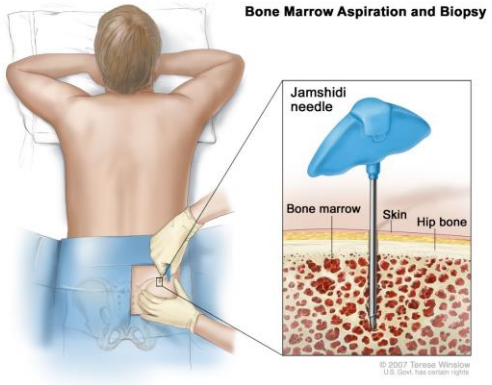
Lymphome und CLL
Was gibt es Neues in Diagnostik und Therapien

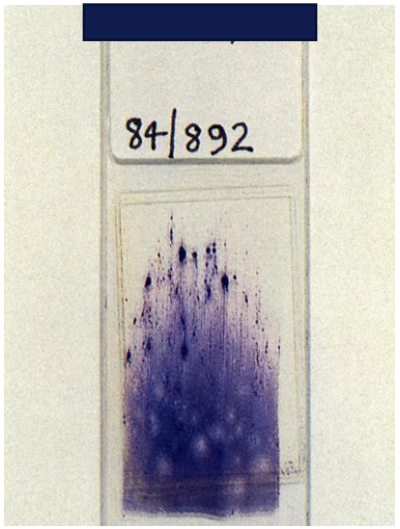
Philipp Staber

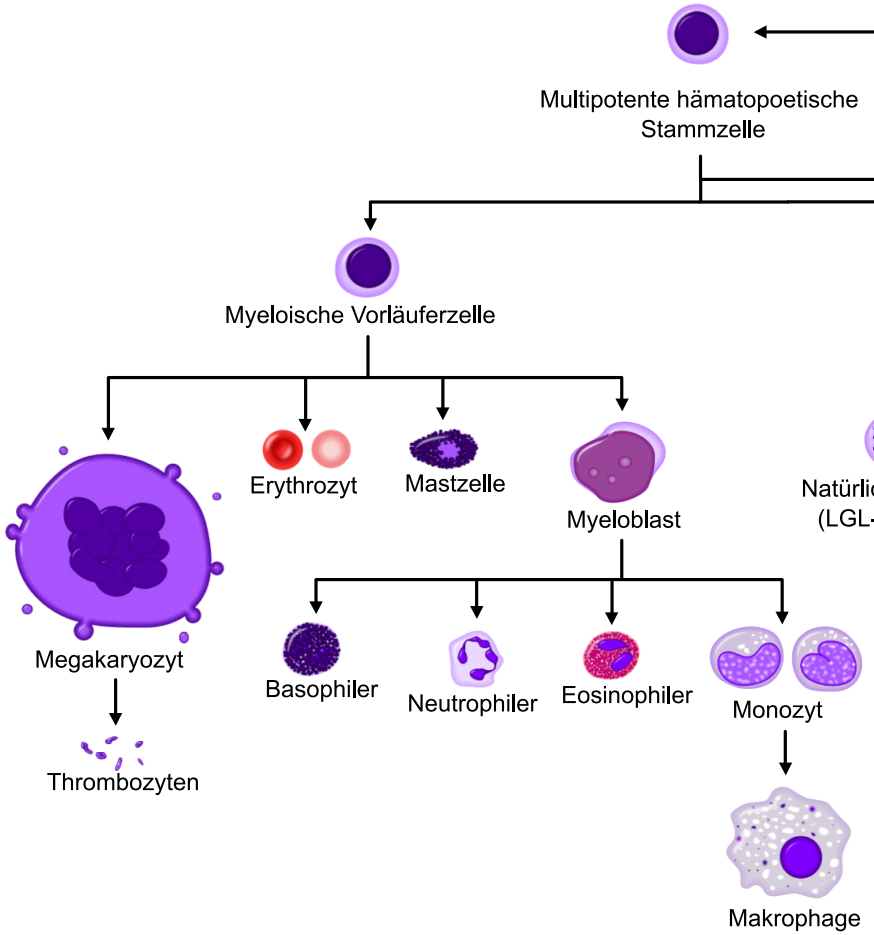
Wien 22.6.2024

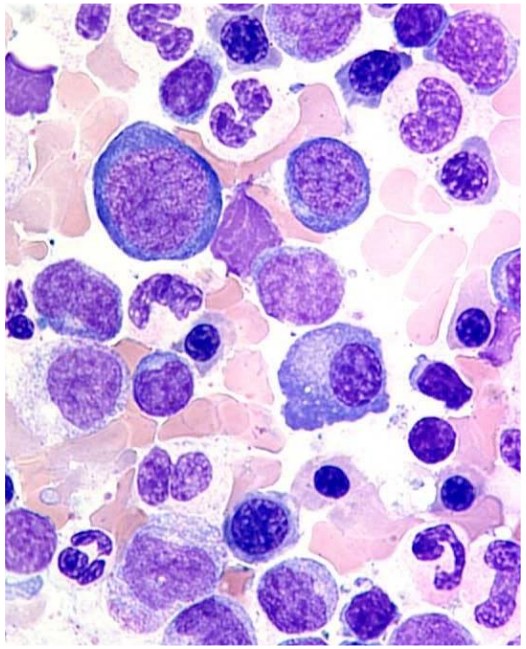
Blutbildung

Aspirat- Knochenmarksausstrich





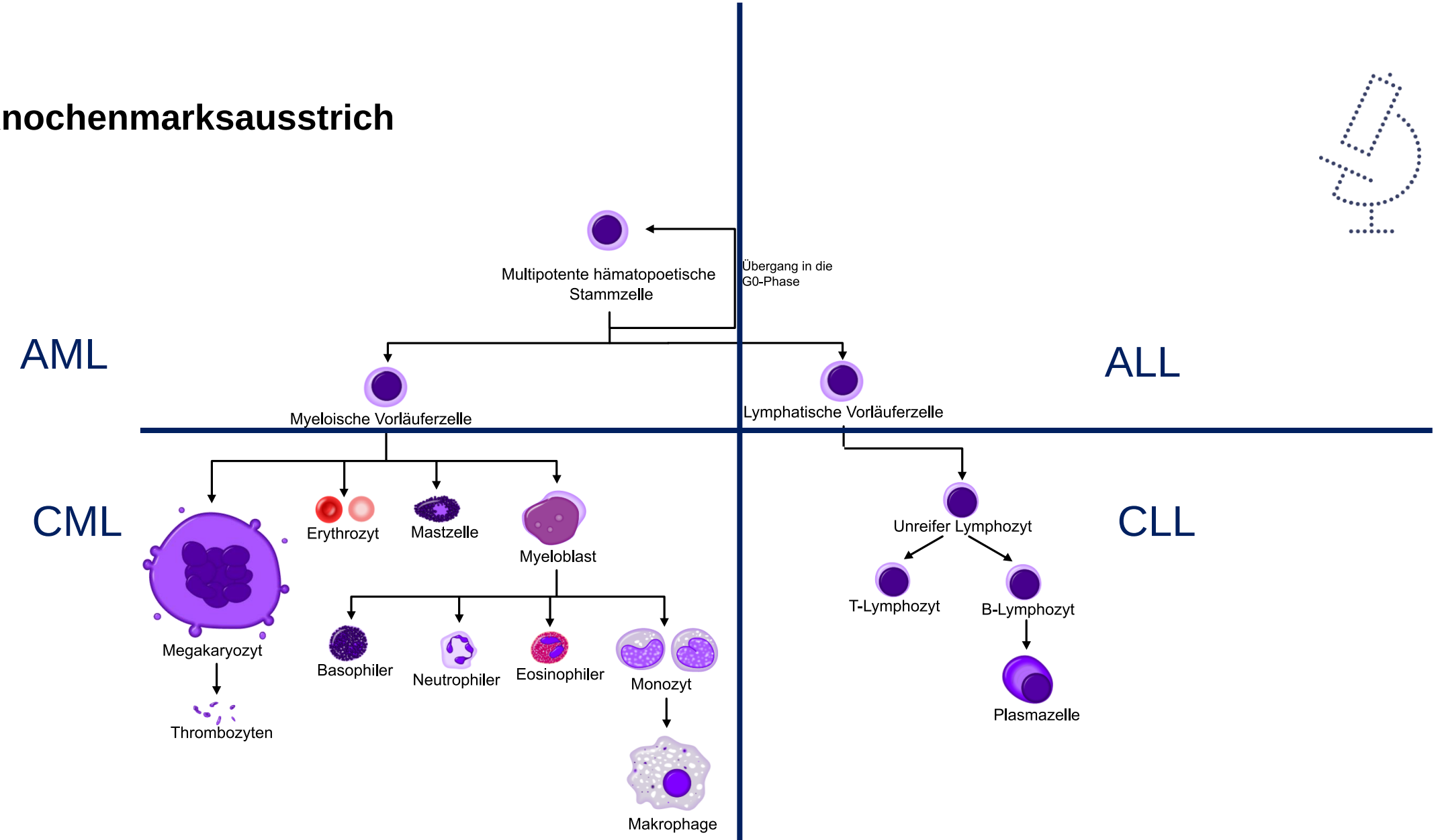




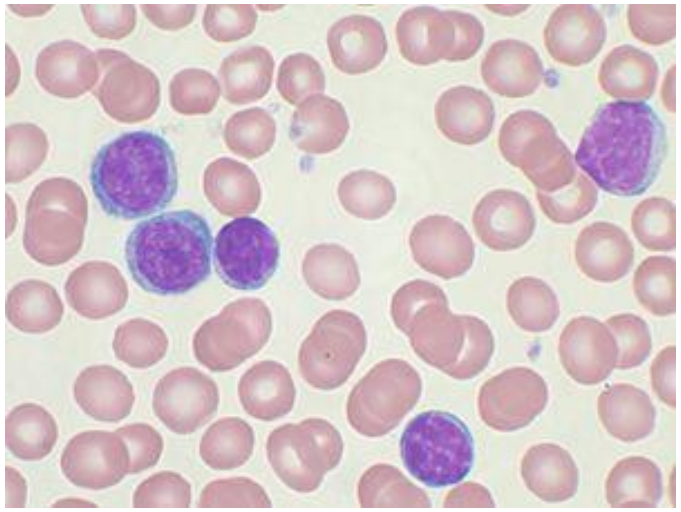
Normales Knochenmark

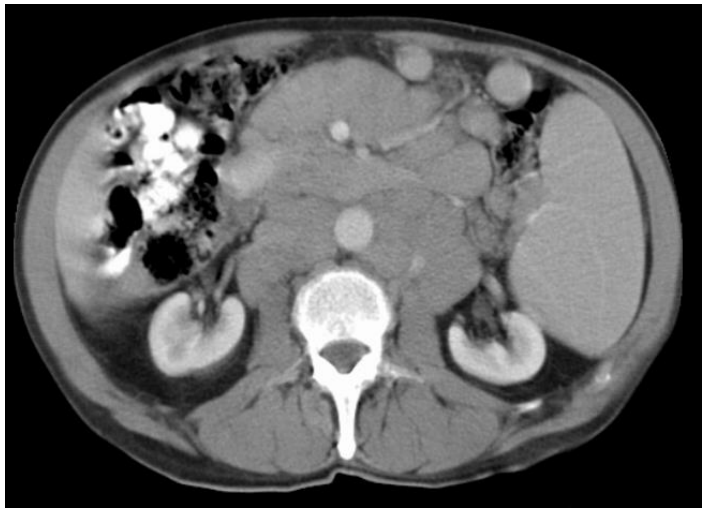
Leukämie

Aspirat- Knochenmarksausstrich



Diagnose CLL (Chronisch Lymphatische Leukämie)





Monoclonal B-cell lymphocytosis
(CD5+, CD19+, CD20-/+, CD23+)

≤5,000/µL	>5,000/µL

Lymphadenopathy
Spleen / liver enlargement
Anemia / thrombocytopenia

Yes → **SLL**

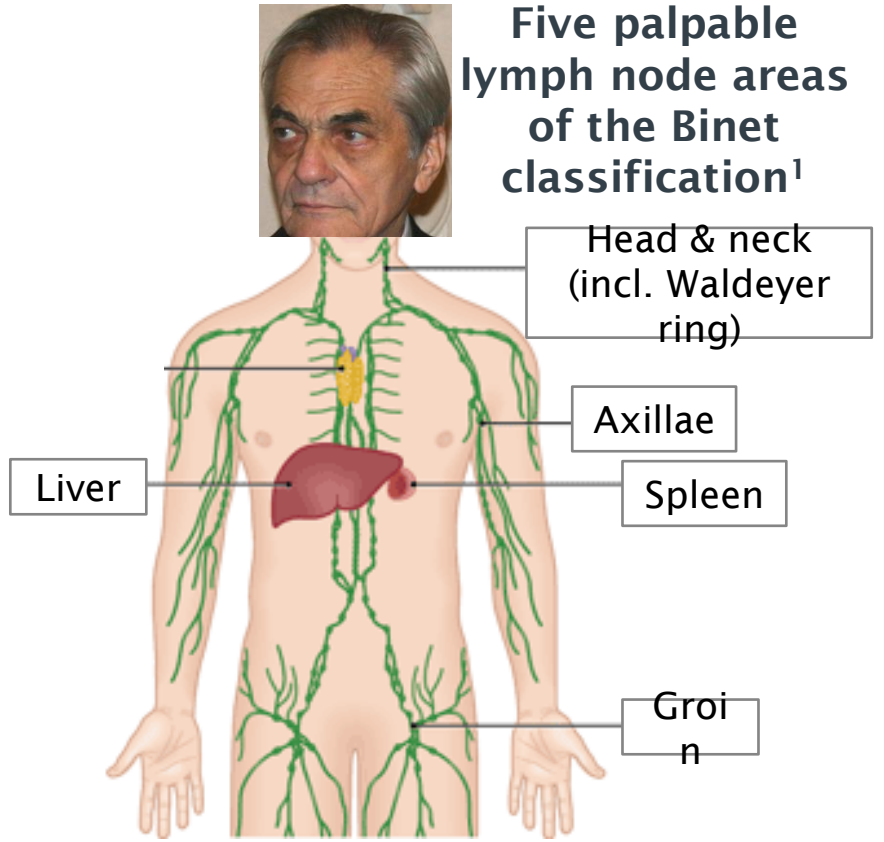
No → **MBL**

>5,000/µL → **CLL**

CLL, chronic lymphocytic leukemia; MBL, monoclonal B lymphocytosis; SLL, small lymphocytic lymphoma.
Rai KR, Stilgenbauer S. *N Engl J Med* 2008; 359 (6): 575–583.

Staging: Binet & Rai classifications

Risk group[1,2]	Binet classification[1]	Modified Rai stage[2]	Median survival[3]
Low	• **Binet A**: Hb ≥10.0 g/dL, platelets ≥100 ×10^9/L, and <3 lymph node areas	• **Stage 0:** Lymphocytosis (lymphoid cells >30%)	>10 years
Intermediate	• **Binet B**: Hb ≥10.0 g/dL, platelets ≥100 ×10^9/L, and ≥3 lymph node areas	• **Stage I:** Lymphocytosis • **Stage II:** Lymphadenopathy, splenomegaly and/or hepatomegaly	>8 years
High	• **Binet C**: Hb <10.0 g/dL and/or Plt: <100 ×10^9/L	• **Stage III:** Hb: <11.0 g/dL • **Stage IV**: Plt: <100 × 10^9/L	~7.5 years



Hb, hemoglobin; plt, platelets.

1. Binet JL *et al*. *Cancer* 1981; 48 (1): 198–206. 2. Rai KR *et al*. *Blood* 1975; 46 (2): 219-234. 3. Pflug N *et al*. *Blood* 2014; 124 (1): 49–62.

