

Post ASH 2024 San Diego Maligne Lymphome/CLL

Stefan Wirths

15. Januar 2025



Klassisches Hodgkin-Lymphom



**Universitätsklinikum
Tübingen**

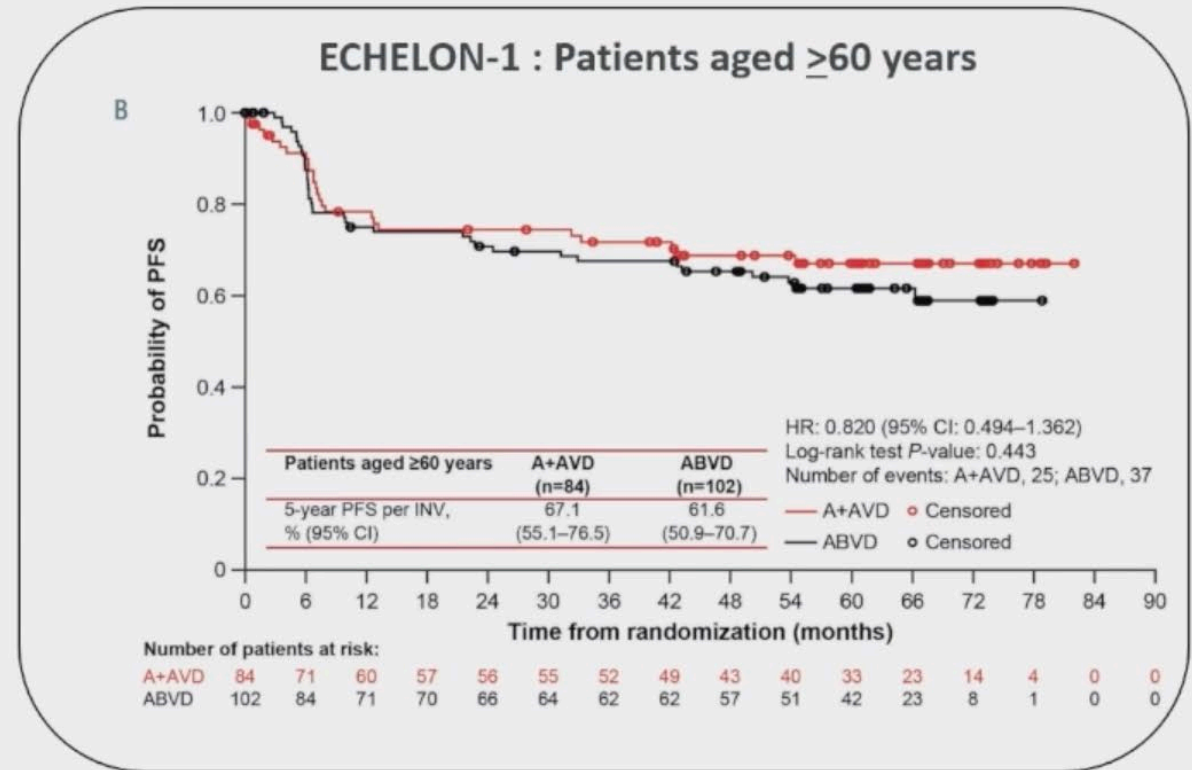
#568 PET-Guided BrECADD in Older Patients with Advanced-Stage Classic Hodgkin Lymphoma: Results of the Phase 2 Part of the GHSG HD21 Trial

Background

Older patients with advanced-stage Hodgkin Lymphoma (AS-cHL) have inferior outcomes and fewer treatment options.

