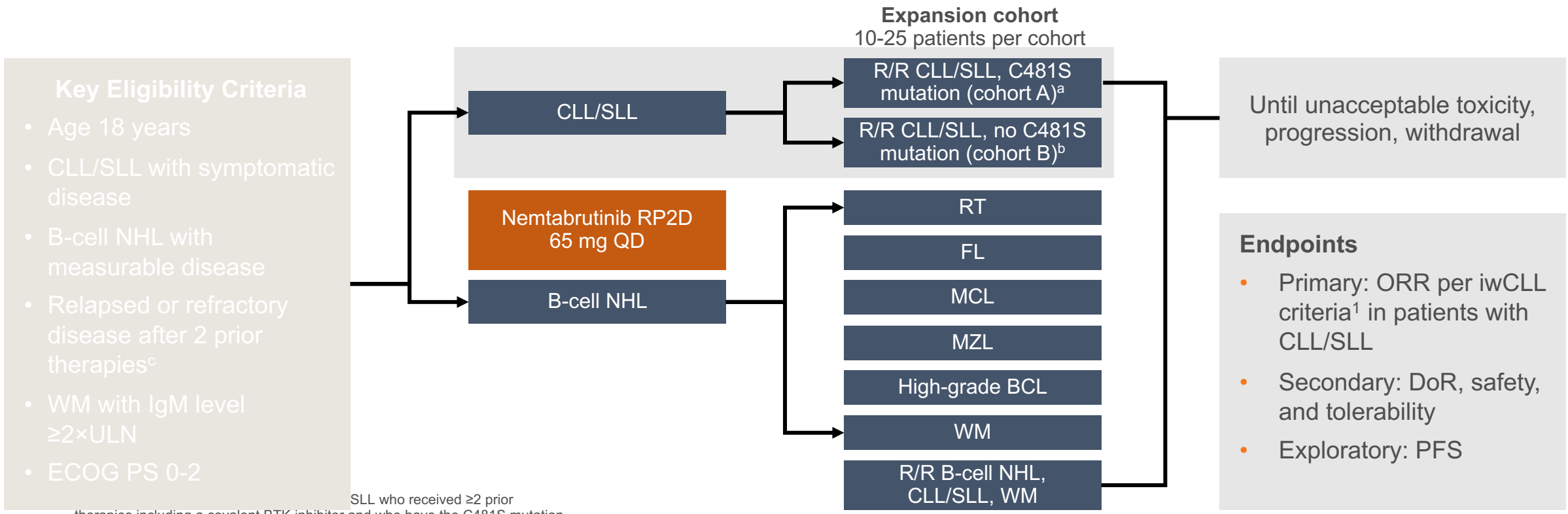




Reiff et al, Caancer Discov 2021

- A Phase 1/2 open-label dose-expansion study of the efficacy and safety of nemtabrutinib for the treatment of B-cell malignancies

BELLWAVE-001: STUDY DESIGN



SLL who received ≥2 prior therapies including a covalent BTK inhibitor and who have the C481S mutation.
[b] Cohort B comprises patients with R/R CLL/SLL who received ≥2 prior therapies, are intolerant to a BTK inhibitor, and have no C481S mutation. [c] Patients with RT had R/R disease after ≥1 prior therapy.
BCL, B-cell lymphoma; **BTK,** Bruton's tyrosine kinase; **CLL**, chronic lymphocytic leukemia; **DoR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **FL**, follicular lymphoma; **IgM**, immunoglobulin M; **iwCLL**, International Workshop on CLL; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **NHL,** non-Hodgkin lymphoma; **ORR**, objective response rate; **PFS**, progression-free survival; **QD,** once daily; **RP2D**,

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

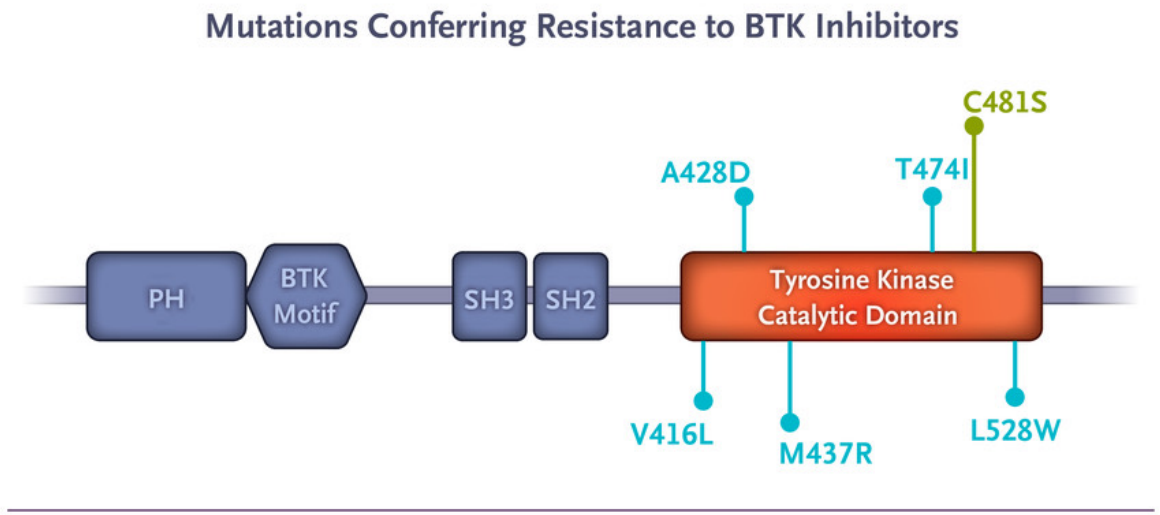
Mechanisms of Resistance to Noncovalent Bruton's Tyrosine Kinase Inhibitors

Wang E et al. DOI: 10.1056/NEJMoa2114110

CLINICAL PROBLEM

Noncovalent inhibitors of Bruton's tyrosine kinase (BTK) are treatment options for several B-cell cancers, including chronic lymphocytic leukemia (CLL), and may be useful in patients in whom resistance to covalent BTK inhibitors (e.g., ibrutinib and acalabrutinib) develops, often as a result of mutations in BTK residue C481. Resistance to a noncovalent BTK inhibitor has now been identified in a phase 1–2 trial of the investigational drug pirtobrutinib.

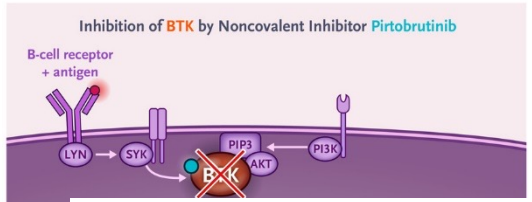
GENOMIC ANALYSIS STUDY



Further study is required to understand the following:

- How mutations in BTK that inactivate its kinase activity can allow ongoing B-cell–receptor signaling.
- Whether similar resistance mechanisms occur in patients who receive noncovalent BTK inhibitors without previous use of covalent BTK inhibitors.
- How frequently these mutations occur in larger groups of patients.