Therapieindikation

Binet C,

Binet B / A +:

- Splenomegalie (>6cm, symptomatisch, progr.)
- Lymphadenopathie (>10 cm, symptomatisch, progr.)
- LDT<6 Monaten; 50% <2 Monaten (min. 30G/l)
- Autoimmunzytopenie
- Gewichtverlust >10 % in 6 Monaten
- Fieber unklarer Ursache >2 Wochen
- Nachtschweiß >1 Monat
- schwerwiegende Fatigue

Cll12 study design

RISK ASSESSMENT

del(17p)	IGHV
del(11q)	ECOG PS
thymidine kinase	sex
β2 microglobulin	age

648 PATIENTS WITH CLL
BINET STAGE A
ASYMPTOMATIC
TREATMENT-NAIVE

152 PATIENTS
NO RISK

363 PATIENTS
INCREASED RISK

152 PATIENTS
WATCH & WAIT

182 PATIENTS
IBRUTINIB

versus

181 PATIENTS
PLACEBO

420 [mg/d] UNTIL SYMPTOMATIC DISEASE PROGRESSION

FPI
APR-2014

EOS
JUL-2022

Primary endpoint analysis demonstrated superior EFS for the ibrutinib group.[1]

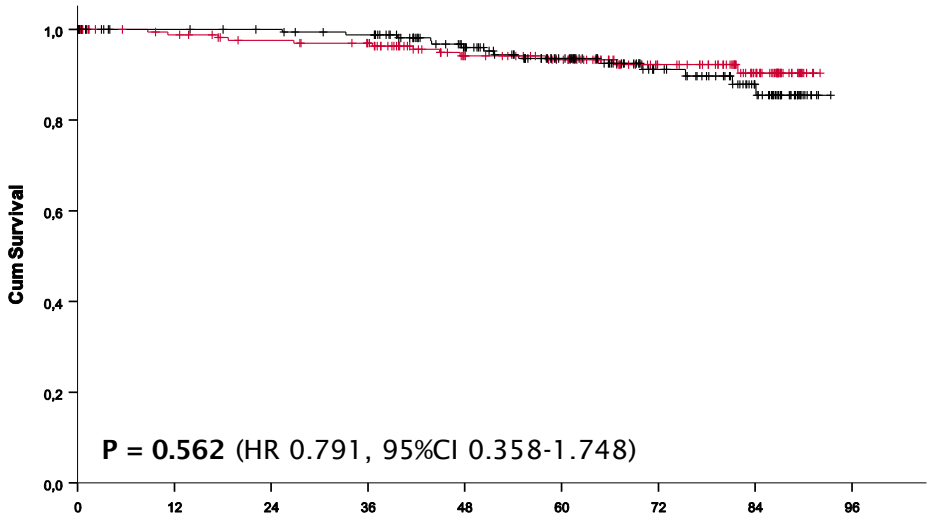
Overall survival was not analyzed due to a lacking number of events.

The final analysis is performed at a median observation time of 69.3 (0 - 93.4) months.

[1]Langerbeins P. et al. Blood. 2022 Jan 13;139(2):177-187.

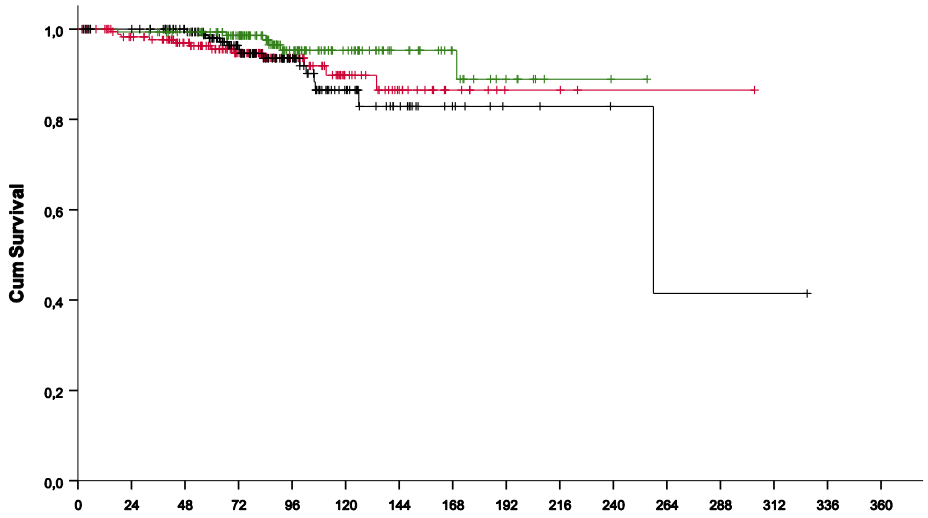
Watch & wait bleibt Standard im frühen Stadium

Overall survival (OS)



OS	Pts, N	Events, N (%)	Median months	1-year Survival, %	2-year Survival, %	3-year Survival, %	4-year Survival, %	5-year Survival, %
All patients [ITT]	**363**	**26 (7.2)**						
Ibrutinib	182	12 (6.6)	NR	98.8	97.6	97.0	94.1	93.3
Placebo	181	14 (7.7)	NR	100.0	100.0	98.8	96.0	93.6

OS FROM DIAGNOSIS



OS from diagnosis	Pts, N	Events, N (%)	Median months	2-year Survival, %	4-year Survival, %	6-year Survival, %	8-year Survival, %	10-year Survival, %
All patients [ITT]	**515**	**32 (6.2)**						
Ibrutinib	182	12 (6.6)	NR	98.2	97.0	94.7	93.6	89.8
Placebo	181	14 (7.7)	258.0	100.0	100.0	96.4	93.5	86.5
Watch & Wait	152	6 (3.9)	NR	99.3	99.3	98.6	95.3	95.3

Langerbeins P. et al. EHA 2023

Cause of death (N=32)

	Ibrutinib N=182	Placebo N=181	Watch & wait N=152
All death cases, N (%)	12 (6.6)	14 (7.7)	6 (3.9)
Progressive CLL	1	1	-
Second malignancy	2	5	2
Infection	2	1	1
Intracranial bleeding	2	-	-
Cardiac decompensation / sudden death	2	1	-
Concomitant disease	-	1	2
Unknown	3	5	1

Langerbeins P. et al. EHA 2023

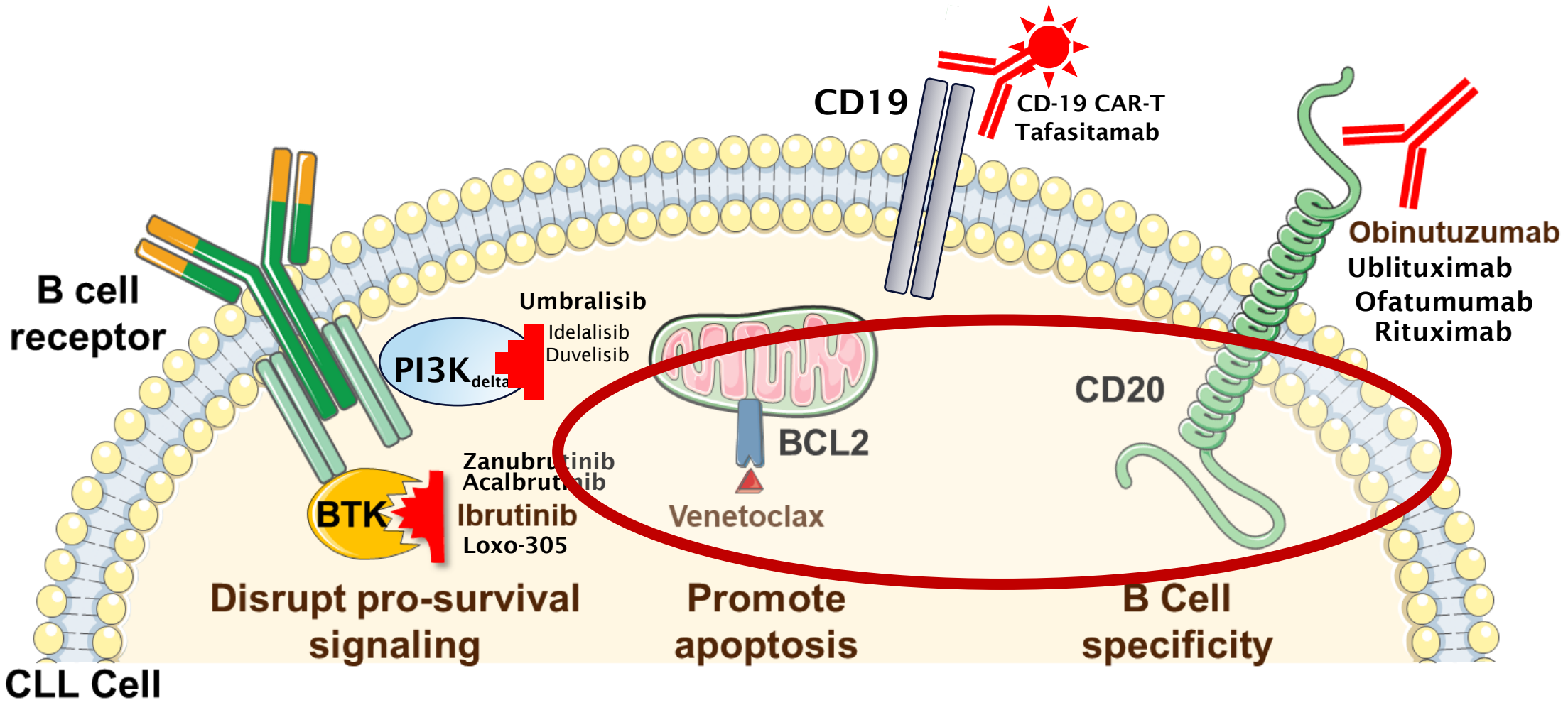
Evaluation of patients with CLL

Diagnostic test	General practice	Clinical trial
Tests to establish the diagnosis		
CBC and differential count	Always	Always
Immunophenotyping of peripheral blood lymphocytes	Always	Always
Assessment before treatment		
History and physical, performance status	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	When clinically indicated (unclear cytopenia)	Desirable
Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always	Always
Chest radiograph	Always	Always
Infectious disease status	Always	Always
Additional tests before treatment		
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI	Desirable
TP53 mutation	Always	Always
IGHV mutational status	Always	Always
Serum β_2-microglobulin	Desirable	Always
CT scan of chest, abdomen, and pelvis	NGI*	Desirable
MRI, PET scans	NGI	NGI
Abdominal ultrasound†	Possible	NGI

*Before BCL2i for TLS evaluation.

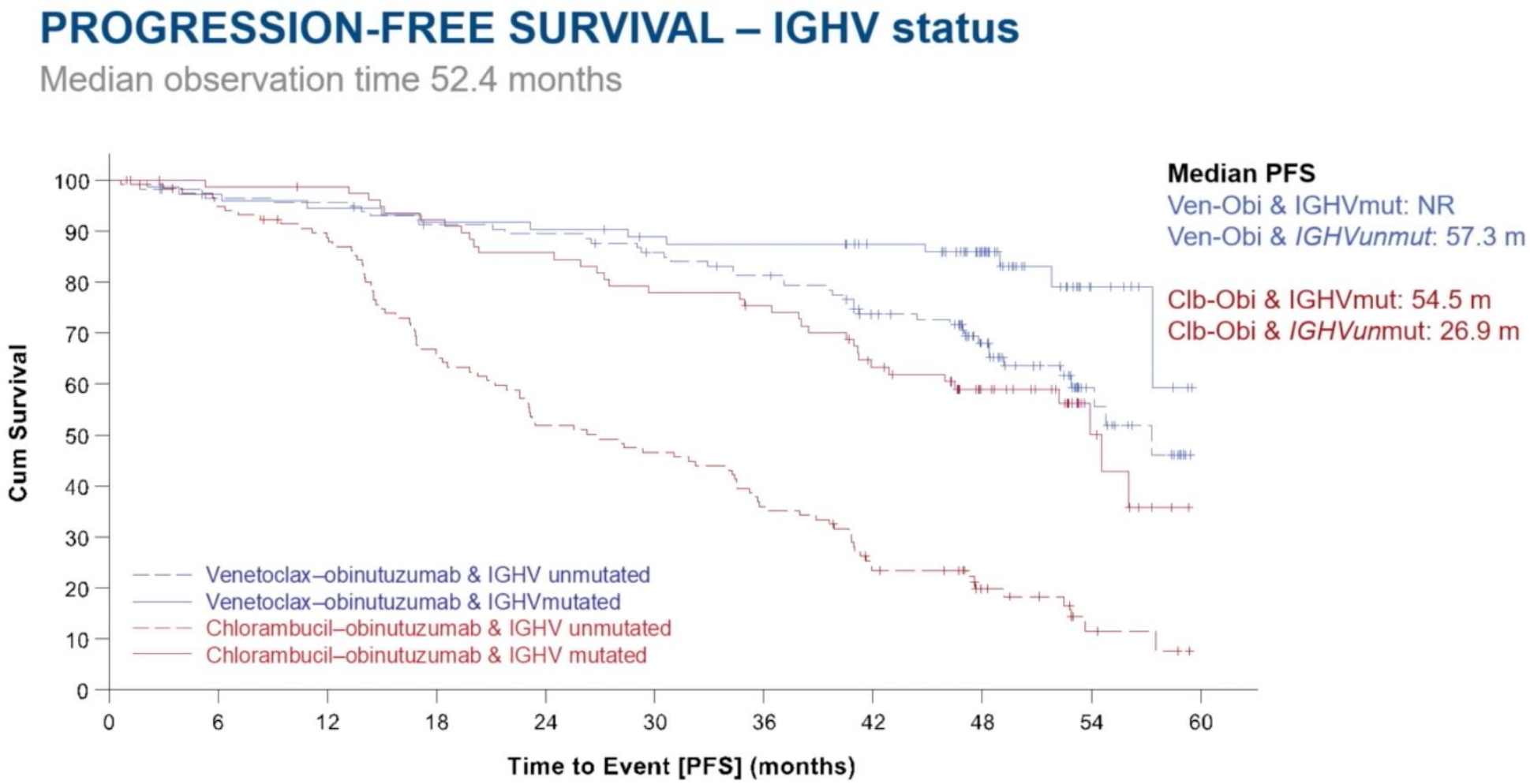
CBC, complete blood count; CLL, chronic lymphocytic leukemia; CT, computerized tomography; del, deletion; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain variable; iwCLL, international workshop on CLL; MRI, magnetic resonance imaging; NGI, not generally indicated; PET, positron emission tomography; TLS, tumor lysis syndrome. Hallek M *et al*. *Blood* 2018; 131 (25): 2745–2760.