- eBEACOPP is not feasible with a treatment-related mortality of approx. 15%.²

- 5y-PFS of A-AVD (67%) and ABVD (62%) is insufficient.¹



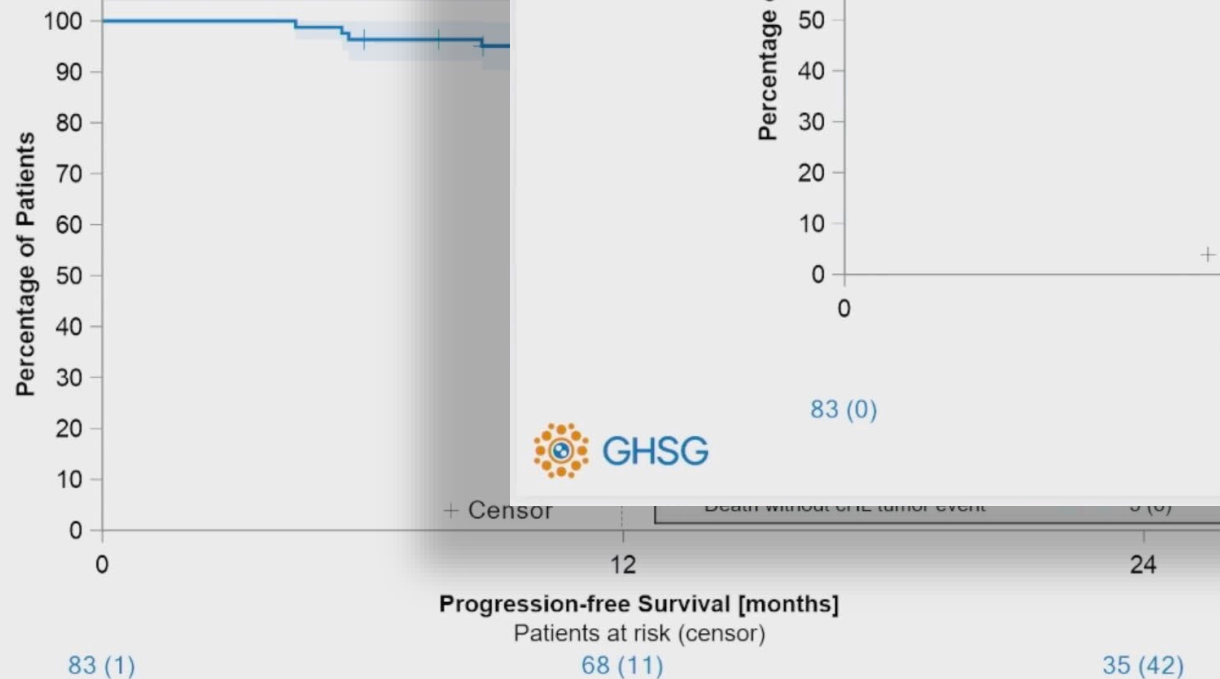
#568 PET-Guided BrECADD in Older Patients – Teil der HD21-Studie