Links: Full Article | NEJM Quick Take



Binding Affinities of BTK Inhibitors

	Noncovalent				Covalent
	Pirtobrutinib	ARQ-531	Vecabrutinib	Fenebrutinib	Ibrutinib
Wild type	Normal	Normal	Normal	Normal	Normal
A428D	None	Decreased	None	None	None
M437R	Decreased	Normal	Decreased	Decreased	Normal
T474I	Decreased	Decreased	Decreased	Normal	Normal
L528W	None	None	Decreased	Normal	None
C481S	Normal	Normal	Normal	Normal	Decreased

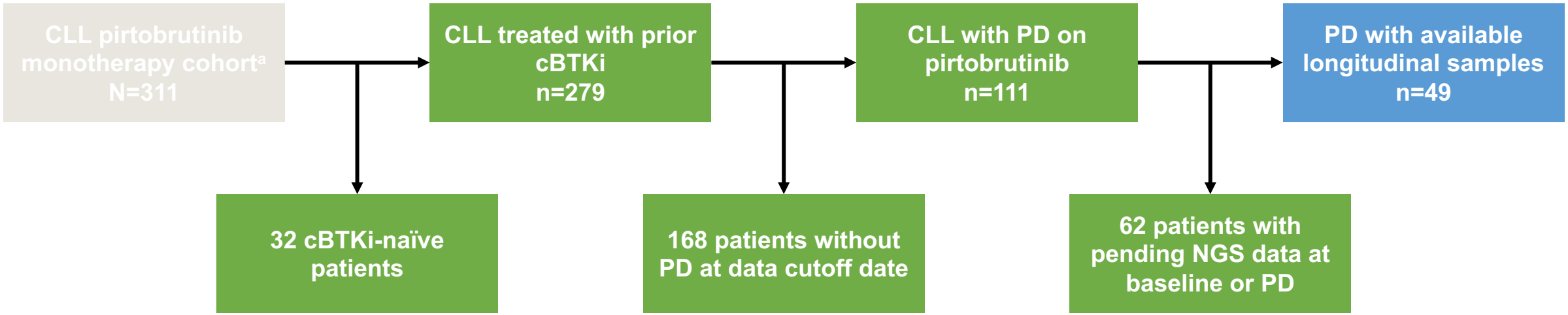
Wild type					
A428D					
M437R					
T474I					
L528W	None	None	Decreased	Normal	None
C481S	Normal	Normal	Normal	Normal	Decreased

CONCLUSIONS

These findings show new mechanisms of acquired resistance to noncovalent and covalent BTK inhibitors in patients with CLL.

- Genomic analysis in the CLL cohort of the Phase 1/2 BRUIN study of pirtobrutinib in patients with B-cell malignancies

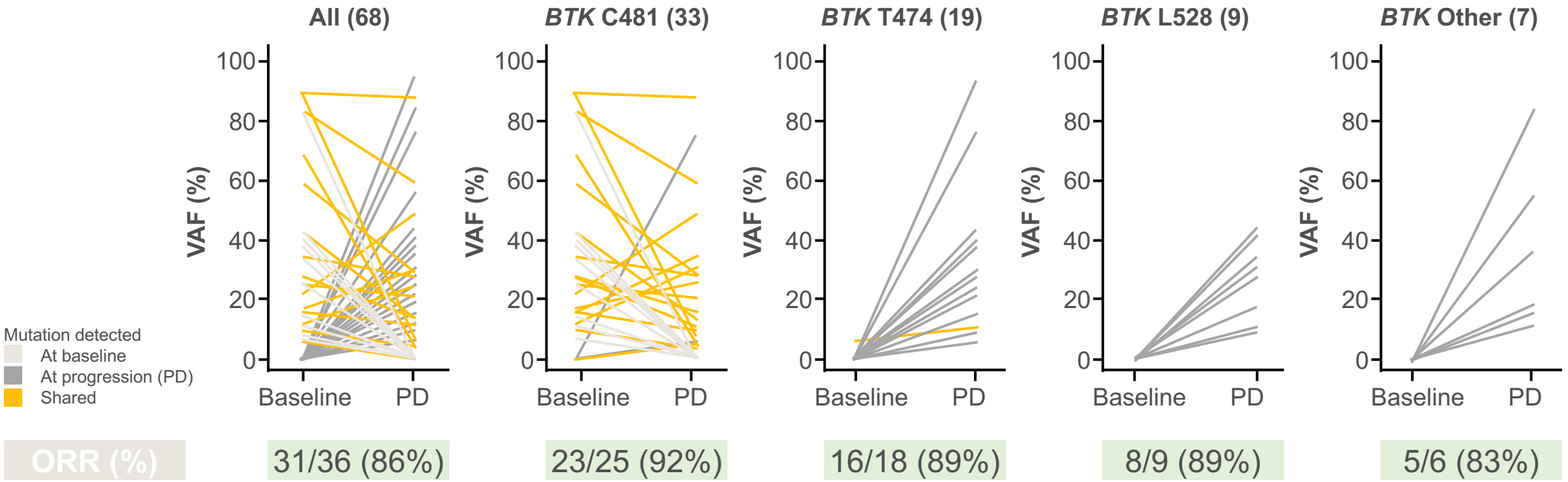
BRUIN: STUDY DESIGN AND METHODS



- NGS of paired baseline and progression PBMC samples from 49 cBTKi pre-treated CLL patients who progressed on pirtobrutinib
- Targeted NGS (5% VAF Limit of Detection) gene list (all exons, 74 genes): *BTK, PLCG2, TP53*…
- Manual inspection (1% VAF cutoff) of acquired *BTK* mutations at corresponding baseline sample

Data cutoff date of 29 July 2022 (NCT03740529).
[a] Patients with SLL were excluded from the analysis.
BTK, Bruton's tyrosine kinase; **cBTKi**, covalent BTK inhibitor; **CLL**, chronic lymphocytic leukemia; **NGS**, next-generation sequencing; **PBMC**, peripheral blood mononuclear cell;
PD, progressive disease; **SLL**, small lymphocytic lymphoma; **VAF** variant allele frequency.

ACQUIRED *BTK* MUTATIONS



	All (68)	*BTK* C481 (33)	*BTK* T474 (19)	*BTK* L528 (9)	*BTK* Other (7)
ORR (%)	31/36 (86%)	23/25 (92%)	16/18 (89%)	8/9 (89%)	5/6 (83%)

- Decrease/clearance of most C481 clones observed at progression on pirtobrutinib in 92% (22/24) patients[a]
- *BTK* C481R/S/Y, T474, L528, and other mutations arose at/near progression (n=27 patients[b])
- The majority of *BTK* acquired mutations were T474, L528
- ORR were similar across groups regardless of the acquired *BTK* mutation

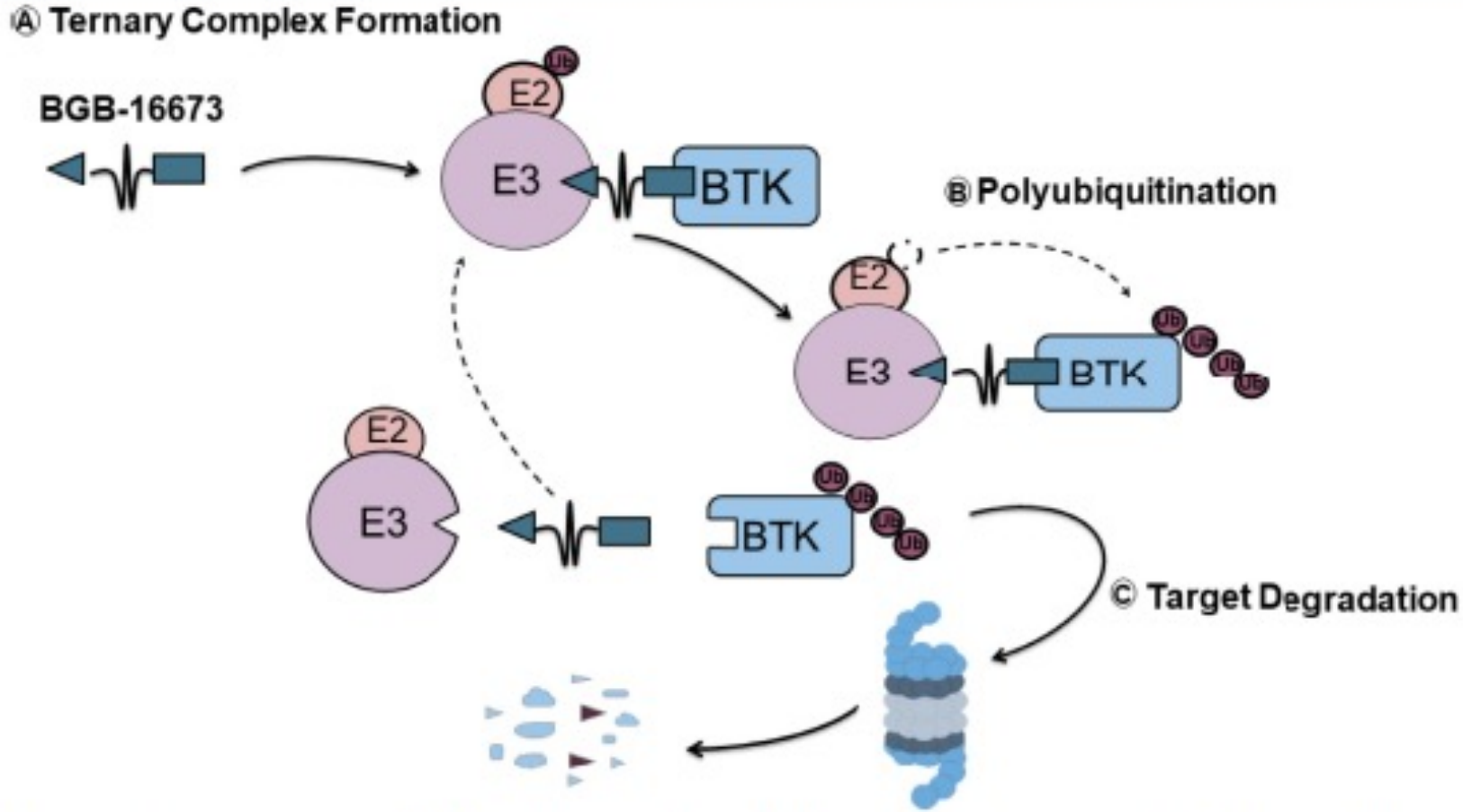
[a] Number of mutations is higher than number of patients because patients had multiple *BTK* mutations. [b] 9 patients acquired multiple BTK mutations.
BTK, Bruton's tyrosine kinase; **ORR**, overall response rate; **PD**, progressive disease; **VAF**, variant allele frequency.
Brown JR, et al. Abstract S146 presented at EHA2023. Patel K, et al. Abstract 116 presented at 17-ICML