Ziel-gerichteten Therapien für die CLL



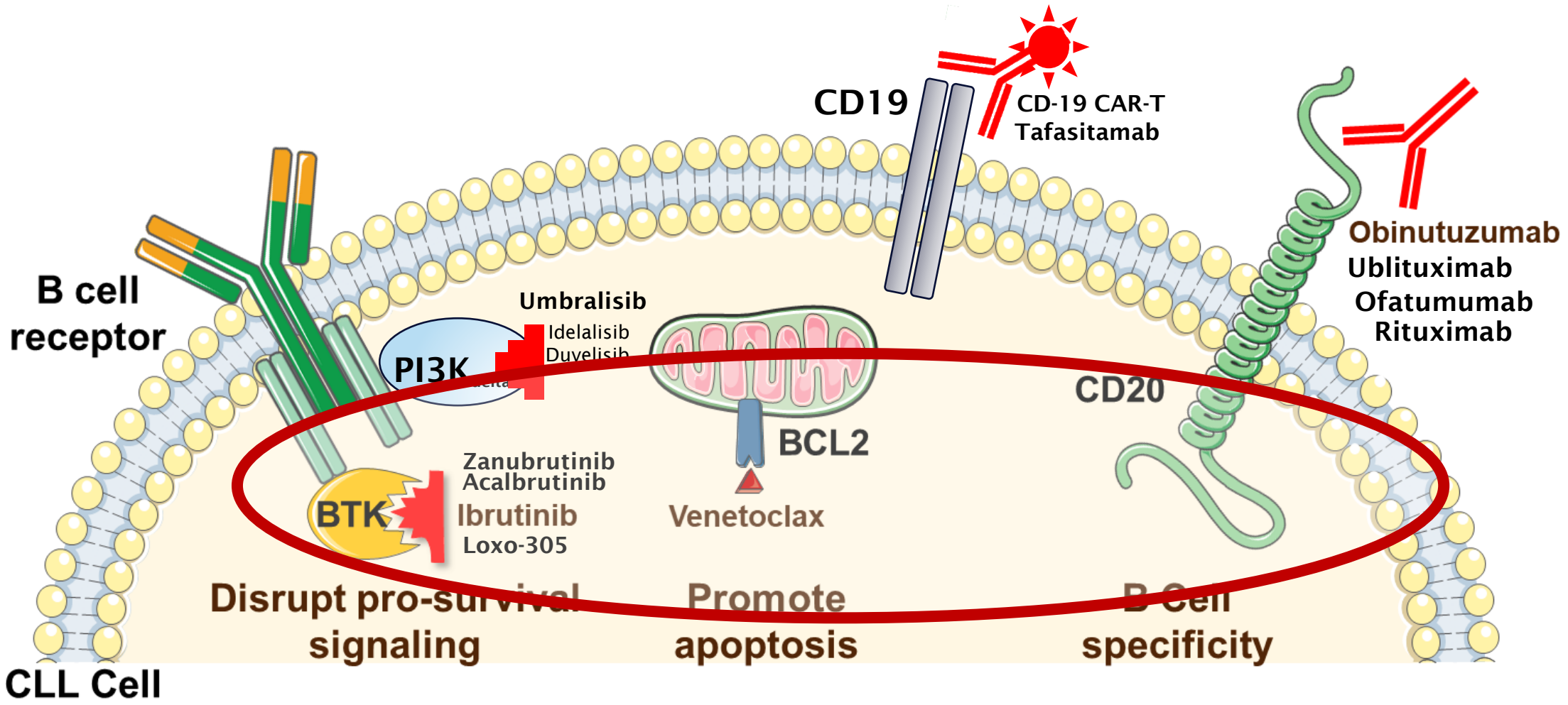
Staber P, Davids M

Obinutuzumab + Venetoclax in 1st Line: CLL-14



Othman Al-Sawaf; EHA2021: # 409-2

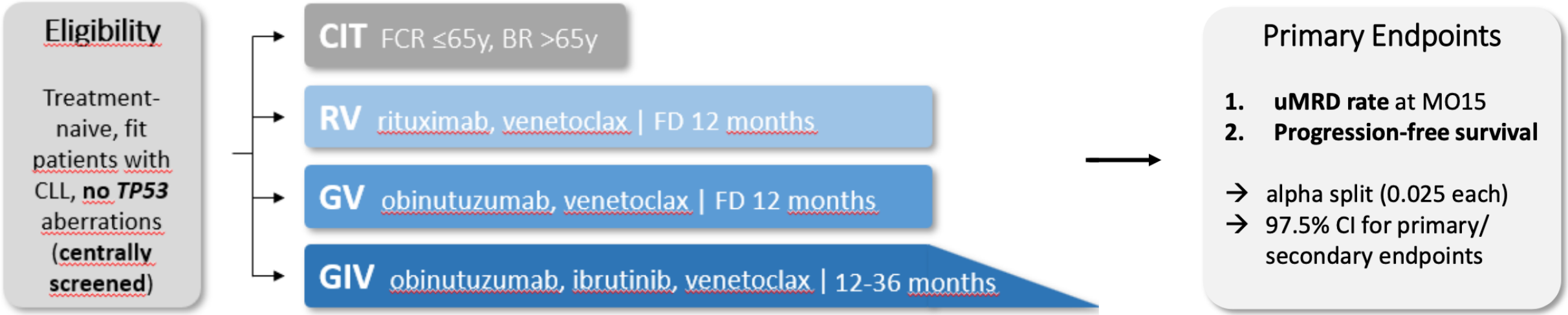
Ziel-gerichteten Therapien für die CLL



Staber P, Davids M

CLL13/GAIA Studie

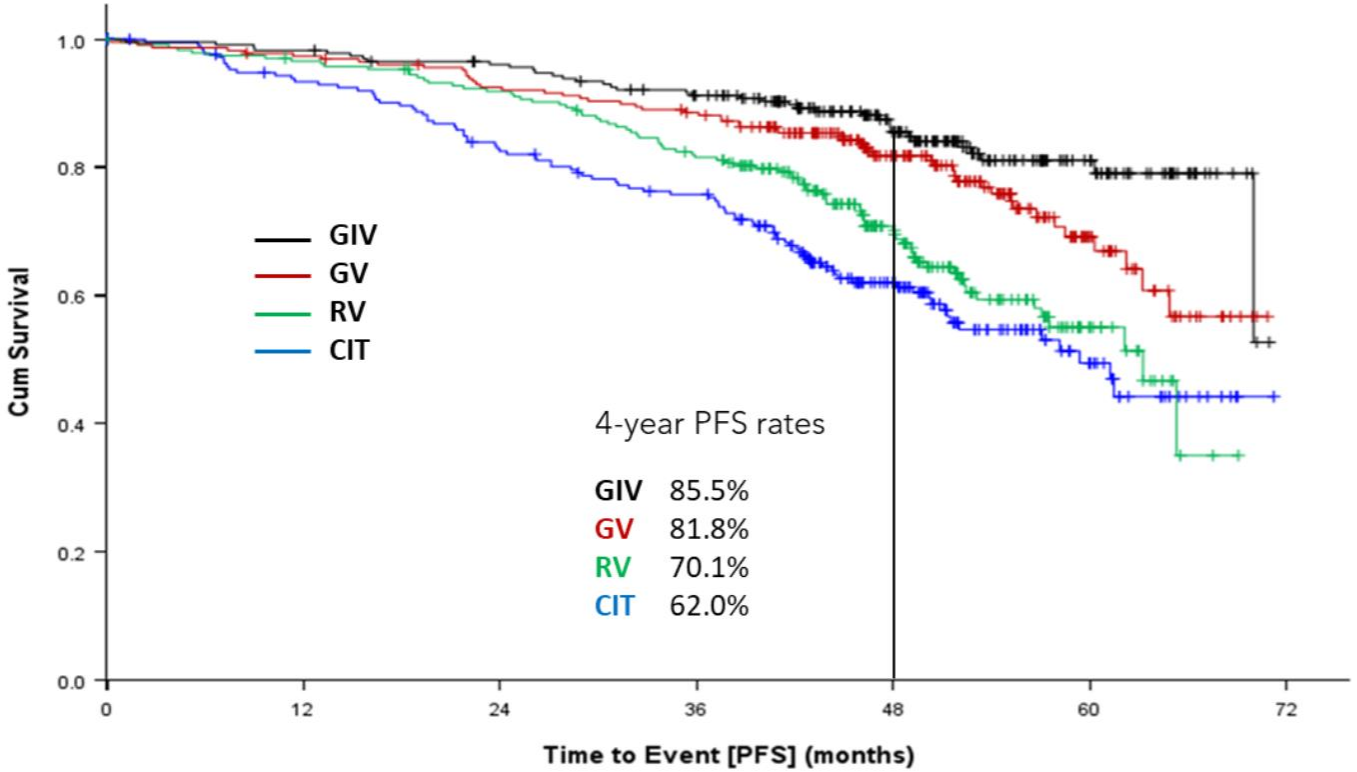
Phase III: Venetoclax + Obinutuzumab + Ibrutinib vs Venetoclax + Obinutuzumab vs Venetoclax + Rituximab vs FCR/BR



Eichhorst B. et al., NEJM 2023
Fürstenau M et al. Lancet Oncol 2024

CLL13/GAIA Studie

PFS nach 50.7 Monaten Beobachtungszeit für Venetoclax + Obinutuzumab (GIV + Ibrutinib vs Venetoclax + Obinutuzumab vs Venetoclax + Rituximab vs FCR/BR



Patients at risk

CIT	229	197	173	156	84	24
RV	237	227	214	188	106	21
GV	229	222	209	198	121	32
GIV	231	227	218	201	130	44

PFS comparisons

GIV *vs* **CIT**: HR 0.30, 97.5%CI: 0.19-0.47, ***p<0.001***
GIV *vs* **RV**: HR 0.38, 97.5%CI: 0.24-0.59, ***p<0.001***
GIV *vs* **GV**: HR 0.63, 97.5%CI: 0.39-1.02, p=0.03

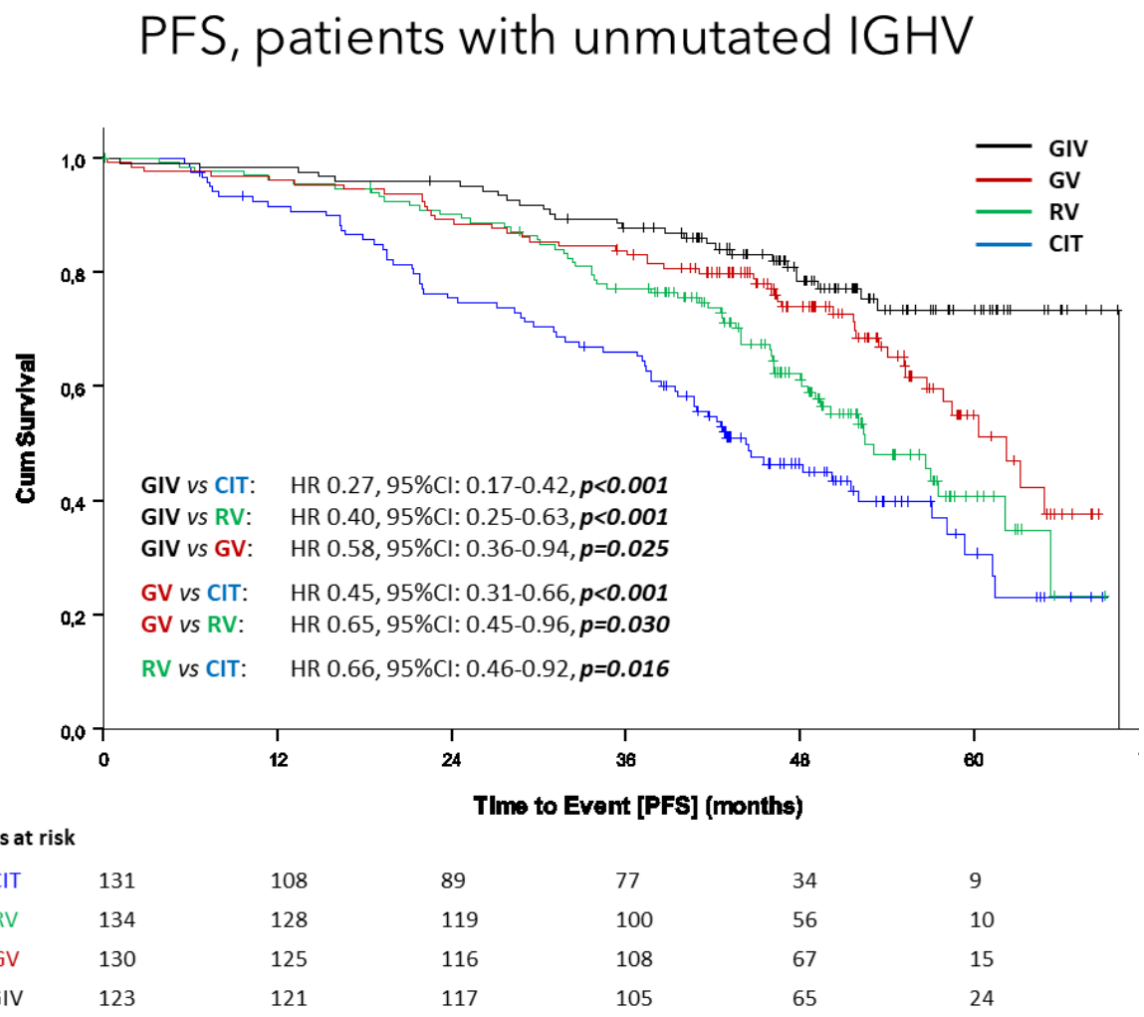
GV *vs* **CIT**: HR 0.47, 97.5%CI: 0.32-0.69, ***p<0.001***
GV *vs* **RV**: HR 0.57, 97.5%CI: 0.38-0.84, ***p=0.001***