Treatment completion and disease-free survival

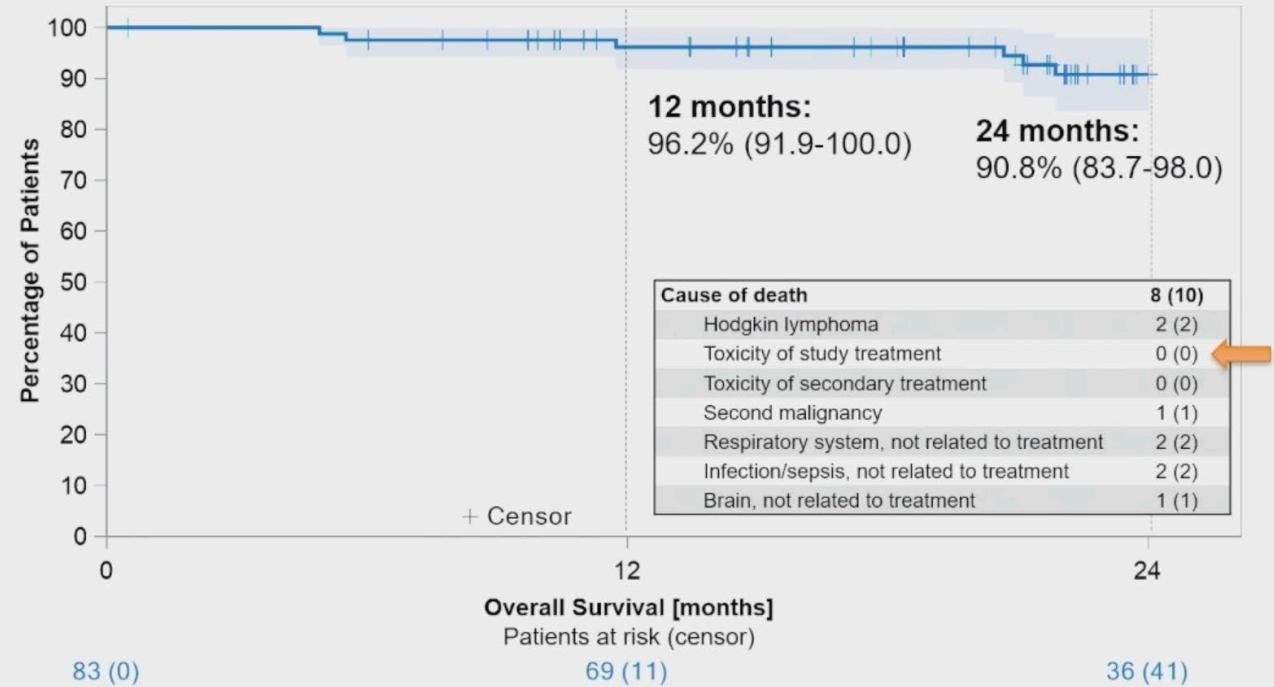
Treatment completion rate



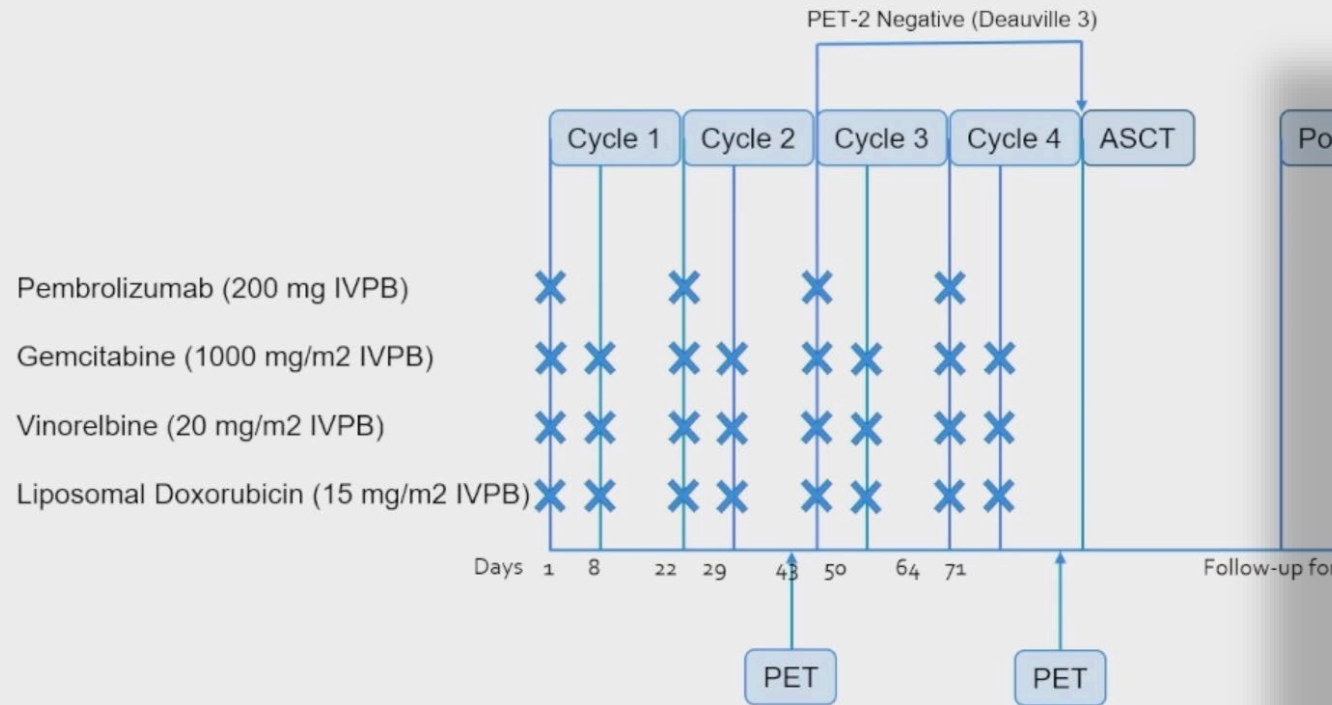