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 28, 2023

First Results from a Phase 1, First-in-Human Study of the Bruton's Tyrosine Kinase (BTK) Degrader Bgb-16673 in Patients (Pts) with Relapsed or Refractory (R/R) B-Cell Malignancies (BGB-16673-101)

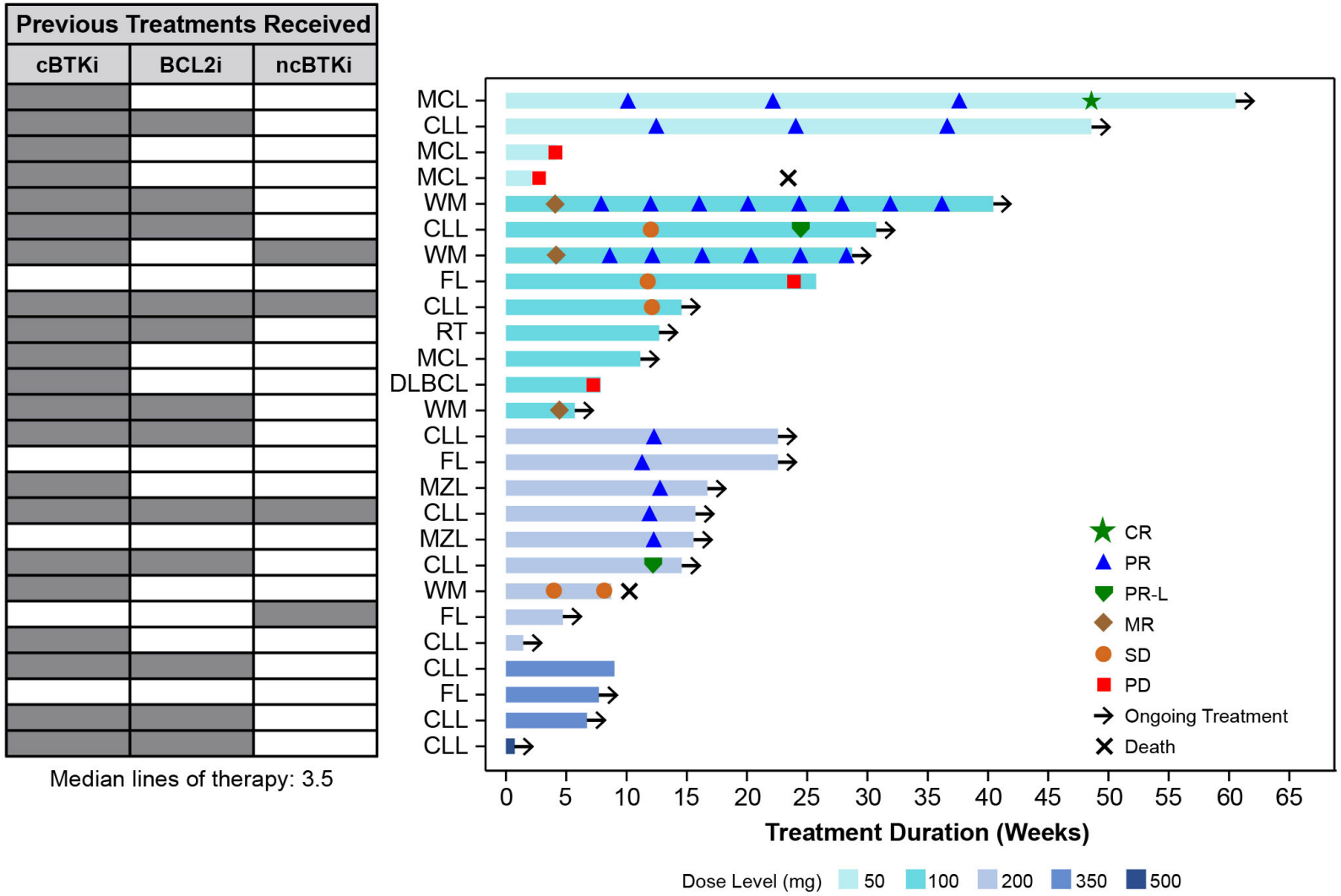
John F. Seymour, Chan Yoon Cheah, Ricardo Parrondo, Meghan C. Thompson, Don A. Stevens, Masa Lasica, Michael L. Wang, Abhijeet Kumar, Judith Trotman, Maan Alwan, Wei Ding, Kunthel By, Bilal Tariq, Xiangmei Chen, Shannon Fabre, Jason Paik, Amit Agarwal, Constantine S. Tam

Figure 1. CDAC mechanism of action



Abbreviations: BTK, bruton tyrosine kinase; CDAC, chimeric degradation activating compound; E2, ubiquitin-conjugating enzymes; E3, ubiquitin ligases; Ub, ubiquitin.