RV *vs* **CIT**: HR 0.78, 97.5%CI: 0.55-1.10, p=0.1

Eichhorst B. et al., NEJM 2023
Fürstenau M et al. Lancet Oncol 2024

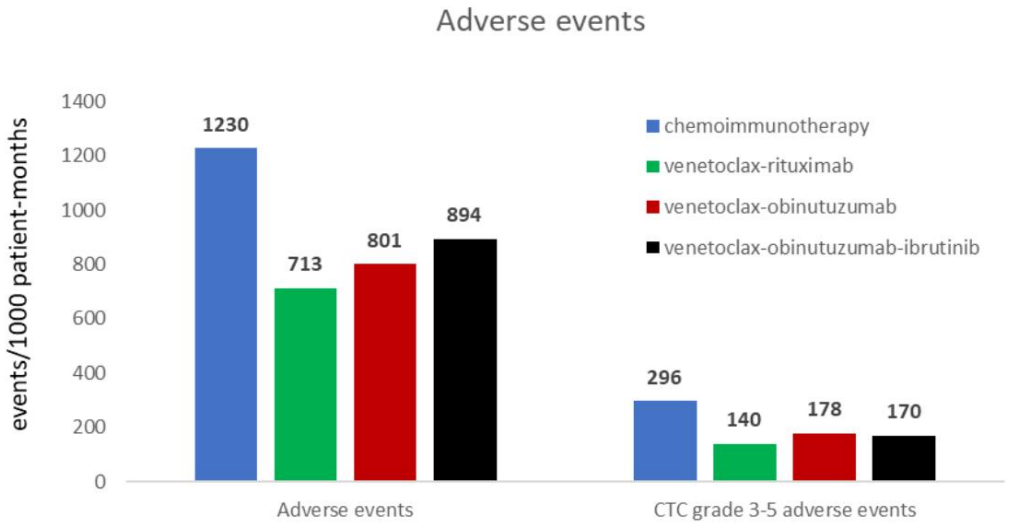
CLL13/GAIA Studie

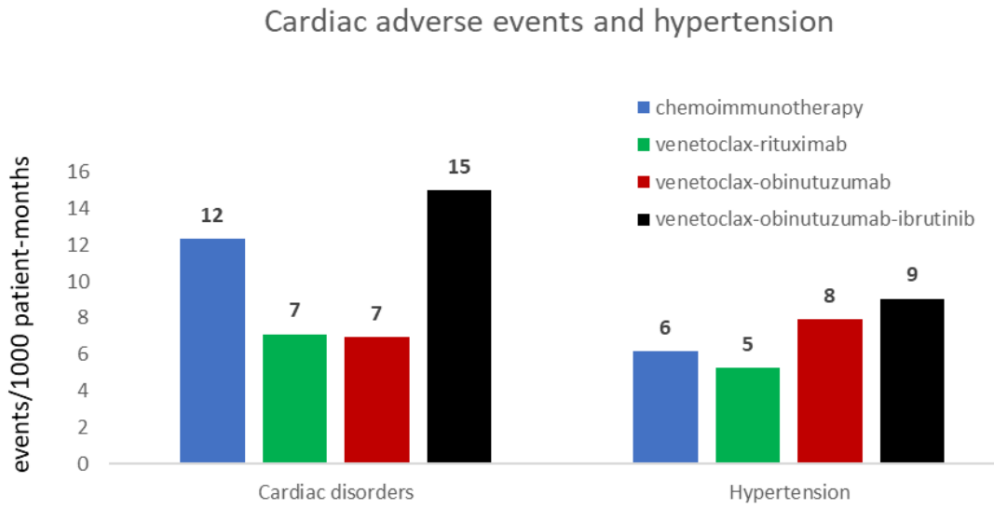
PFS nach IGHV Status



Pts at risk

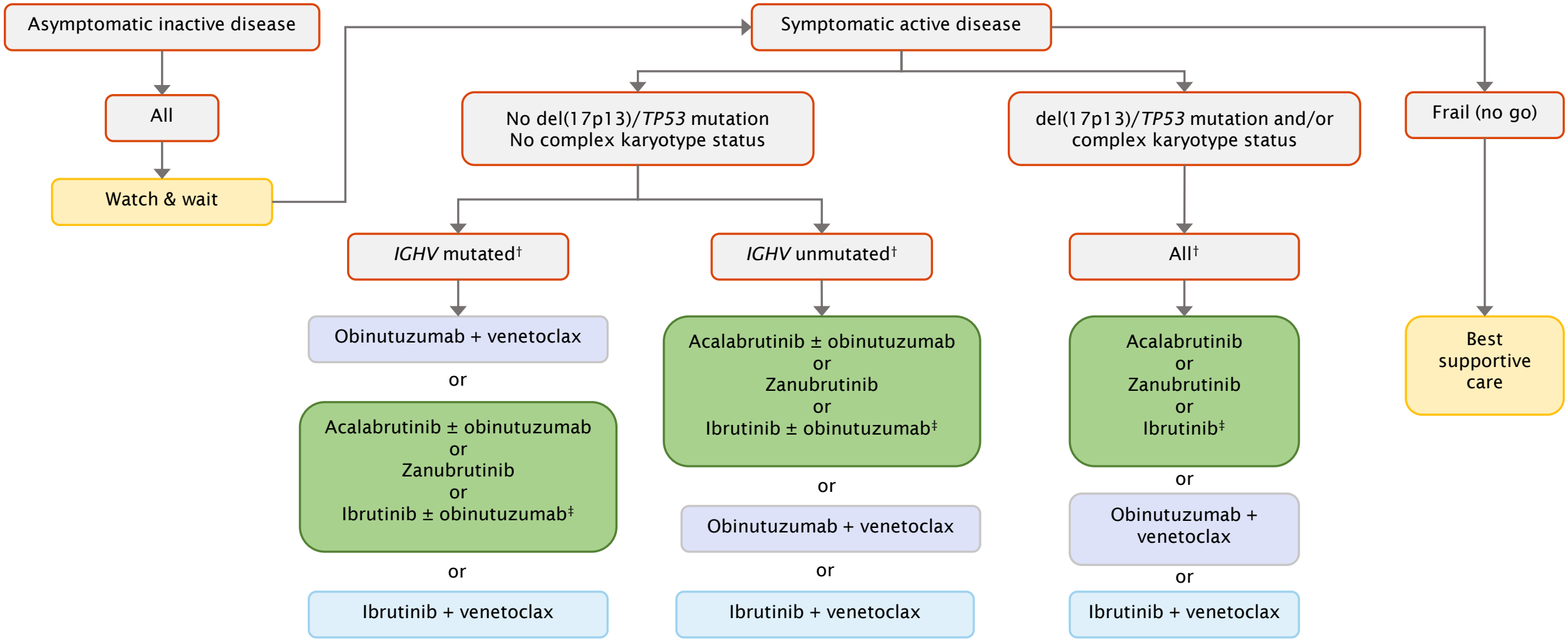
CIT	131	108	89	77	34	9
RV	134	128	119	100	56	10
GV	130	125	116	108	67	15
GIV	123	121	117	105	65	24





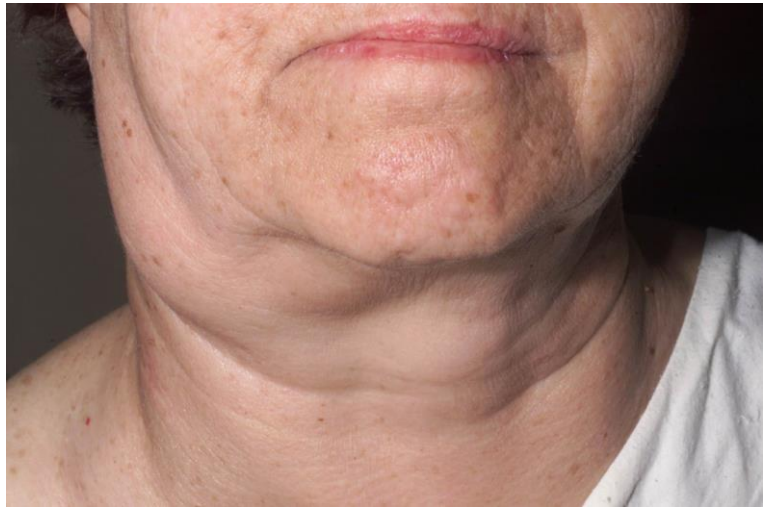
Eichhorst B. et al., NEJM 2023
Fürstenau M et al. Lancet Oncol 2024

Onkopedia Leitlinie CLL 2023

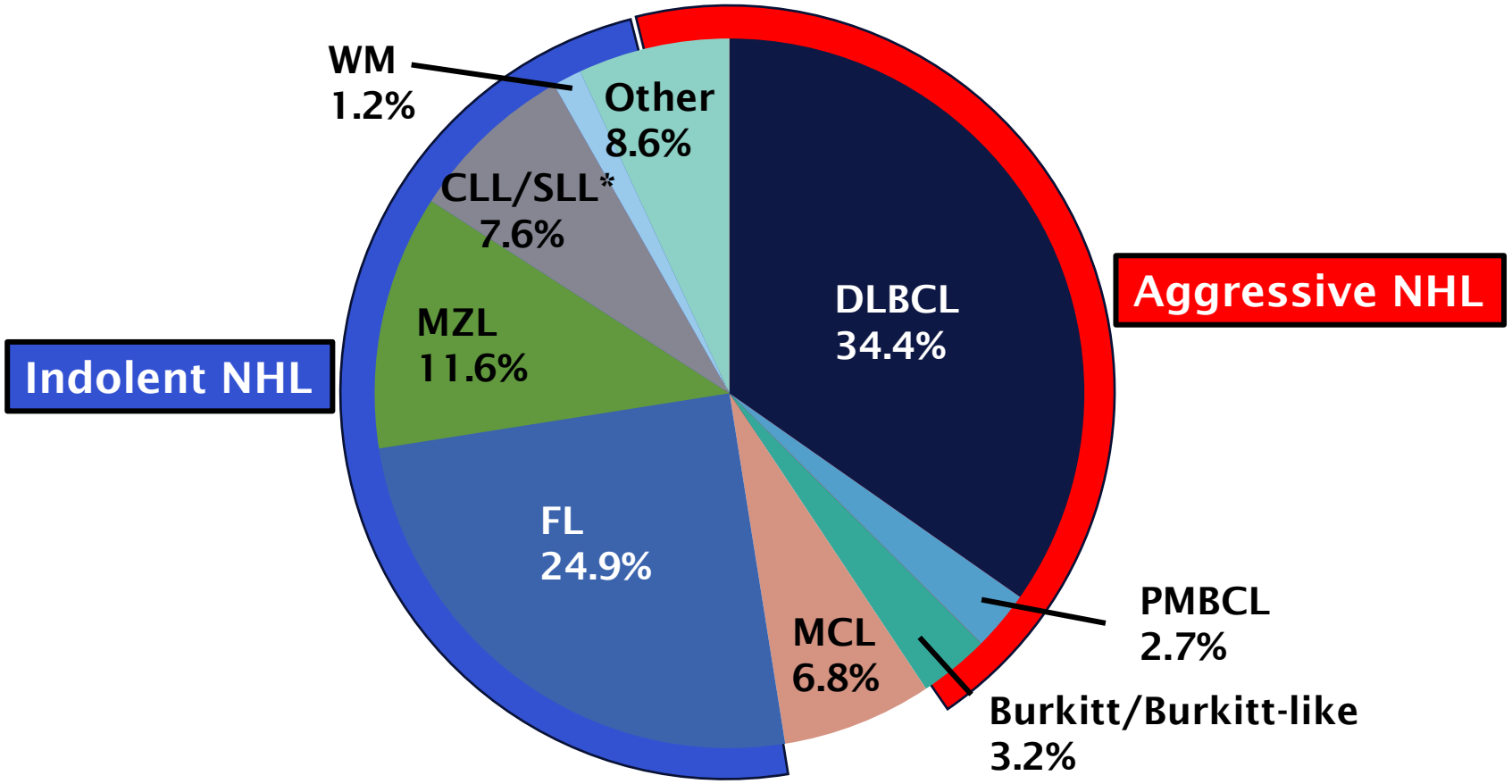


Fallbeispiel

Eine 52-jährige Röntgen-Technische Assistentin berichtet über eine seit 3 Monaten zunehmende indolente Schwellung am M.Sternocleidomastoideus links. Im Ultraschall war ein 4 cm großer Lymphknoten ohne eindeutig nachweisbaren Hilus sichtbar. Die Serum LDH betrug zuletzt 310 U/L.



B-zell Lymphome

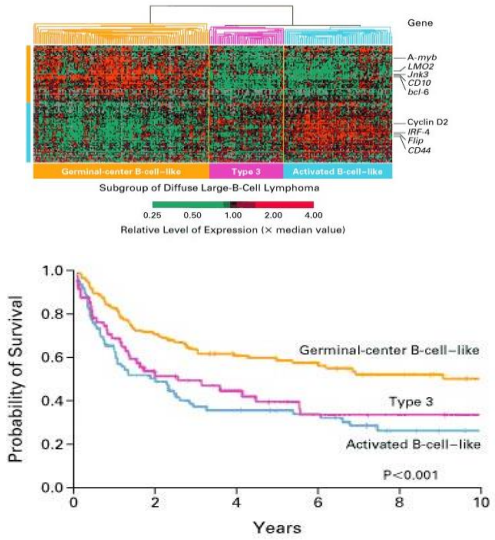


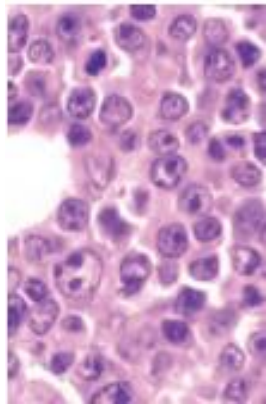
CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; iNHL = indolent NHL;
MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; PMBCL = primary mediastinal B-cell lymphoma;
SLL = small lymphocytic lymphoma; WM = Waldenström's macroglobulinemia.
* CLL/SLL included as a subcategory of iNHL in this classification but is usually treated differently;
† 'Other' includes some rarer types of both indolent and aggressive NHL.

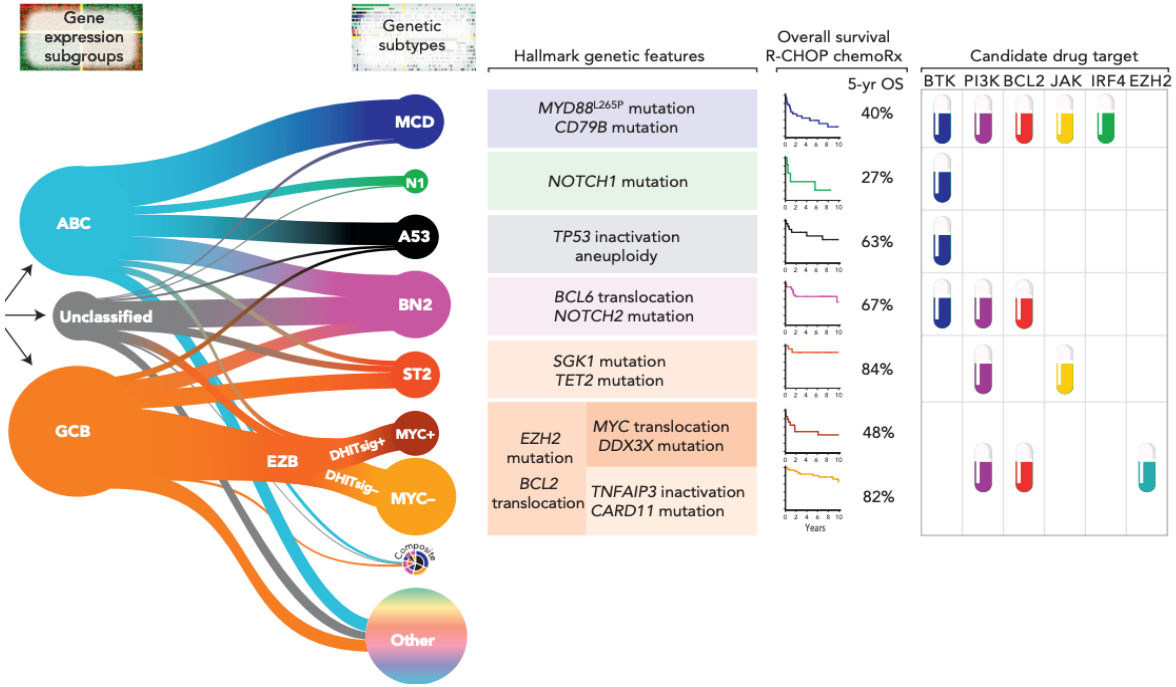
Based on 1,131 patients with B-cell malignancies at 9 sites worldwide

The Non-Hodgkin's Lymphoma Classification Project. *Blood* 1997; 89:3909–3918.

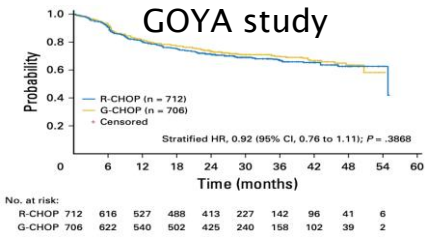
Diffus großzelliges B-Zell-Lymphom: Heterogene Erkrankung
Eine 1L-Therapie: R-CHOP ?