Progression-free survival mFU 23 months



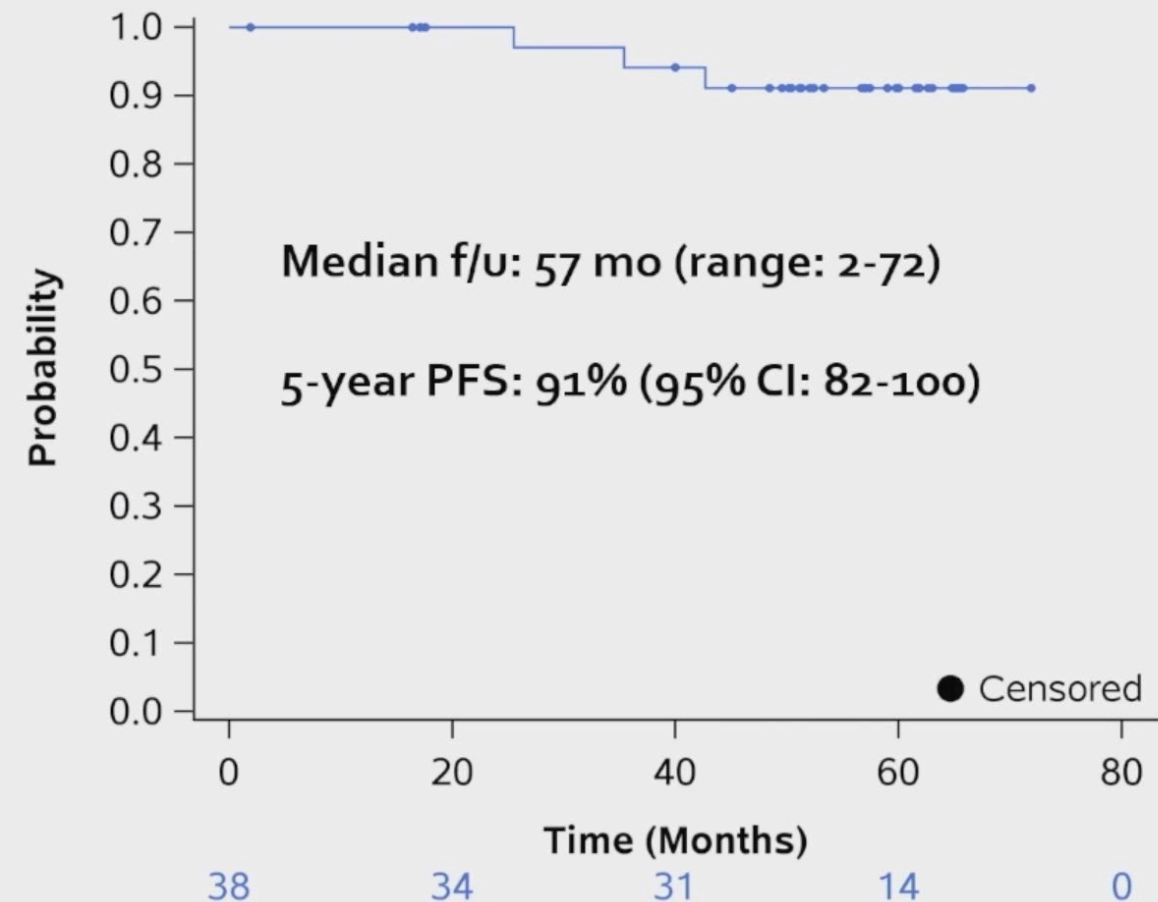
Overall survival mFU 24 months



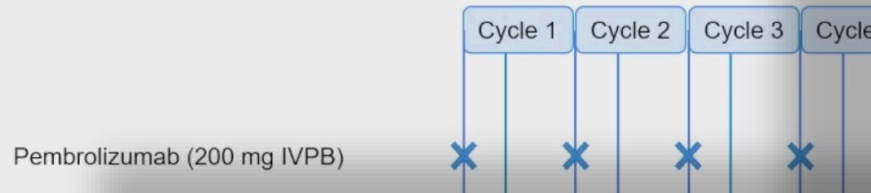
#569 Pembrolizumab Maintenance Instead of autoSCT for Patients with Relapsed or Refractory Hodgkin Lymphoma in Complete Response after Pembrolizumab, Gemcitabine, Vinorelbine, and Liposomal Doxorubicin