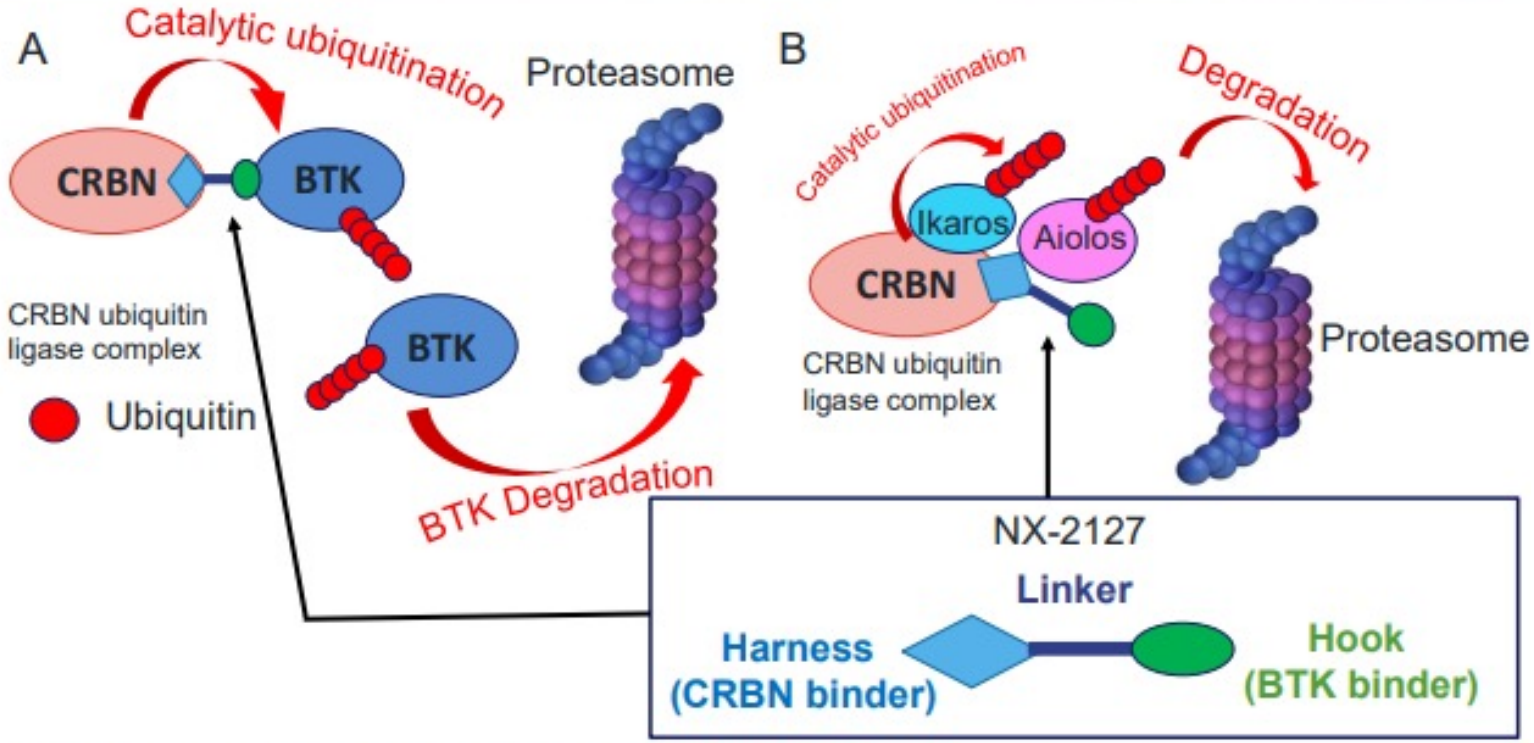
Figure. Patient Response to BGB-16673 Treatment by Dose-Level and B-Cell Malignancy



BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent BTKi; CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MR, minor response; MZL, marginal zone lymphoma; ncBTKi, non-covalent BTKi; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; RT, Richter transformation; SD, stable disease; WM, Waldenström macroglobulinemia.

NX-2127 has a dual degradation mechanism of action for two clinically validated targets

- BTK is a tyrosine kinase involved in B cell development, differentiation and signaling
- BTK inhibitors are approved for treatment of B cell malignancies
- Mutations to BTK have conferred resistance to approved agents indicating an area of unmet medical need
- IMiD therapies have shown efficacy in some aggressive B-cell malignancies
- The dual action of BTK degradation and IMiD activity may provide a unique treatment strategy for relapsed/refractory B-cell malignancies

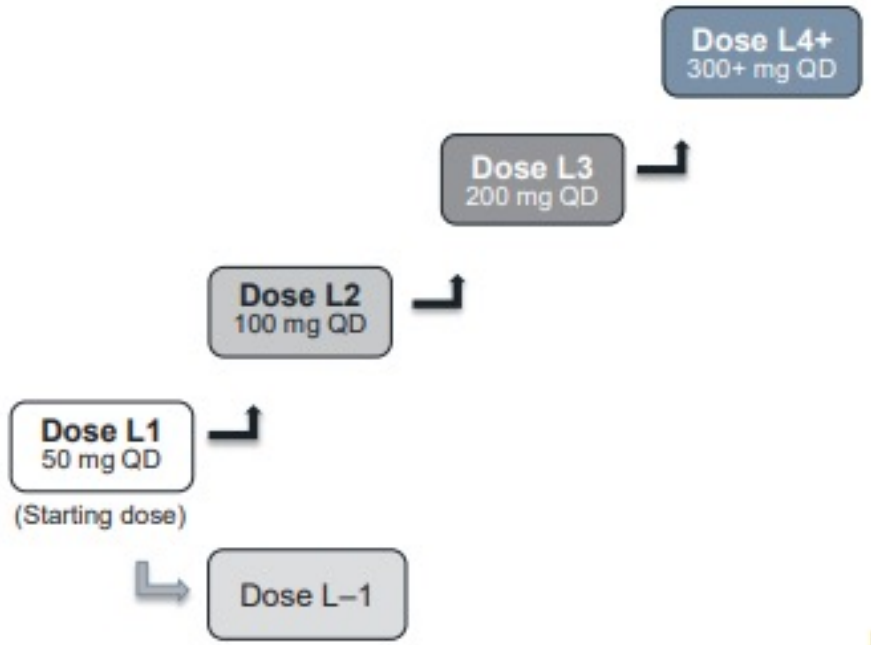


(A) NX-2127 is a novel, hetero-bifunctional, orally administered, Chimeric Targeting Molecule (CTM) that induces the degradation of Bruton's Tyrosine Kinase (BTK) in cells through recruitment of cereblon (CRBN), a component of the CRL4-CRBN ubiquitin ligase complex

(B) The engagement of NX-2127 also catalyzes neosubstrate degradation of Aiolos (IKZF3) and Ikaros (IKZF1), two transcription factors regulating T-cell function

nurix

Phase 1a dose escalation
B cell malignancies, including CLL (N = up to 30 patients)



Potential Phase 1b dose expansion[a]
(N = up to 80 patients)

Cohort A (n=20)
CLL/SLL; prior BTKi and BCL-2i

Cohort B (n=20)
DLBCL[b,c] or MCL[c]; prior anti-CD20 CIT + 1 LoT[d]

Cohort C (n=20)
FL[c], MZL[c], WM[c]; ≥2 prior LoT

Cohort D (n=20)
PCNSL who have progressed or had no response to ≥2 prior LoT

Recommended dose:
MTD or biologically active dose

[a]Potential dose-expansion cohorts are expected to open in the second half of 2023; [b]Subtypes include: transformed indolent lymphoma (e.g., grade 3b/transformed FL), Richter-transformed DLBCL, high-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 rearrangements, high-grade B-cell lymphomas NOS; [c]Includes patients with secondary CNS involvement; [d]Additional lines of therapy include anthracycline for non-GCB DLBCL and BTKi for MCL; *Abbreviations:* BCL-2i, B-cell lymphoma-2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CIT, chemo-immunotherapy; CLL, chronic lymphocytic leukemia; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; GCB, germinal center B cell; L, level; MCL, mantle cell lymphoma; LoT, line of therapy; MALT, mucosa-associated lymphoid tissue; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; NOS, not otherwise specified; PCNSL, primary central nervous system lymphoma; SLL, small lymphocytic lymphoma; SMZL, splenic marginal zone lymphoma; WM, Waldenströms macroglobulinemia.

E MAIS UNO BTK? SI, DE 4 GENERACION...

416 Targeting Covalent and Non-Covalent Btki-Resistant CLL Using the Dual Irreversible/Reversible 4th Generation BTK Inhibitor LP-168

Program: Oral and Poster Abstracts

Type: Oral

Session: 605. Molecular Pharmacology and Drug Resistance: Lymphoid Neoplasms: Targeted Therapy in Lymphoid Leukemias

Hematology Disease Topics & Pathways:

Lymphoid Leukemias, Research, CLL, Translational Research, drug development, Diseases, Therapies, Lymphoid Malignancies