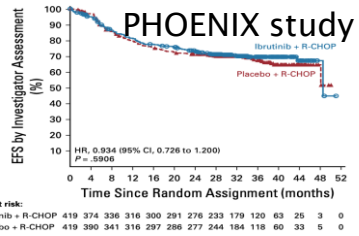


Rituxi vs Obi +CHOP
GOYA study



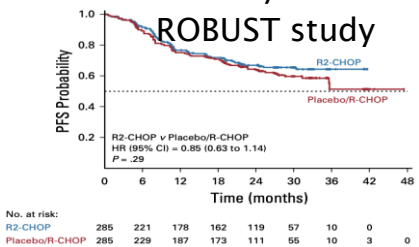
Vitolo U et al. JCO 2017

R-CHOP +/- ibrutinib
PHOENIX study



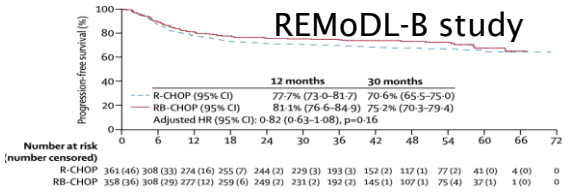
Younes A et al. JCO 2019

R-CHOP +/- lenalidomid
ROBUST study



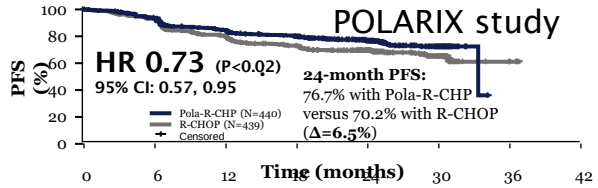
Nowakowski G et al. JCO 2019

R-CHOP +/- bortezomib
REMoDL-B study



Davies A et al Lancet Oncol. 2019

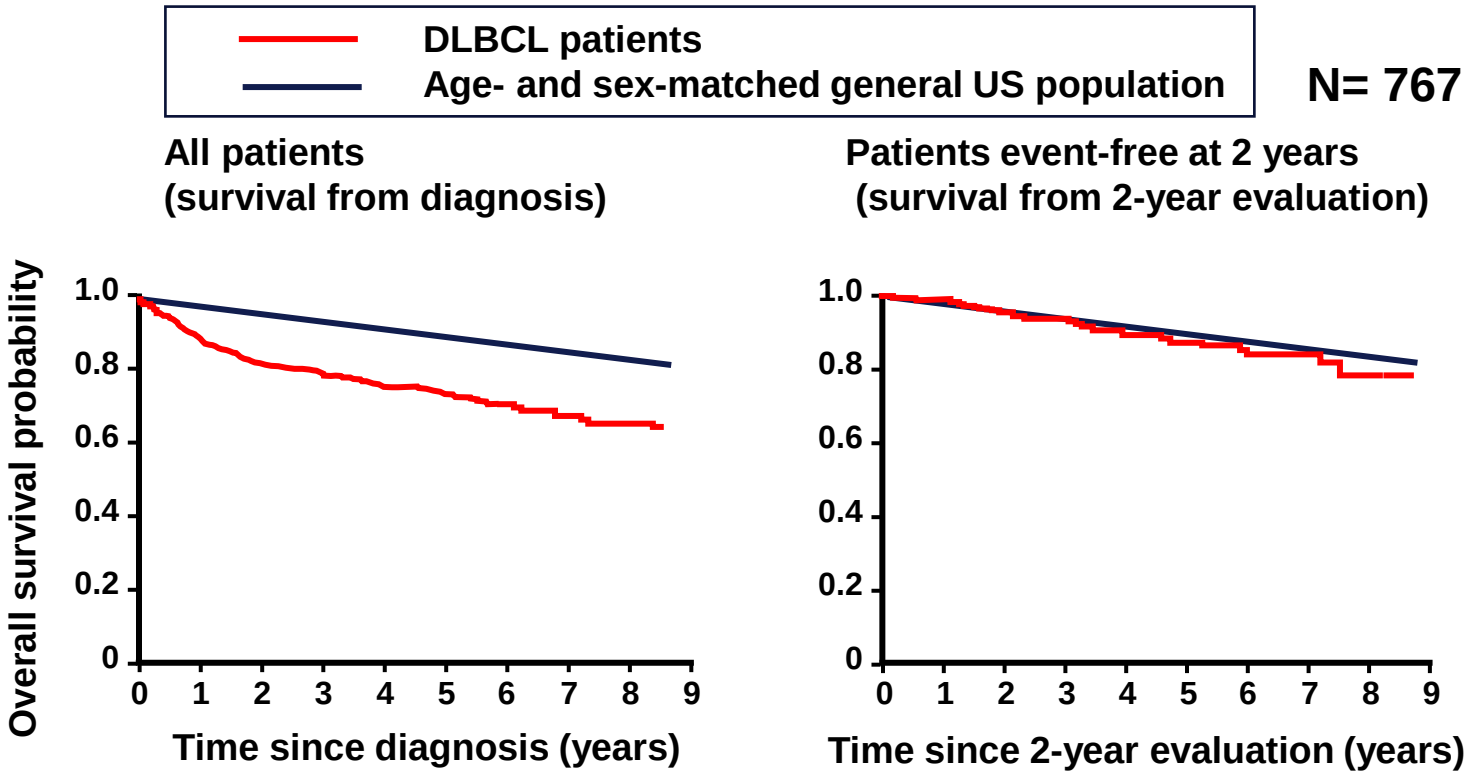
R-CH(O)P +/- PolatuzumabVedotin
POLARIX study



Tilly T. et al NEJM 2021

Alizadeh A et al. Nature 2000; Rosenwald A et al, N Engl J Med 2002; Chapuy B et al Nat.Med. 2018; Wright et al, Cancer Cell 2020; de Leval et al Blood 2022

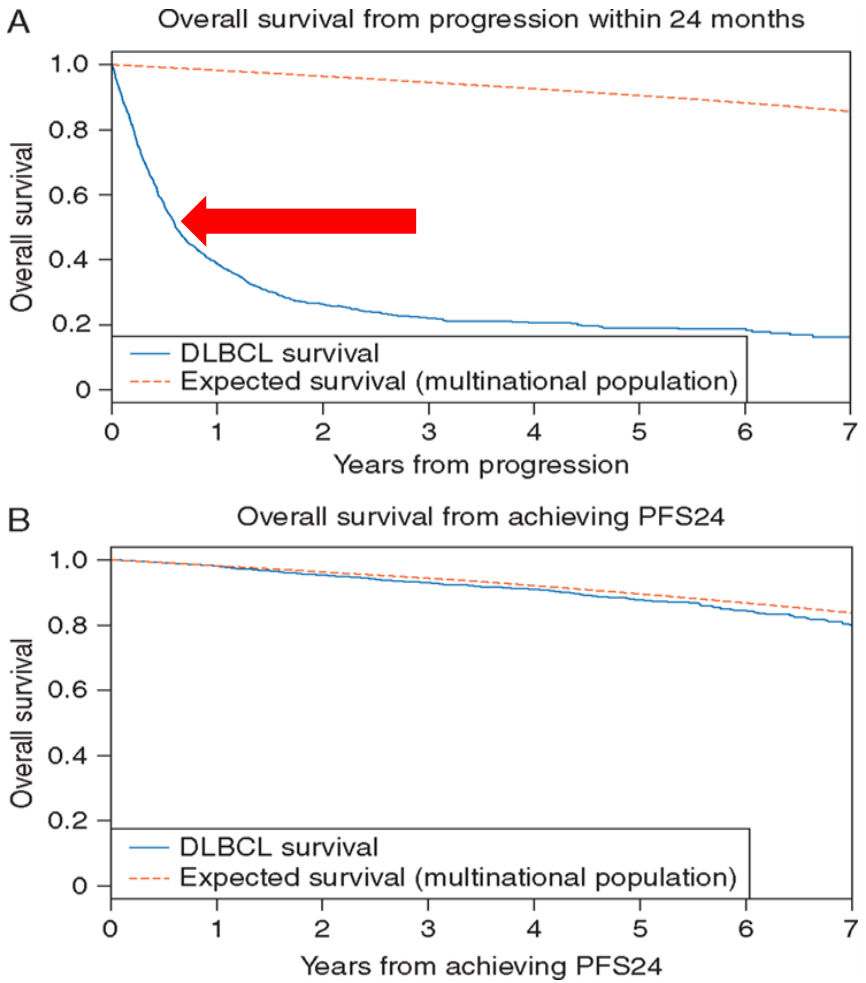
Diffus großzelliges B-Zell-Lymphom: Patienten mit PFS >2a, normales Überleben



DLBCL patients who are event free after 2–3 years can expect a normal lifespan

Maurer MJ, *et al*. *J Clin Oncol* 2014; 32:1066–1073.

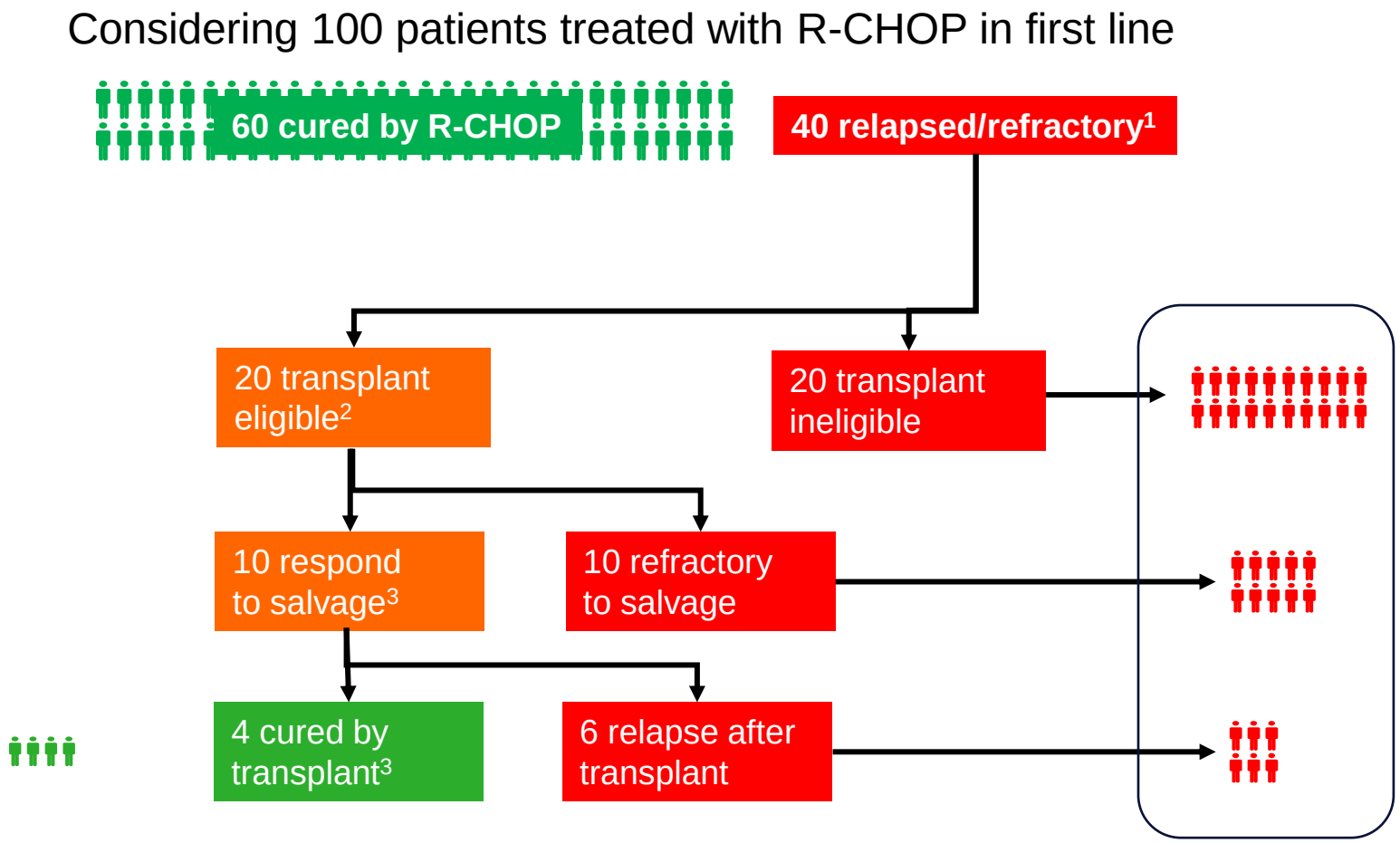
OS from progression for pts. who failed to achieve PFS24 versus expected survival



SEAL trial
n=3678

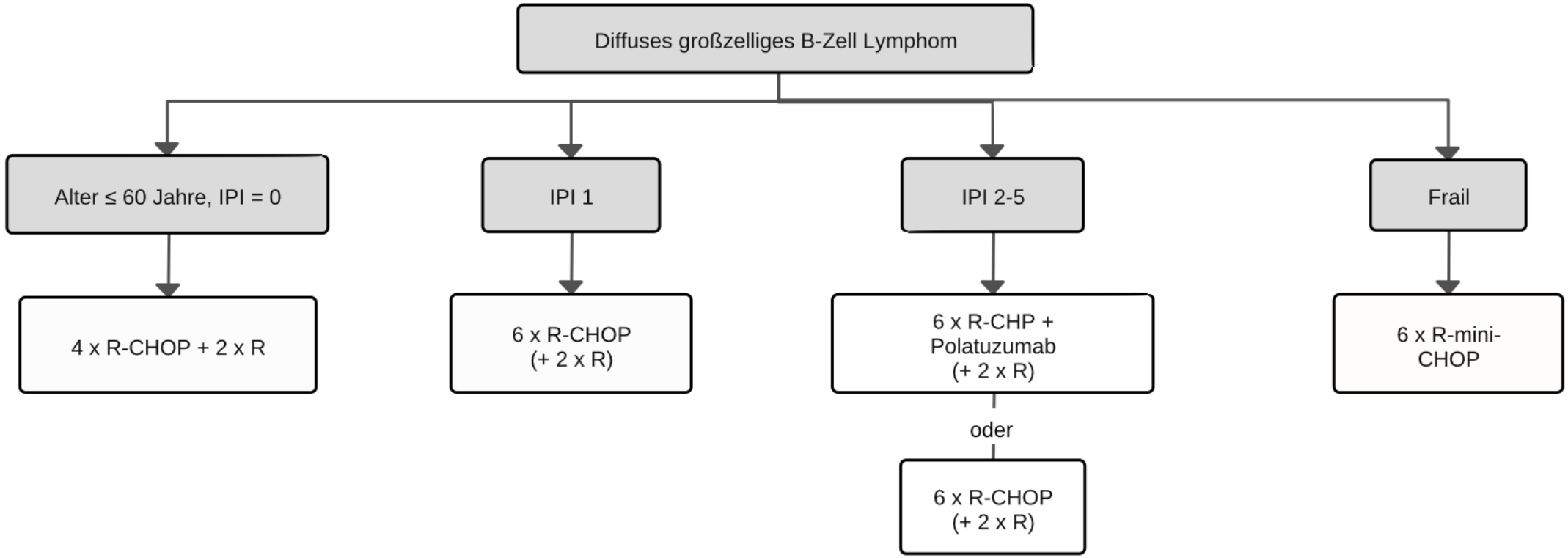
Maurer MJ, Annals of Oncology, 2018

Summary of outcome in aggressive B-NHL: We have a situation

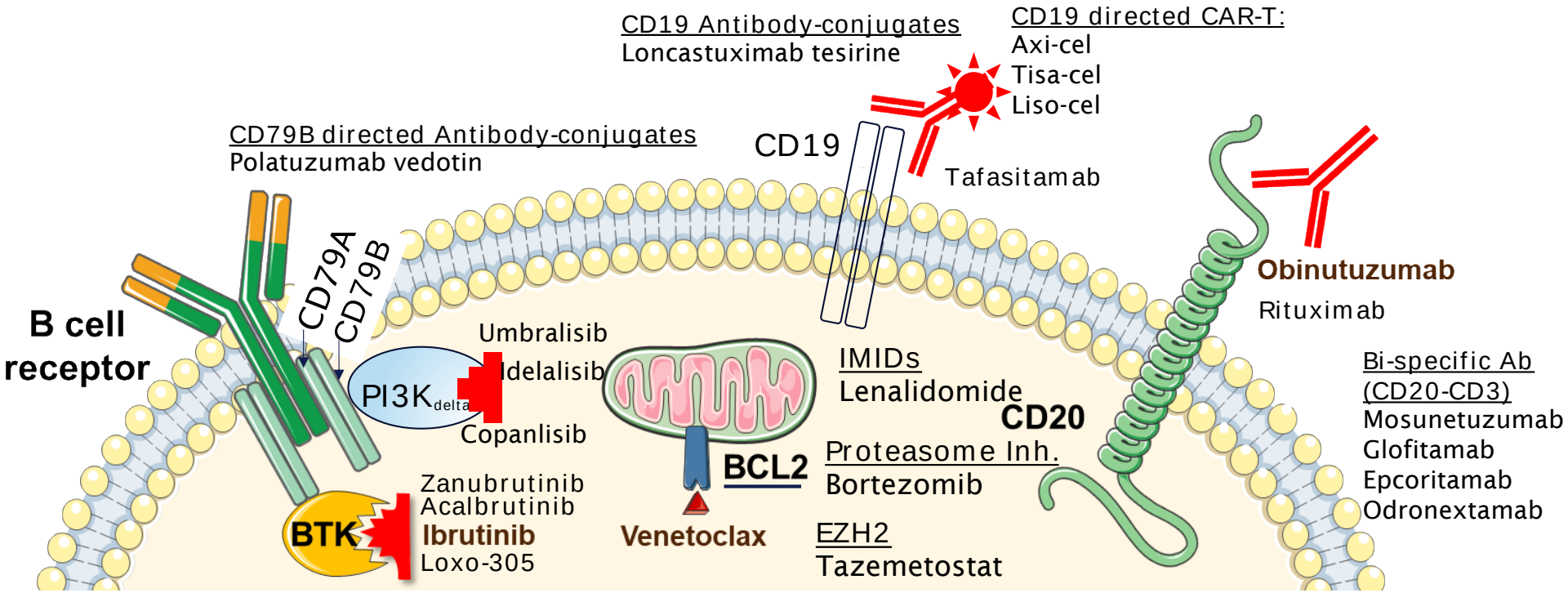


1. Friedberg J. Hematology 2011; 498–505;
2. Gisselbrecht C, *et al.* *J Clin Oncol* 2010; 28:4184–4190.;
3. Gisselbrecht C, *et al.* *J Clin Oncol* 2012; 30:4462–4469..