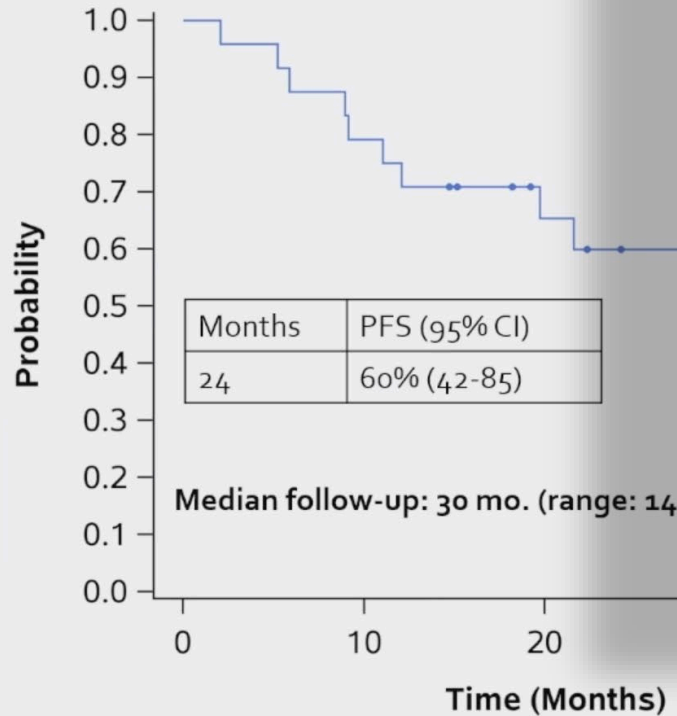
Progressions-freies Überleben



#569 Pembrolizumab Maintenance Instead of autoSCT

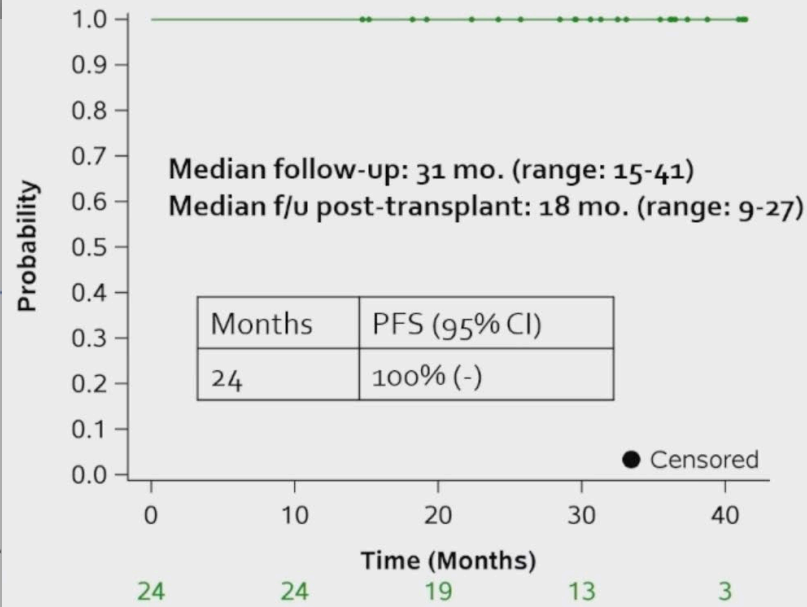


Pembrolizumab (200 mg IVPB)
Gemcitabine (1000 mg IV)
Vinorelbine (20 mg IV)
Liposomal Doxorubicin (30 mg IV)

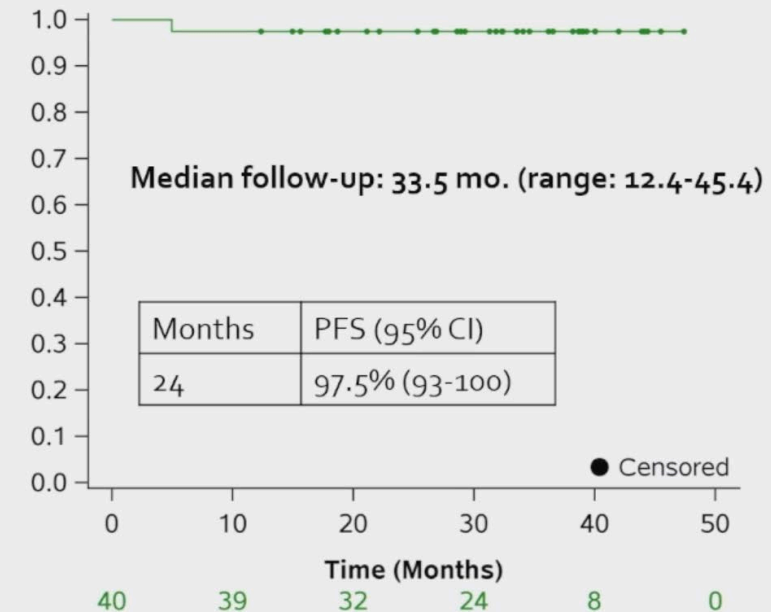


Freedom from third relapse

Patients who received pembro maintenance



All 40 patients enrolled



Chronische lymphatische Leukämie



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#1009 Fixed-Duration Acalabrutinib Plus Venetoclax with or without Obinutuzumab Versus Chemoimmunotherapy for First-Line Treatment of Chronic Lymphocytic Leukemia: Interim Analysis of the Multicenter, Open-Label, Randomized, Phase 3 AMPLIFY Trial

TN CLL (N=867)

Key inclusion criteria

- Age ≥ 18 years
- TN CLL requiring treatment per iwCLL 2018 criteria¹
- Without del(17p) or TP53^a
- ECOG PS ≤ 2

Key exclusion criteria

- CIRS-Geriatric >6
- Significant cardiovascular disease

Stratification

- Age (>65 vs ≤ 65 years)
- IGHV mutational status
- Rai stage (≥ 3 vs <3)
- Geographic region

NCT03836261. Data cutoff: April 30, 2024.
^aAssayed by central lab.