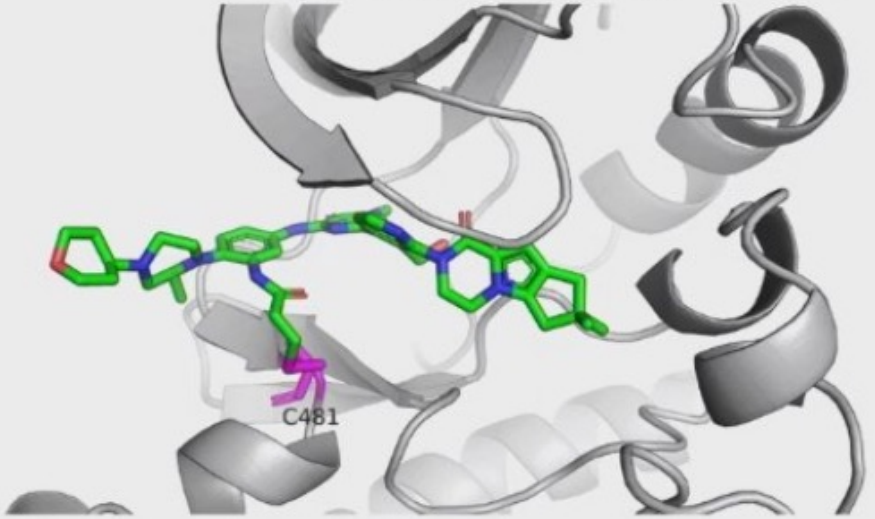
Background

- Covalent inhibitors of Bruton's Tyrosine Kinase (BTKi) have been transformative in the treatment of CLL and other B cell malignancies. Mutations in BTK that confer resistance have been effectively targeted with noncovalent BTKi, but additional mutations in BTK, including T474 mutations, can emerge

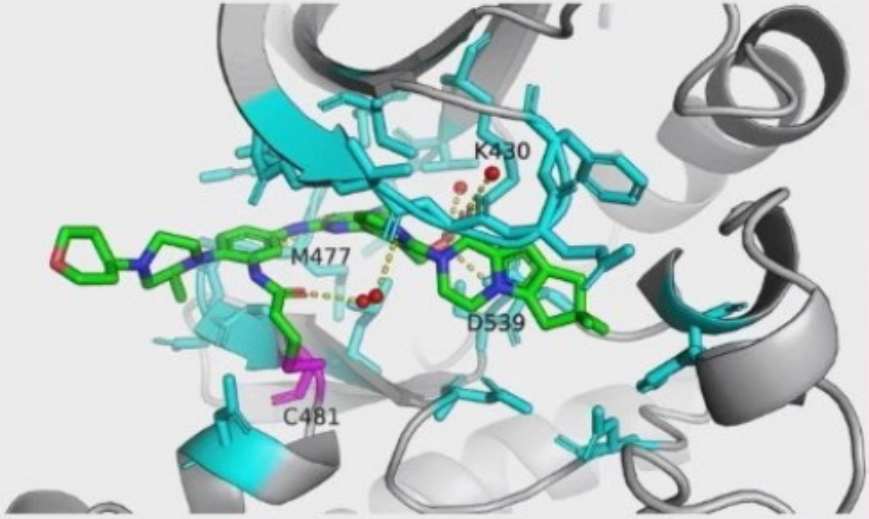
- LP-168 is an extremely selective, orally available inhibitor of BTK with a dual mechanism of action. LP-168 can bind BTK covalently in the presence of WT BTK, and non-covalently in the presence of C481 mutated BTK

- Here we present initial data from the Phase 1 dose escalation study of LP-168

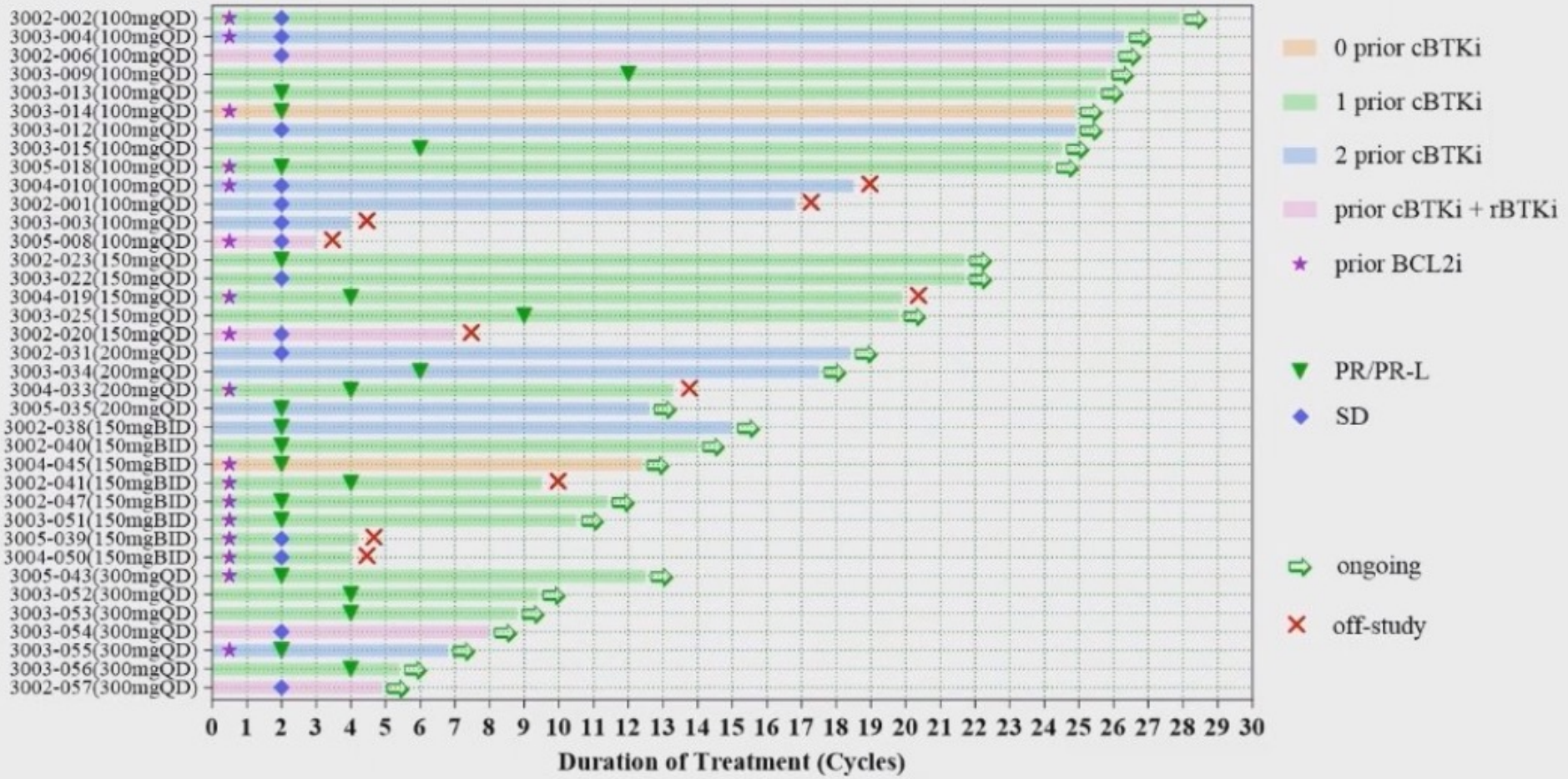
Covalent Binding



Non-Covalent Interactions



Duration of Therapy (CLL/SLL Cohort, n=37)