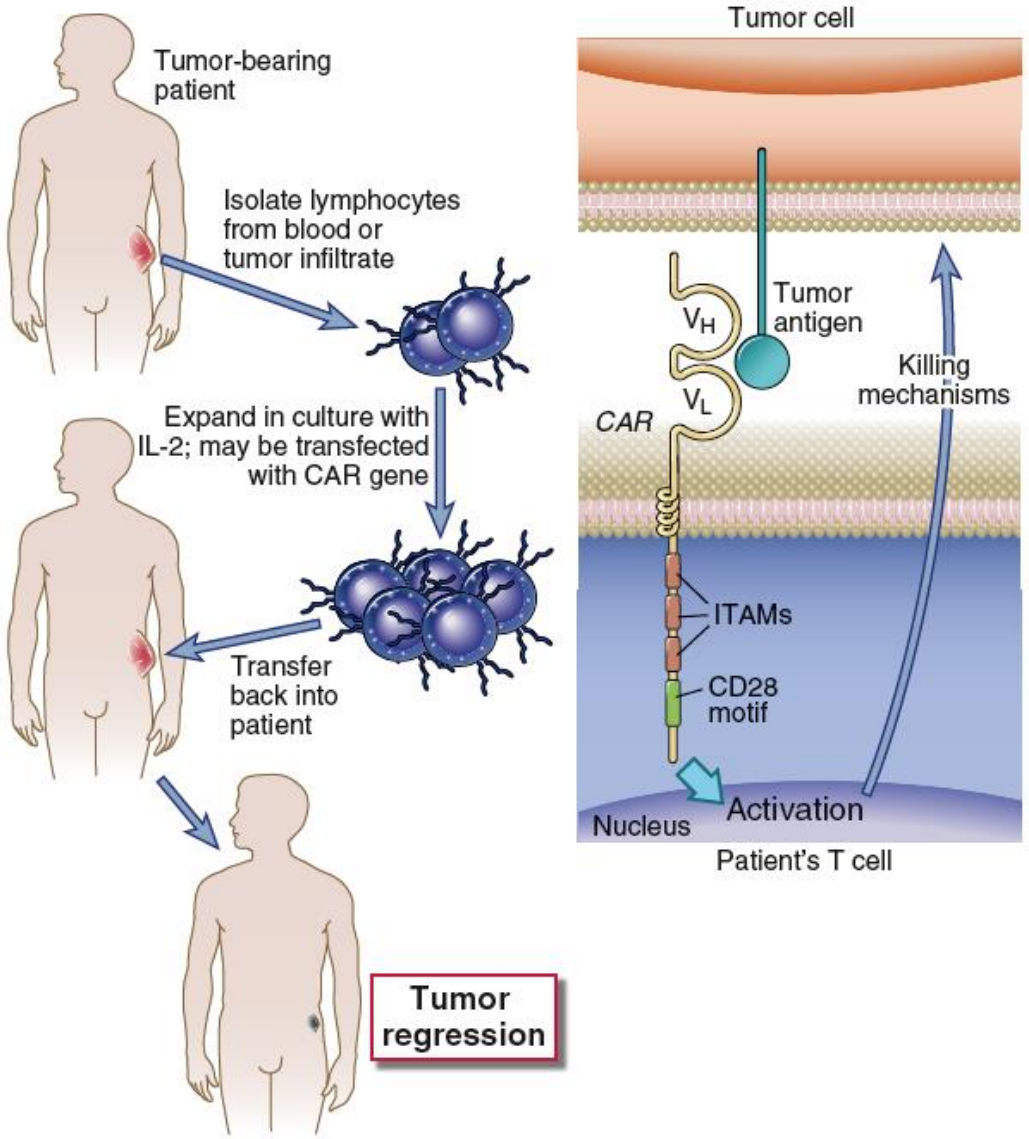
Update Jan 2024



Therapeutische Zielstrukturen für B-Zell Lymphome



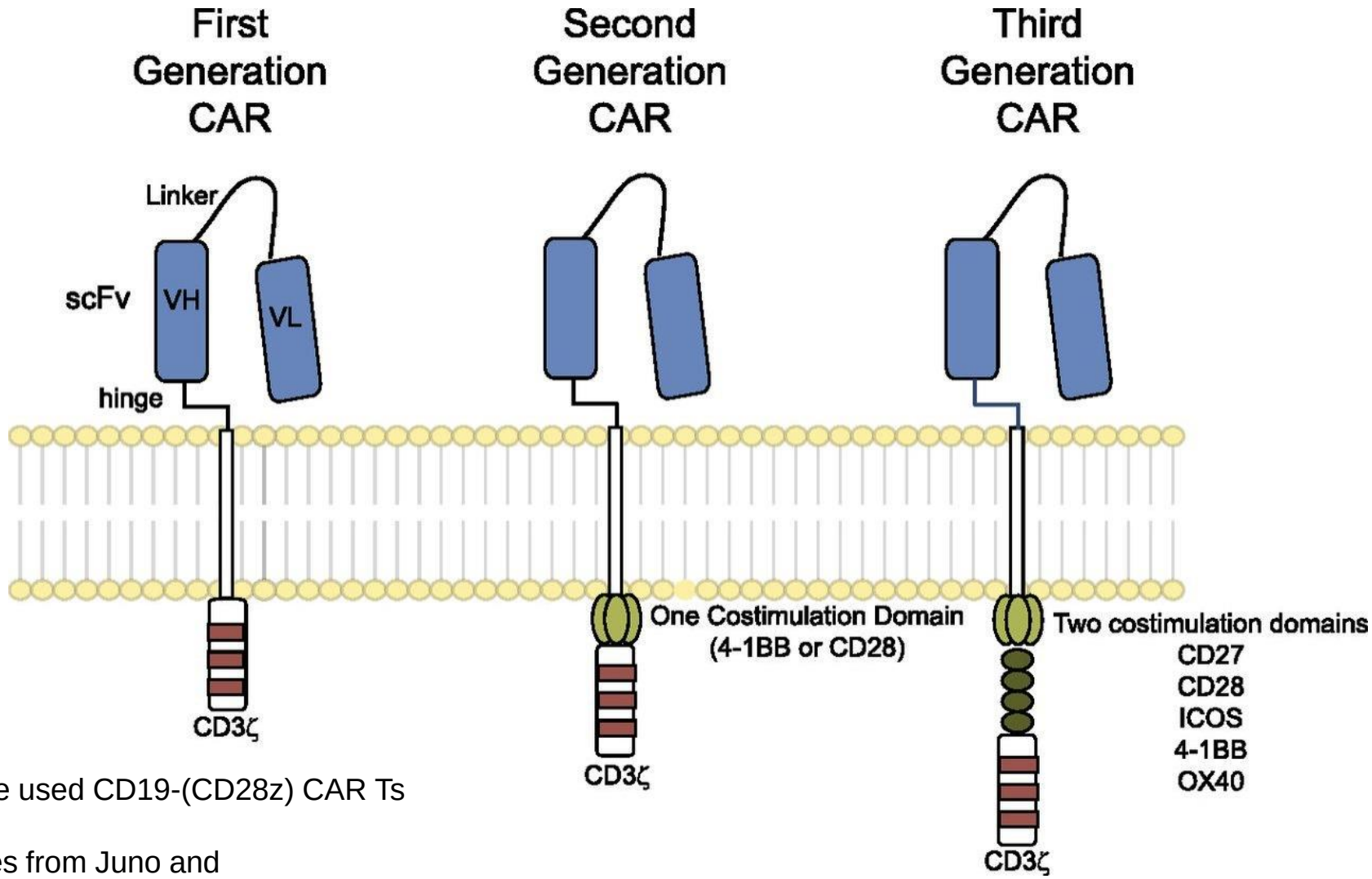
Chimeric antigen receptors



- *Remarkable success in B cell acute leukemia (targeting CD19); up to 90% complete remission*
- *Early results in solid tumors are encouraging*
- *Risk of cytokine storm*
- *Outgrowth of antigen-loss variants of tumors?*

N Engl J Med 2014; 371:1507-1517, October 16, 2014

Development of chimeric antigen receptors



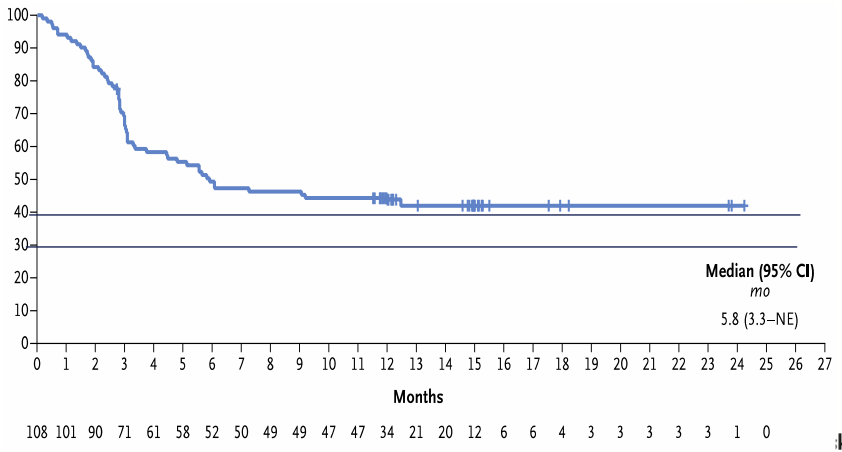
ZUMA trials from Kite used CD19-(CD28z) CAR Ts

TRANSCEND studies from Juno and
JULIET studies from Novartis used CD19-(4-1BBz) CAR Ts.

Axi-cel	Tisa-cel	Liso-cel

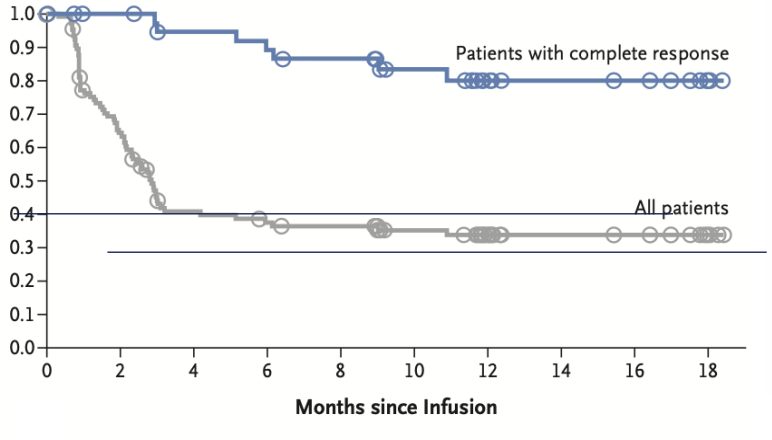
Patienten ab der 3. Therapielinie

PFS



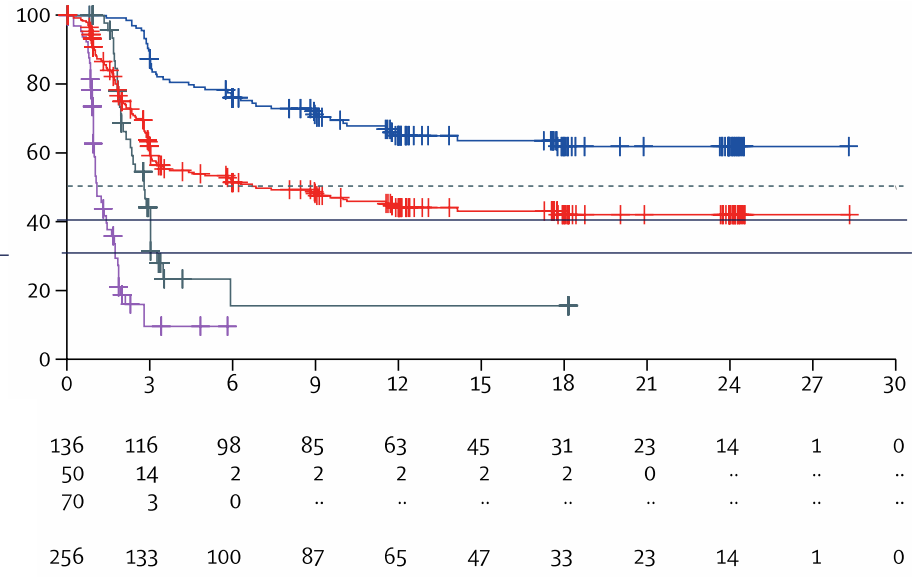
Lancet Oncol 2019; 20: 31–42

PFS



N Engl J Med 2019;380:45-56

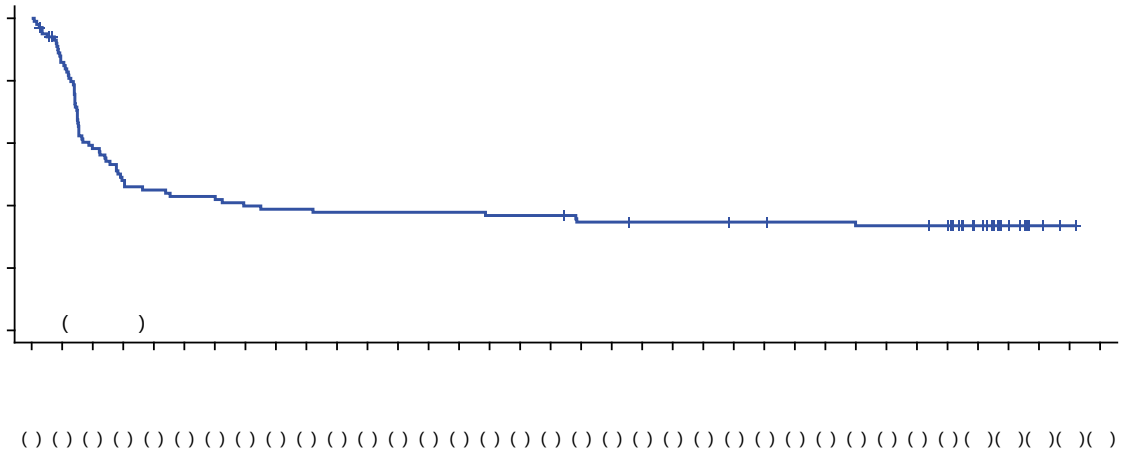
PFS

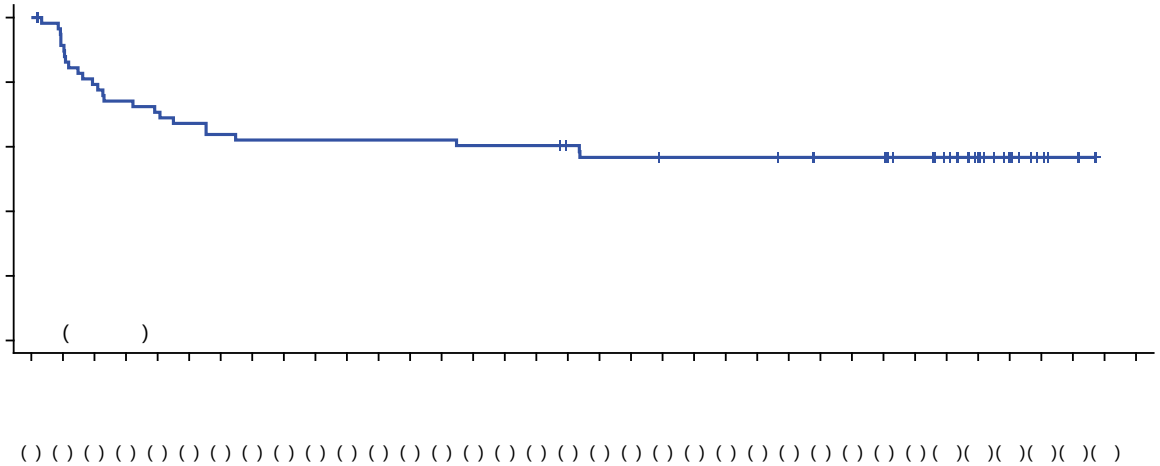


Lancet 2020; 396: 839–52

Axi-Cel Monotherapy in R/R DLBCL (>2L)