Median duration of treatment 14 cycles (range 3.0-27.9 cycles) as of 11/14/2023

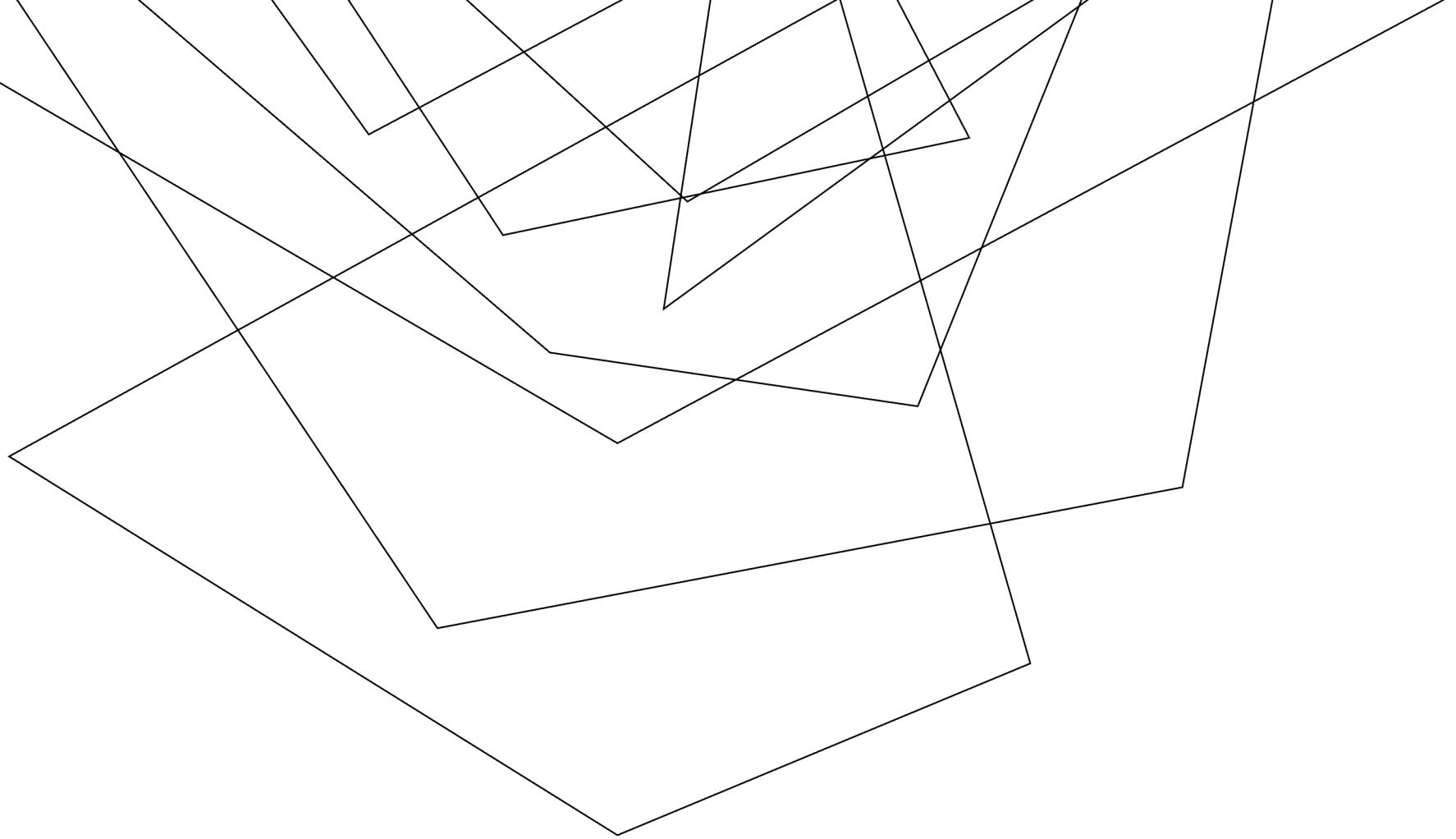
EL SHOW DE BTKIS CONTINÚA

Nuevos esquemas para situaciones complejas – BOVEN

Nuevas aprobaciónes para Linfoma Folicular – Rosewood

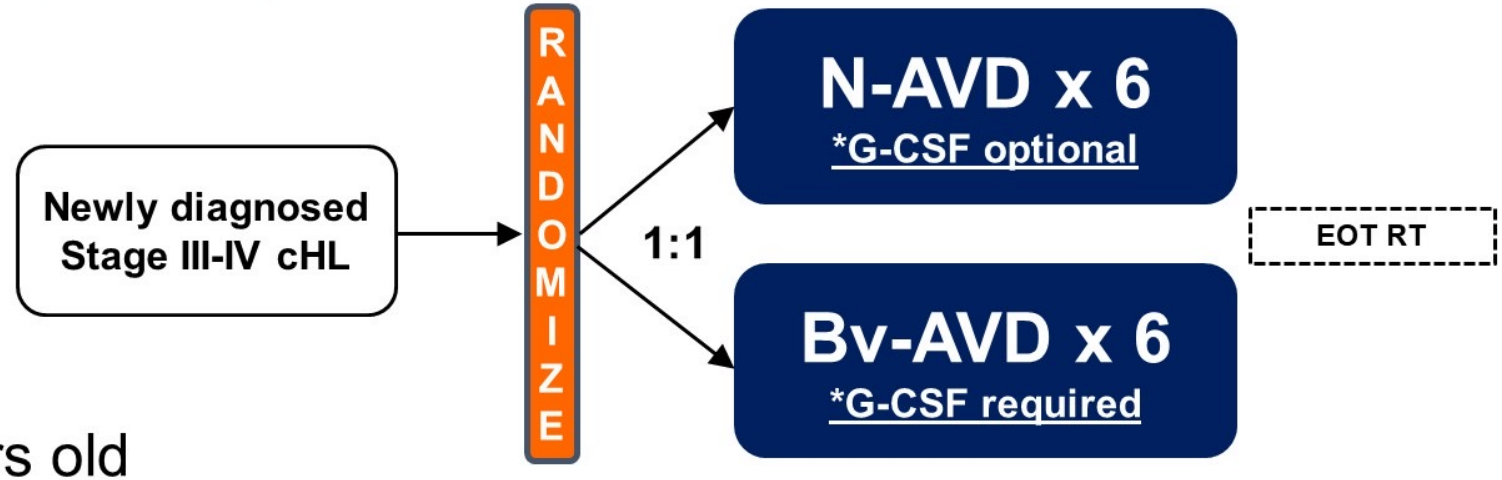
Nuevos BTKis

- No Covalentes
- Degraders
- Dual



CPI EN LINFOMA DE HODGKIN

S1826 Eligibility Criteria (abbreviated)