Curative Potential of Axicabtagene Ciloleucel (Axi-Cel): an Exploratory Long-Term Survival Assessment in Patients with Refractory Large B-Cell Lymphoma from ZUMA-1



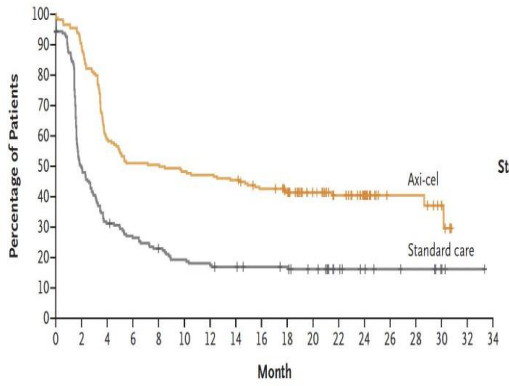


With ≥5 years of follow-up (median 63.1 months), the **5-year LREFS rate was 33.5%** (95% CI, 24.4-42.9)

The **5-year estimate of DOCR (n=59) was 56.7%** (95% CI, 43.0-68.3)

CAR T-cells vs. SOC in 2L LBCL

Axi-cel (ZUMA-7) NCT 03391466	
CAR T	SOC



	No. of Patients	Median Event-free Survival (95% CI) mo
Axi-cel	180	8.3 (4.5–15.8)
Standard Care	179	2.0 (1.6–2.8)

Stratified hazard ratio for event or death, 0.40 (95% CI, 0.31–0.51)
P<0.001

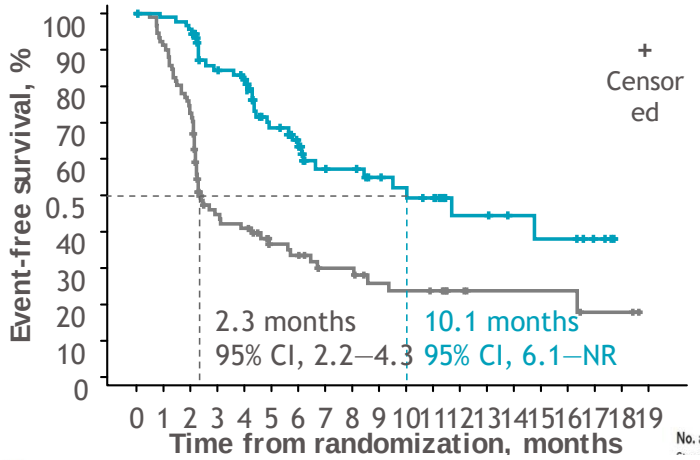
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

F.L. Locke, D.B. Miklos, C.J. Jacobson, M.A. Perales, M.E. Kersten, O.O. Oluwole, A. Ghobadi, A.P. Rapoport, J. McGuirk, J.M. Pagel, J. Muñoz, U. Farooq, T. van Meerten, P.M. Reagan, A. Sureda, I.W. Flinn, P. Vandenberghe, K.W. Song, M. Dickinson, M.C. Minnema, P.A. Riedell, L.A. Leslie, S. Chaganti, Y. Yang, S. Filosto, J. Shah, M. Schupp, C. To, P. Cheng, L.I. Gordon, and J.R. Westin, for All ZUMA-7 Investigators and Contributing Kite Members*

Liso-cel (TRANSFORM) NCT 03575351	
CAR T	SOC

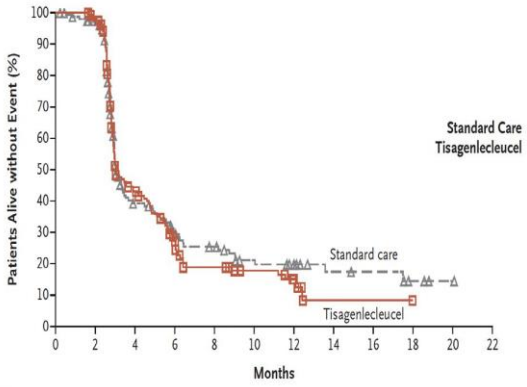


Articles

Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial

Manali Kamdar, Scott R Solomon, Jon Arnason, Patrick B Johnston, Bertram Glass, Veronika Bachanova, Sami Ibrahimi, Stephan Mielke, Pim Mutsaers, Francisco Hernandez-Ilizaliturri, Koji Izutsu, Franck Morschhauser, Matthew Lunning, David G Maloney, Alessandro Crotta, Sandrine Montheard, Alessandro Previtali, Lara Stepan, Ken Ogasawara, Timothy Mack*, Jeremy S Abramson, for the TRANSFORM Investigators†

Tisa-cel (BELINDA) NCT 03570892	
CAR T	SOC



	No. of Patients	No. of Events	Median Event-free Survival (95% CI) mo
Standard Care	160	104	3.0 (3.0–3.5)
Tisagenlecleucel	162	117	3.0 (2.9–4.2)

Hazard ratio for event or death (tisagenlecleucel vs. standard care), 1.07 (95% CI, 0.82–1.40)
P=0.61

ORIGINAL ARTICLE

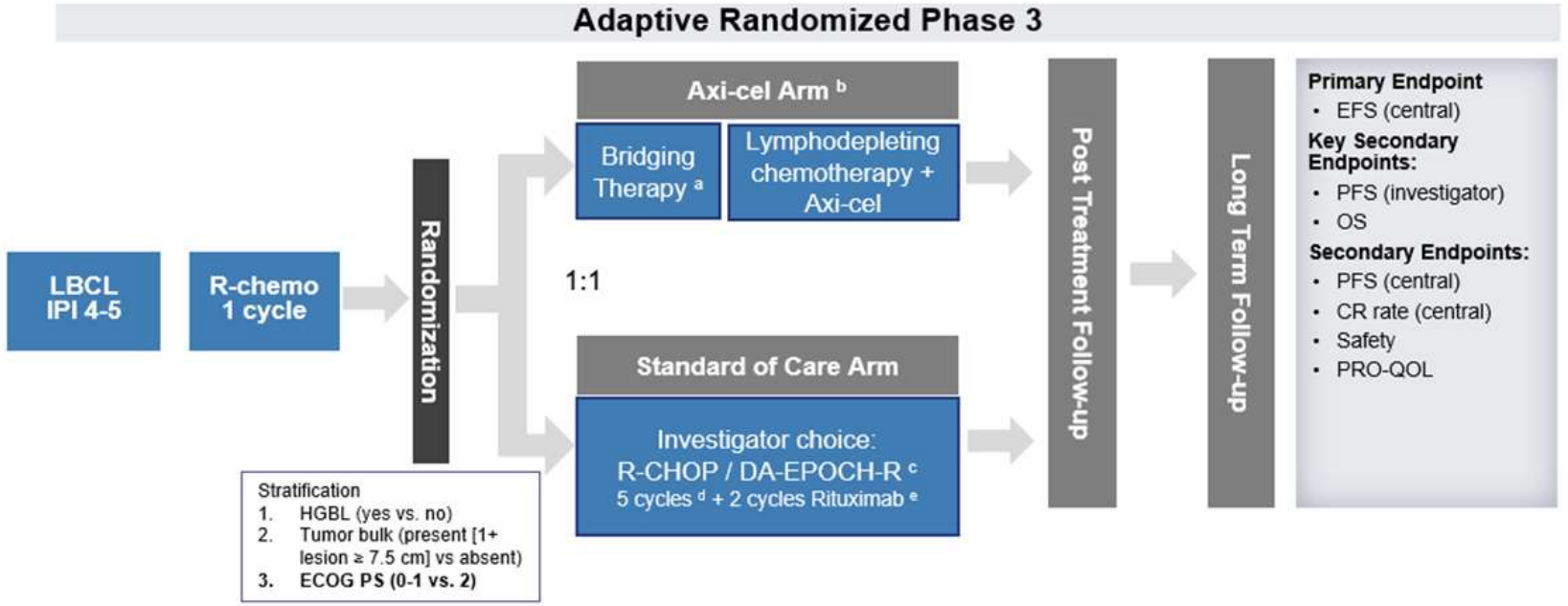
Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

M.R. Bishop, M. Dickinson, D. Purtill, P. Barba, A. Santoro, N. Hamad, K. Kato, A. Sureda, R. [illegible], W. Rabitsch, Y.-L. [illegible], J. Martinez-Lopez, A.M. [illegible], S. Le Gouill, M. Dreyling, H. Hari[illegible], D. Bond, C. Andreadis, P. McSweeney, M. Kharfan-Dabaja, S. Newsome, E. Degtyarev, R. Awasthi, C. del Corral, G. Andreola, A. Masood, S.J. Schuster, U. Jäger, P. Borchmann, and J.R. Westin

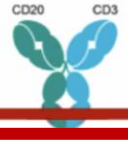
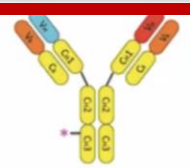
positive positive negative

Zuma-23: CAR-T in 1L HR DLBCL

An Adaptive Phase 3, Randomized, Open-Label, Multicenter Study to Compare the Efficacy and Safety of Axicabtagene Ciloleucel versus Standard of Care Therapy as First-Line Therapy in Subjects with High-Risk Large B-Cell Lymphoma (**ZUMA-23**)



Bi-specific antibodies (> 2 previous therapies)

Molecule*	Molecular structure	Dosing	Development program status
Epcoritamab	Full-length, human IgG1 CD20:CD3 1:1[1] 	SC Every 28 days†	• **Phase I/II** epcoritamab in R/R B-cell lymphoma‡[2,3] • **Phase I/II** epcoritamab + SOC in B-cell NHL (EPCORE NHL-2)[4]
Mosunetuzumab ***CHMP recommend conditional approval[18]***	Full-length, humanised IgG1 CD20:CD3 1:1[5] 	IV or SC Every 21 days†	• **Phase I/II** mosunetuzumab -/+ atezolizumab in R/R B-cell NHL‡[6,7] • **Phase II** SC mosunetuzumab in B-cell NHL (MorningSun)[8] • **Phase III** mosunetuzumab + lenalidomide vs rituximab + lenalidomide in R/R FL (CELESTIMO)[9]
Glofitamab	Full-length, humanised IgG1 CD20:CD3 2:1[10] 	IV Every 21 days†	• **Phase I/II** glofitamab -/+ obinutuzumab in R/R B-cell NHL‡[11,12] • **Phase Ib/II** glofitamab + polatuzumab or atezolizumab in R/R B-cell NHL[13]
Odronextamab	Hinge-stabilised, fully human IgG4 CD20:CD3 1:1[14] 	IV or SC Weekly,† followed by maintenance Q2W	• **Phase I** odronextamab in R/R B-cell malignancies (ELM-1)‡[15,16] • **Phase II** odronextamab in R/R B-cell NHL (ELM-2)[17]

1. Engelberts et al. eBioMed 2020;52:102625; 2. NCT03625037; 3. Hutchings et al. Lancet 2021;398:1157–1169 | 4. NCT04663347; 5. Sun et al. Sci Transl Med 2015;7:287ra70; 6. Budde et al. ASH 2021; 7. NCT02500407
8. NCT05207670 ; 9. NCT04712097; 10. Bacac et al. Clin Canc Res 2018;24:4785–4797; 11. NCT03075696 , 12. Morschhauser et al. ASH 2021; 13. NCT03533283 ; 14. Smith et al. Sci Rep 2015;5:17943; 15. NCT02290951;
16. Bannerji et al. Lancet Hematol 2022;S2352-3026; 17. NCT03888105; 18. Lunsumio: Pending EC decision (EMA)

M-DE-000123

RESEARCH SUMMARY

Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Dickinson MJ et al. DOI: 10.1056/NEJMoa2206913

CLINICAL PROBLEM

Patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) have a poor prognosis, and effective and readily available third-line therapies are needed. Glofitamab is a T-cell–engaging bispecific antibody that may hold promise for these patients.

CLINICAL TRIAL

Design: A phase 2 open-label trial assessed the efficacy and safety of glofitamab monotherapy in adults with relapsed or refractory DLBCL who had received two or more lines of therapy previously.

Intervention: 155 patients were enrolled to receive intravenous glofitamab. Intravenous obinutuzumab was given 7 days before initiation of glofitamab to mitigate cytokine release syndrome. Glofitamab was then given for 12 cycles or until disease progression or an unacceptable level of toxic effects occurred. The primary efficacy end point was complete response as assessed by an independent review committee.

RESULTS

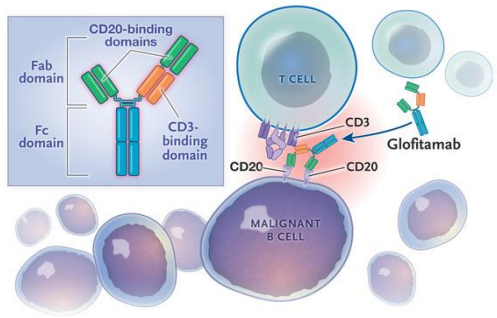
Efficacy: At a median follow-up of 12.6 months, 39% of the patients had a complete response.

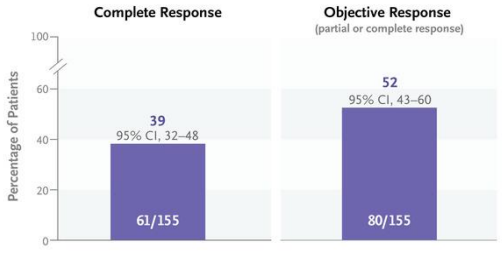
Safety: Adverse events leading to treatment discontinuation were uncommon. Overall, the most common adverse event was cytokine release syndrome, which was usually of low grade. Grade 3 or 4 adverse events occurred in more than half the participants; neutropenia was the most common of these events and rarely led to treatment discontinuation.

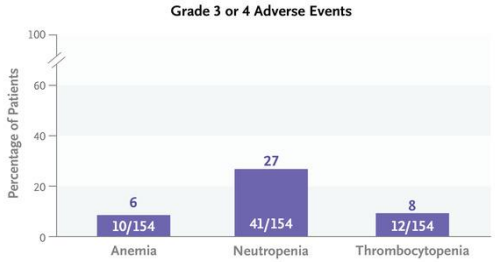
LIMITATIONS AND REMAINING QUESTIONS

- The trial was conducted primarily in Europe and Australia, largely in academic institutions. Accordingly, the racial diversity of the study population may not reflect that of affected patients in those regions or worldwide.
- How glofitamab compares with other treatments (for example, chimeric antigen receptor T-cell therapies) is unknown. Cross-trial comparisons should be made with caution, given differences in patient populations and trial design.

Links: Full Article | NEJM Quick Take | Editorial | Science behind the Study

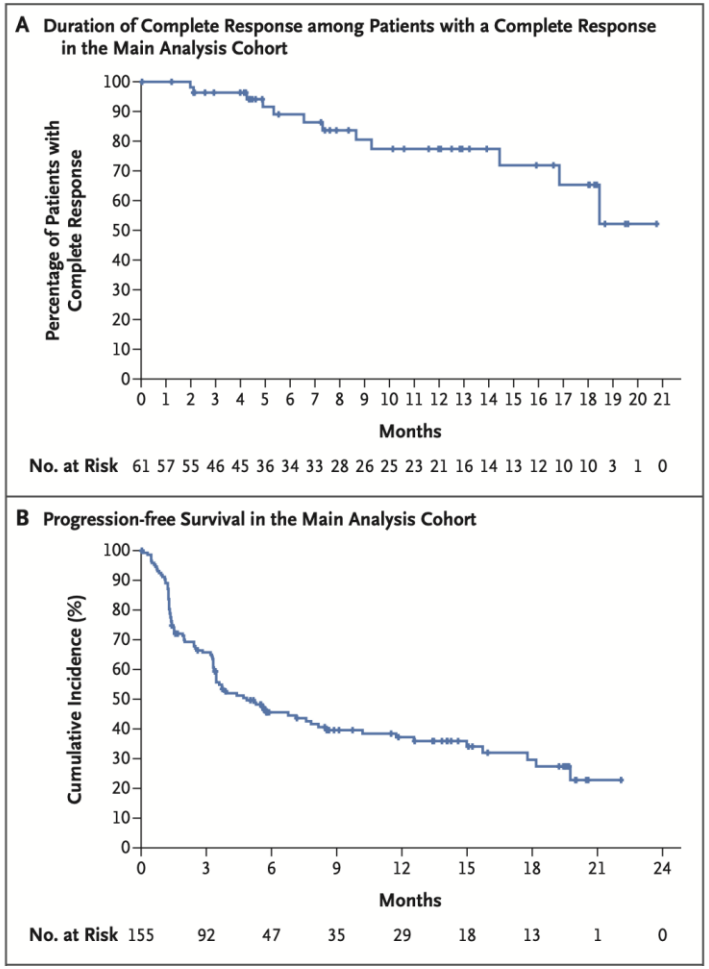






CONCLUSIONS

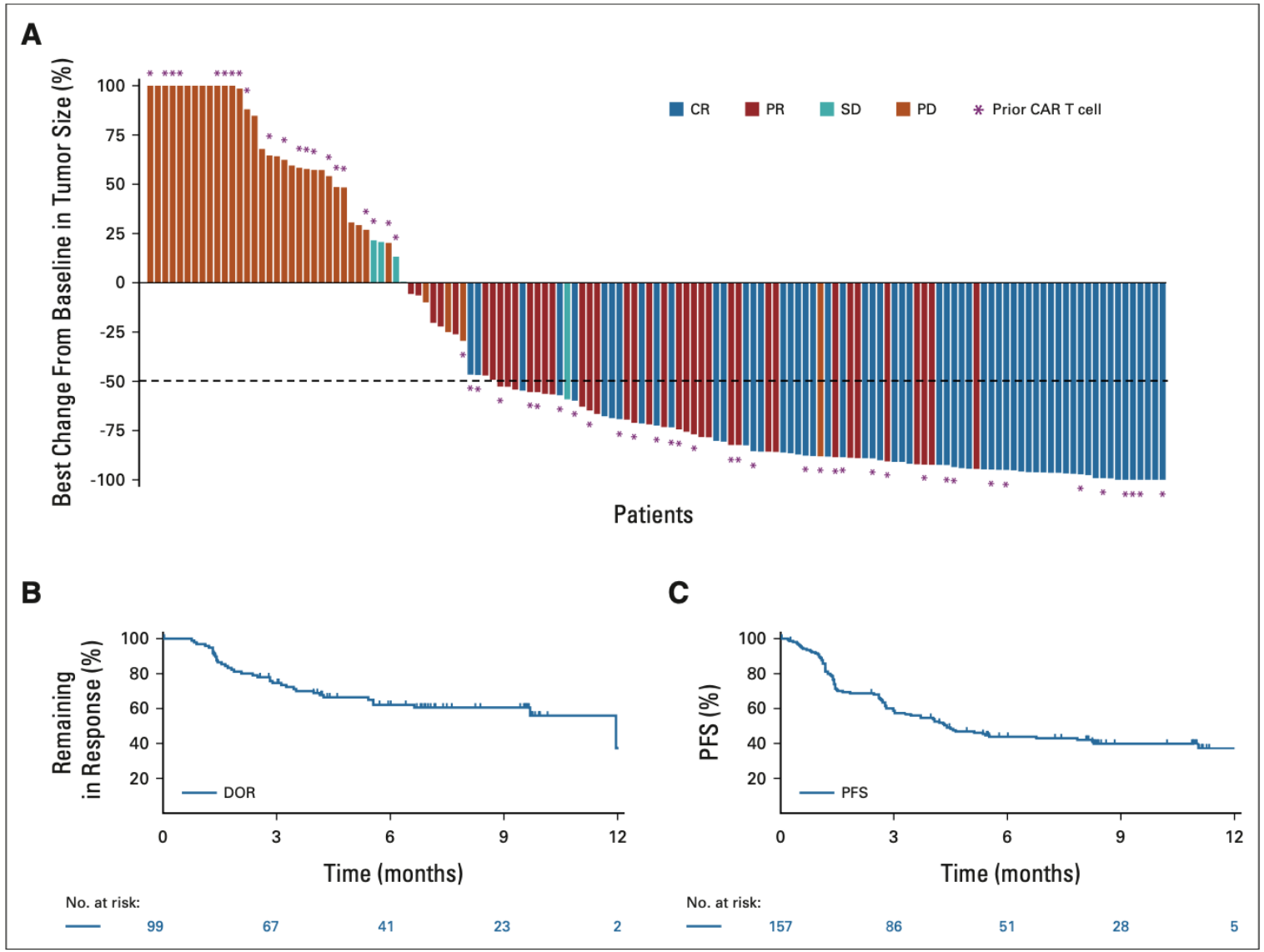
More than one third of patients with relapsed or refractory DLBCL had a complete response to treatment with glofitamab, although grade 3 or 4 adverse events were common.



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

Catherine Thieblemont, MD, PhD[1]; Tycel Phillips, MD[2]; Herve Ghesquieres, MD, PhD[3]; Chan Y. Cheah, MBBS, DMSc[4,5]; Michael Roost Clausen, MD, PhD[6]; David Cunningham, MD[7]; Young Rok Do, MD, PhD[8]; Tatyana Feldman, MD[9]; Robin Gasiorowski, MBBS, PhD[10]; Wojciech Jurczak, MD, PhD[11]; Tae Min Kim, MD, PhD[12]; David John Lewis, MD[13]; Marjolein van der Poel, MD, PhD[14]; Michelle Limei Poon, MD[15]; Mariana Cota Stirner, MD, PhD[16]; Nurgul Kilavuz, MSc[17]; Christopher Chiu, PhD[17]; Menghui Chen, PhD[17]; Mariana Sacchi, MD[17]; Brian Elliott, MD[17]; Tahamtan Ahmadi, MD, PhD[17]; Martin Hutchings, MD, PhD[18]; and Pieternella J. Lugtenburg, MD, PhD[19]

Patient	Any Grade (N = 157), No. (%)	Grade ≥ 3 (N = 157), No. (%)
Any AE	156 (99.4)	96 (61.1)
Any treatment-related AE	130 (82.8)	42 (26.8)
SAE	89 (56.7)	—
Serious treatment-related AE	55 (35.0)	—
Treatment-emergent AE leading to treatment discontinuation	12 (7.6)	11 (7.0)
AEs of special interest		
CRS[c]	78 (49.7)	4 (2.5)
ICANS[d]	10 (6.4)	1 (0.6)
Clinical tumor lysis syndrome	2 (1.3)	2 (1.3)



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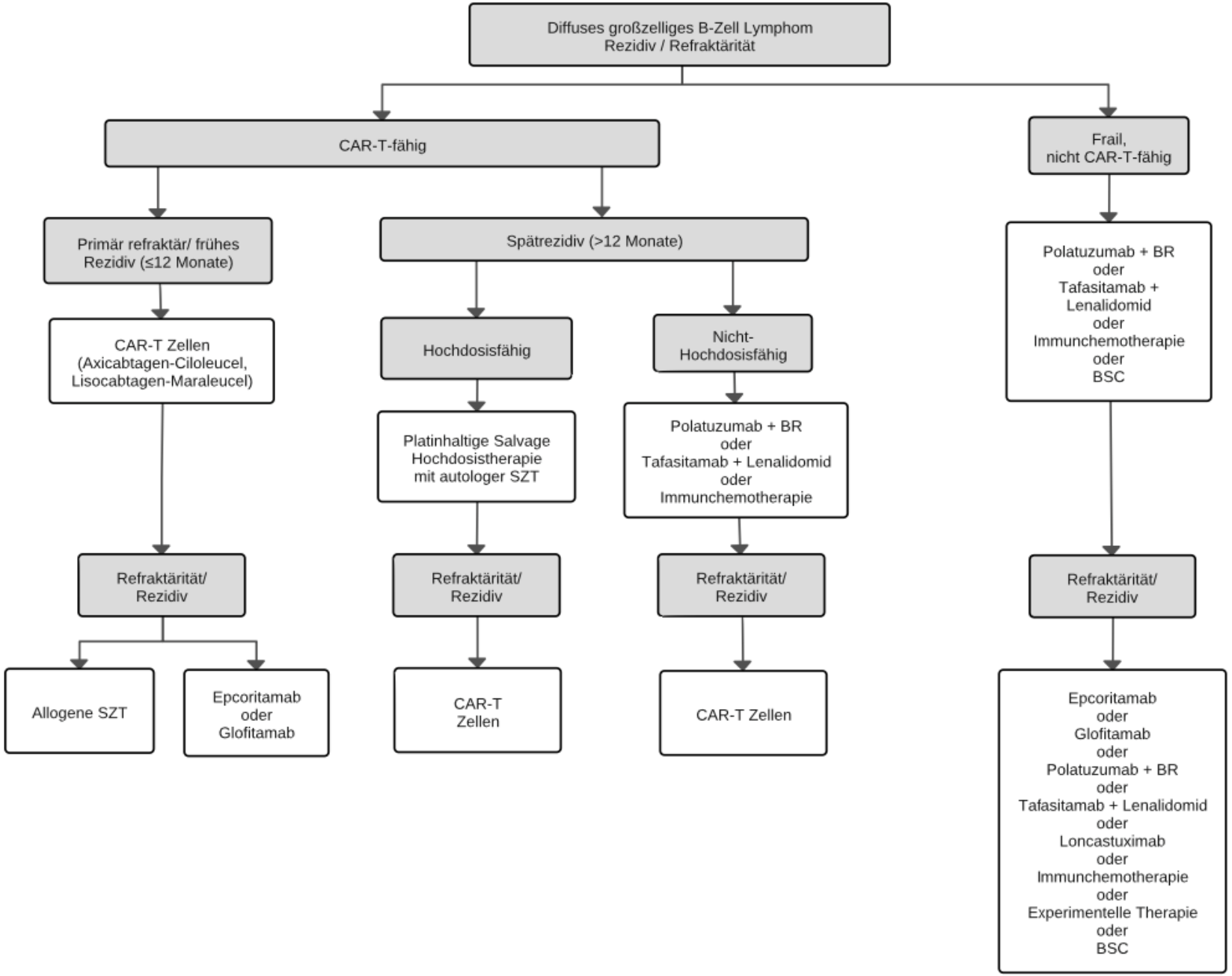
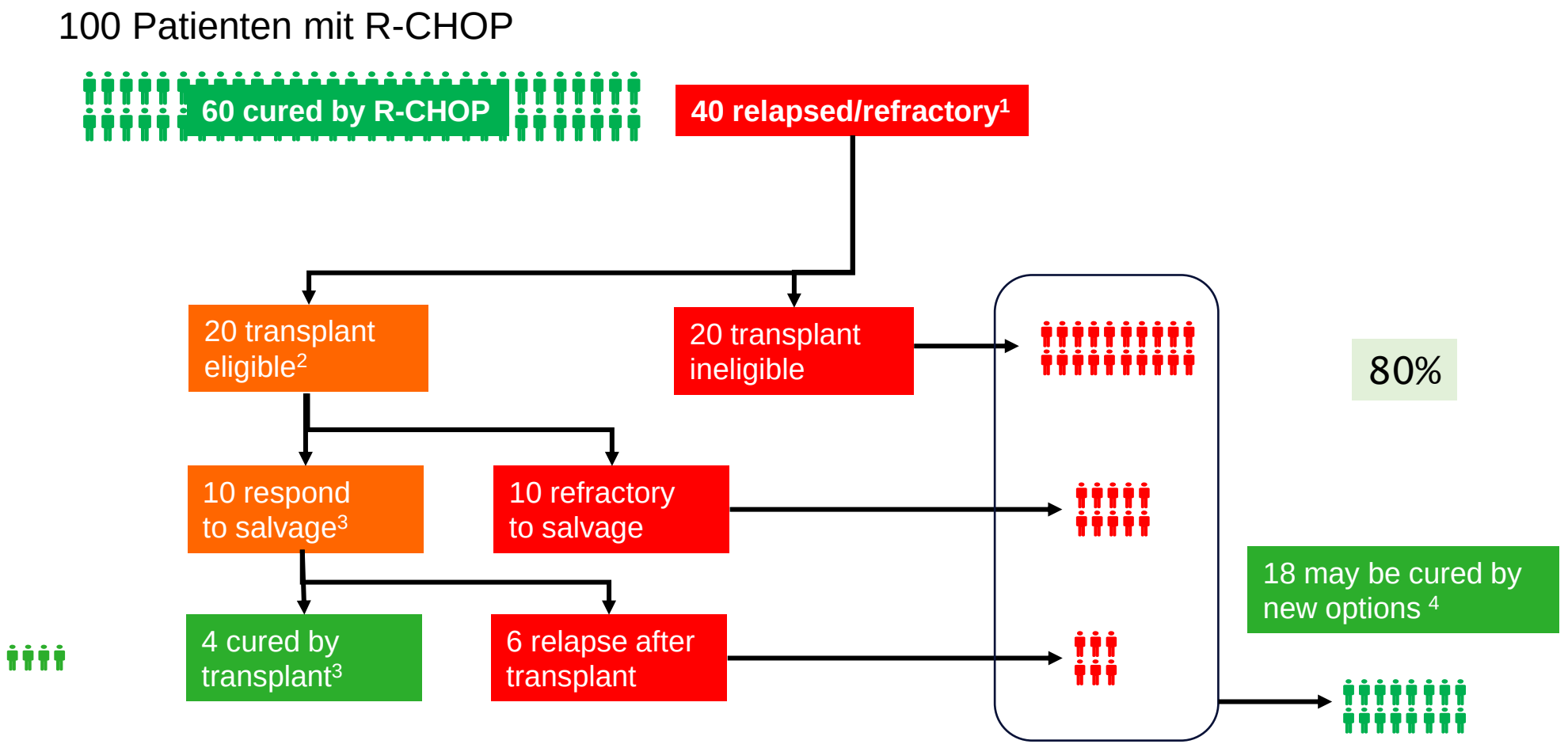
Update Jan 2024



Zusammenfassung aggressive B-zell Lymphome



1. Friedberg J. Hematology 2011; 498–505;
2. Gisselbrecht C, *et al.* *J Clin Oncol* 2010; 28:4184–4190.;
3. Gisselbrecht C, *et al.* *J Clin Oncol* 2012; 30:4462–4469..
4. Neelapu S. et al NEJM 2017 and others …

Vielen Dank für Ihre Aufmerksamkeit!

Noch Fragen?