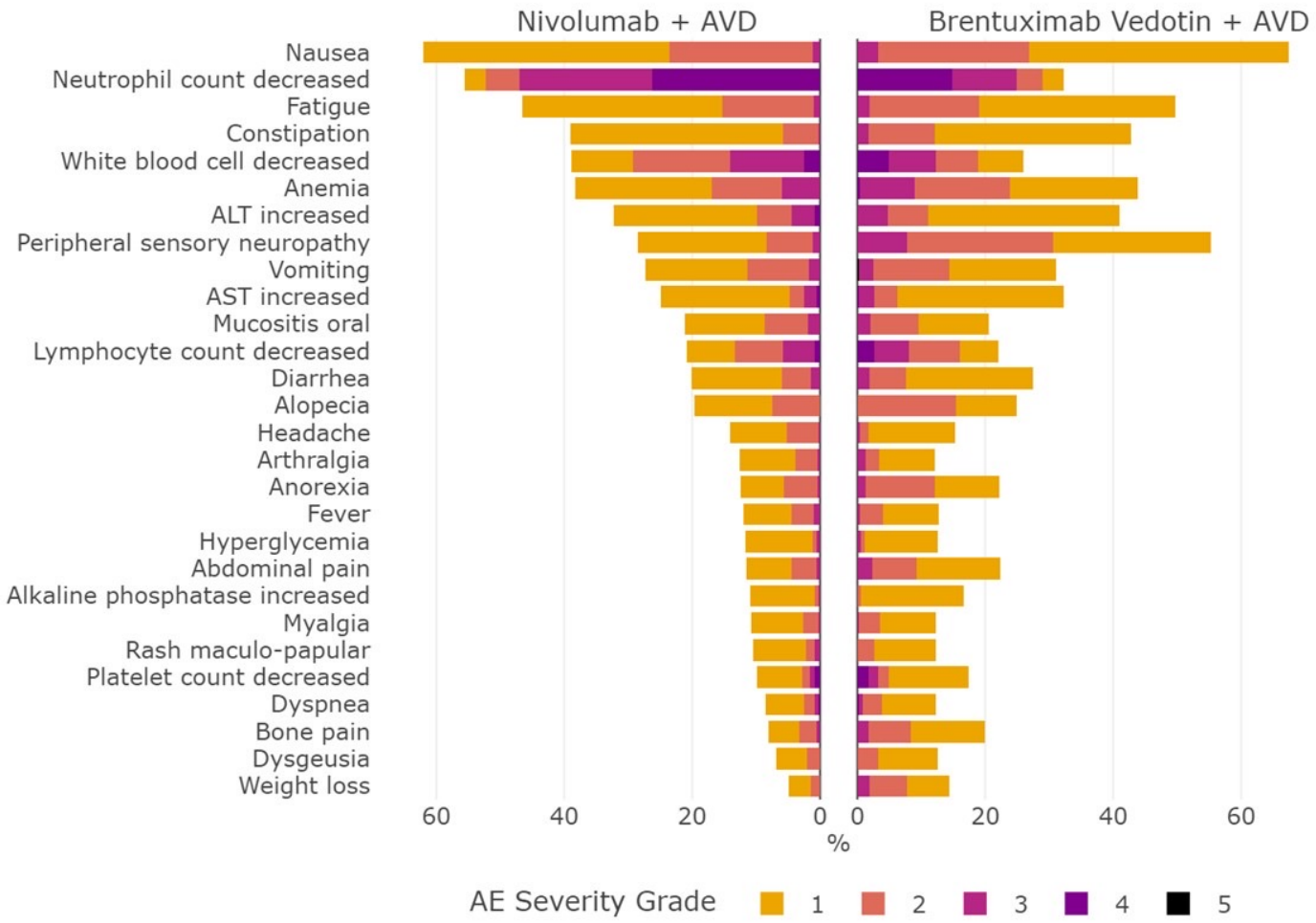
Key Inclusion

- Age ≥ 12 years old
- HIV+ eligible, if controlled
- Zubrod PS 0-2 (Peds: Lansky)
- LVEF ≥ 50% (or SF ≥ 27%)
- CrCl ≥ 30 mL/min (Peds: CrCl/GFR ≥ 70, SCr ≤ 1.5 ULN)
- Tbili ≤ 2 x ULN and AST/ ALT ≤ 3 x ULN

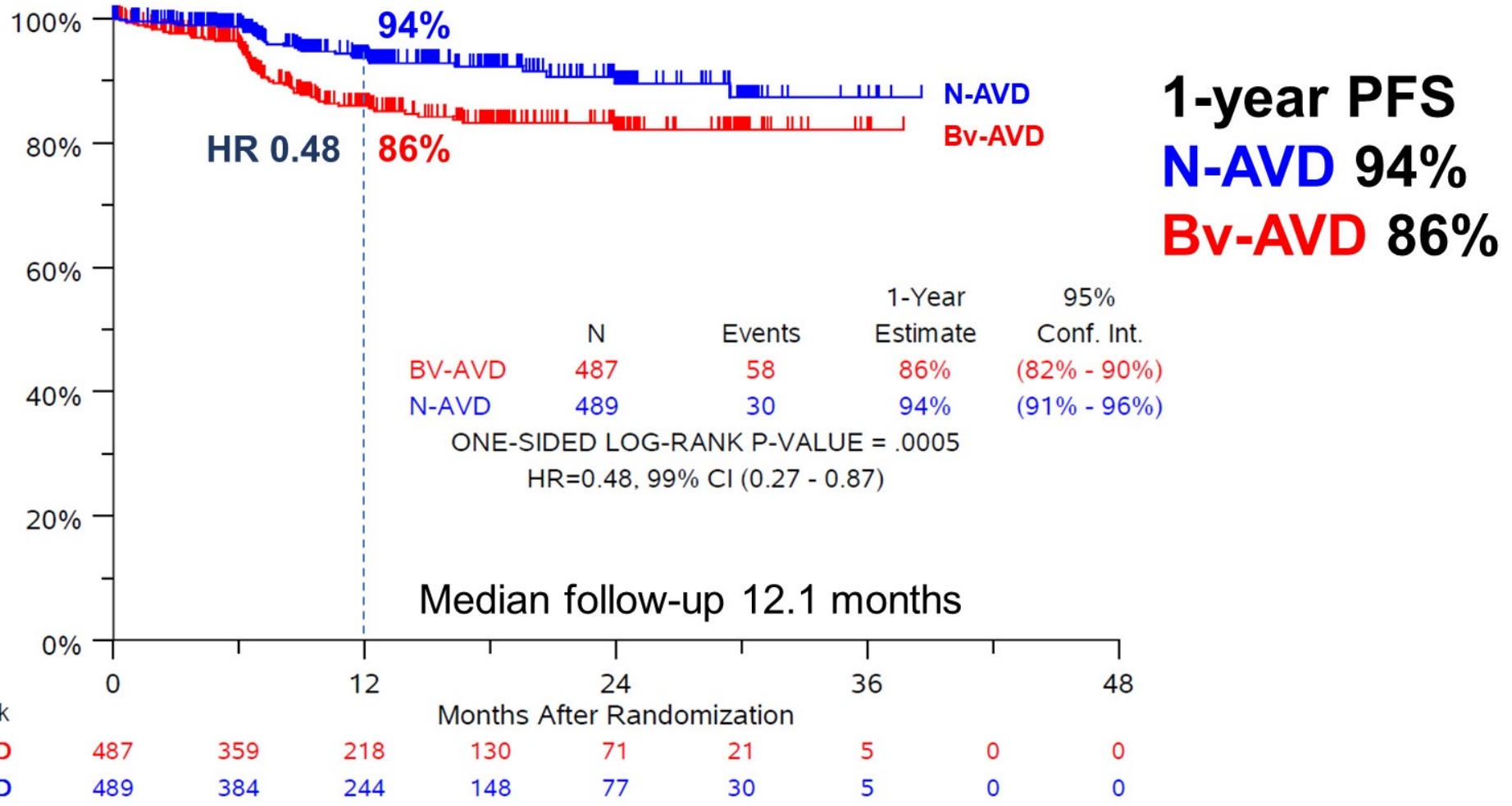
Key Exclusion

- Interstitial lung disease or pneumonitis
- Peripheral neuropathy ≥ Gr2
- Active autoimmune disease

Adverse Events in ≥ 10% patients by Arm



N-AVD improves PFS compared to Bv-AVD



1-year PFS
N-AVD 94%
Bv-AVD 86%

PRESENTED BY: Alex F. Herrera, MD

S1826 Older Pts Baseline Characteristics

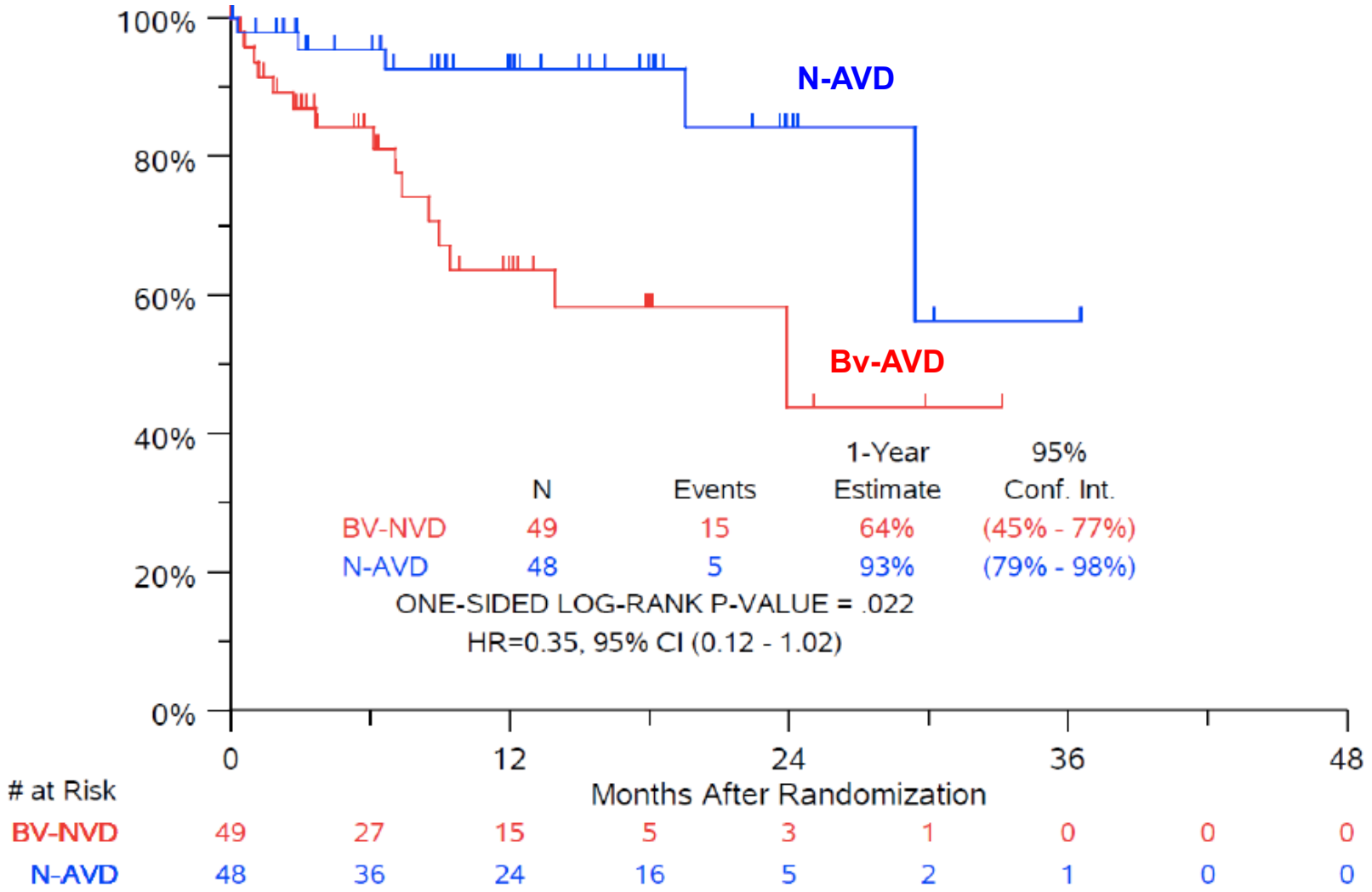
Baseline characteristics	N-AVD N = 48 N (%)	Bv-AVD N = 49 N (%)
Age, median (range)	66.4 (60-84 y)	67.1(60-87 y)
Age 60-69	31 (65%)	36 (74%)
Age 70-79	14 (29%)	12 (24%)
Age ≥80	3 (6%)	1 (2%)
Female Sex	19 (40%)	18 (37%)
Race		
White	43 (90%)	40 (82%)
Black	1 (2%)	2 (4%)
Asian	1 (2%)	1 (2%)
Other/Unknown	3 (6%)	6 (12%)
Hispanic	5 (10%)	5 (10%)

One-third of pts on Bv-AVD discontinued treatment early including 10% who died

Disposition	N-AVD N = 48, N (%)	Bv-AVD N = 49, N (%)
Treatment ongoing	1 (2%)	2 (4%)
Completed treatment	42 (88%)	31 (63%)
Discontinued all treatment early	**5 (10%)**	**16 (33%)**
Adverse event	2 (4%)	7 (14%)
Refusal unrelated to AE	1 (2%)	2 (4%)
Progression/relapse	0 (0%)	1 (2%)
Death on treatment	**1 (2%)**	**5 (10%)**
Other – not protocol specified	1 (2%)	1 (2%)
Received protocol radiotherapy	0 (0%)	0 (0%)

15% discontinued nivolumab and 39% discontinued Bv early, primarily due to AEs

N-AVD markedly improves PFS over Bv-AVD in older patients with cHL

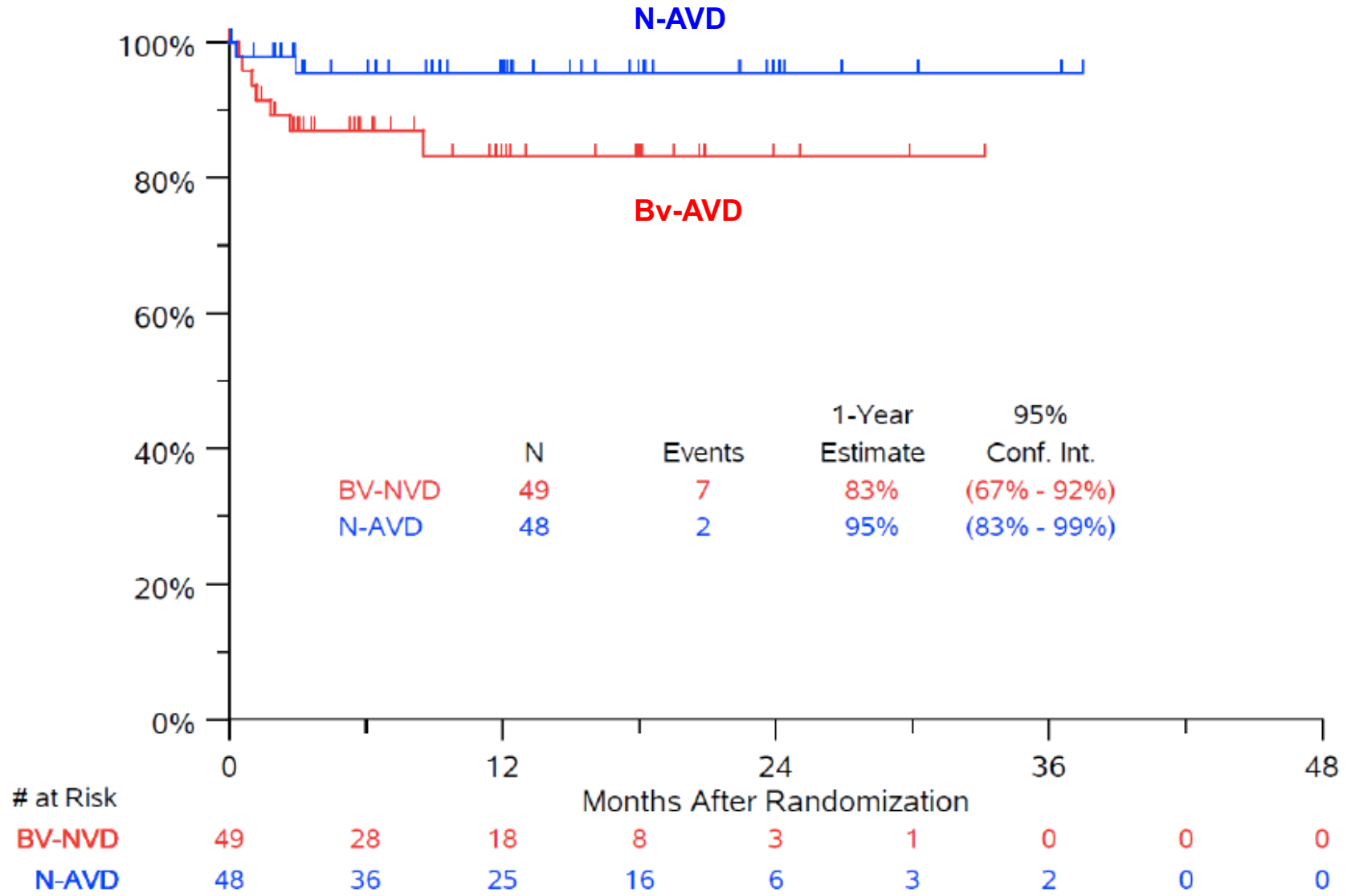


1-year PFS
N-AVD 93%
Bv-AVD 64%

Median follow-up
12.1 months

p-value = 0.022
HR=0.35,
95% CI (0.12-1.02)

Fewer deaths occurred on N-AVD vs Bv-AVD



1-year OS

N-AVD 95%

Bv-AVD 83%

Median follow-up
12.1 months

p-value = 0.091
HR=0.35,
95% CI (0.07-1.75)

CPI EN HODGKIN – A REAL GAME CHANGER

HL finalmente encontró un Anticuerpo con impacto similar a Rituximab en LNH

Todos los escenários fueron impactados com CPI

- Enfermedad R/R
- Pré ASCT
- Primera linea
- Ancianos

Linfoma de Hodgkin R/R se está convirtiendo en una especie en peligro de extinción

ALGUNAS COSAS, TODAVIA, NO CAMBIARAN EN 2024

Vina del Mar, 2023

Puerto Montt, 2024

1. Me gusta mucho es soy muy honrado por la invitacion para Lex e por su Amistad
2. Soy terrible en sacar selfies!
3. Vamos a tener Karaoke en Lex 2024 Tambien?

MUCHAS GRACIAS!

Guilherme.Perini@einstein.br