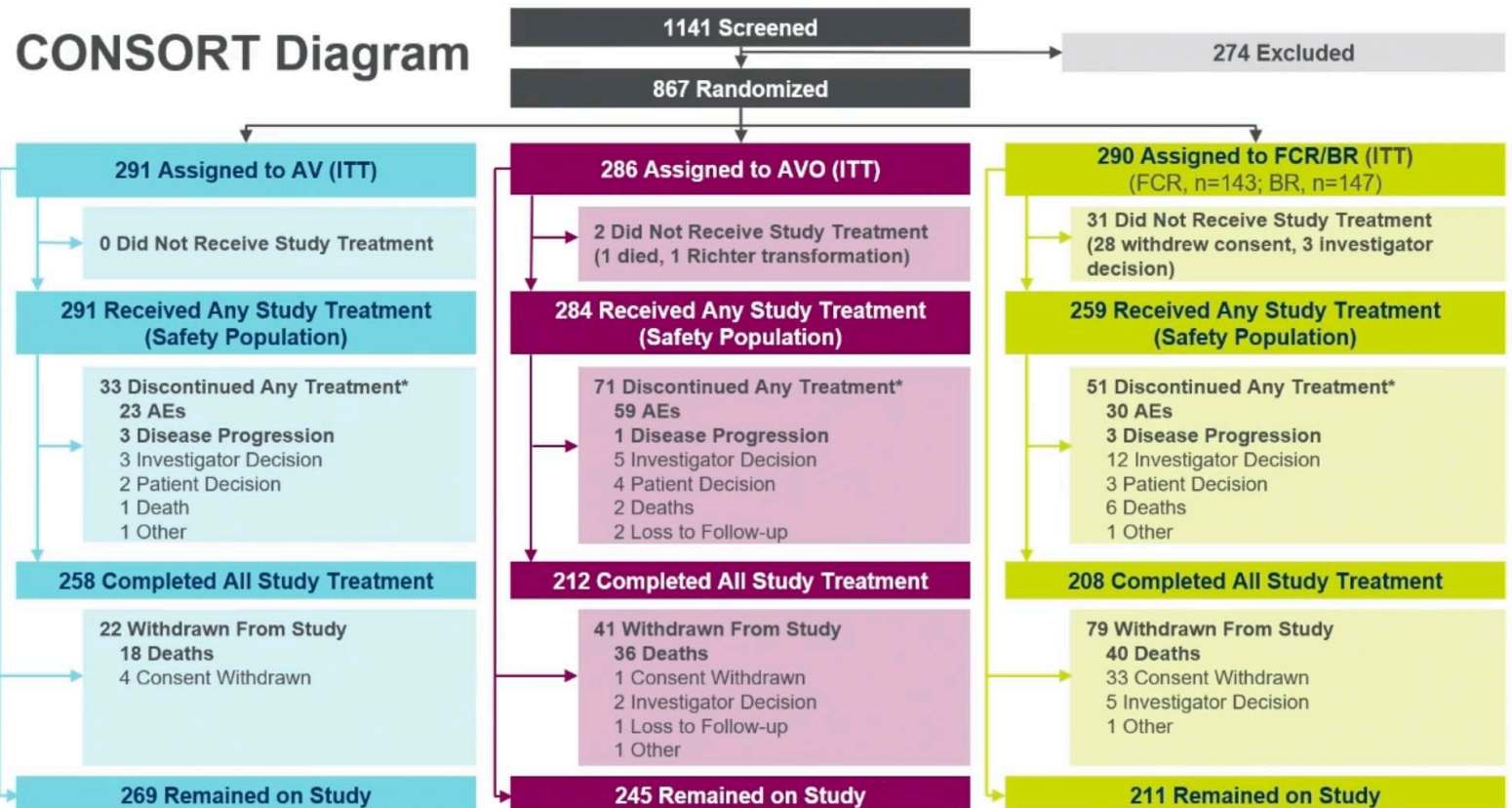
AMPLIFY: randomized, multicenter, open-label, Ph 3 trial

RANDOMIZE 1:1:1

AV and AVO dosing schedule

Cycles (28 day)

CONSORT Diagram



⁴ *A reason for discontinuation was reported for each drug discontinued, and subjects are counted a maximum of once per discontinuation reason and may be counted under multiple discontinuation reasons. AE, adverse event; AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; FCR, fludarabine-cyclophosphamide-rituximab; ITT, intent-to-treat.

#1009 AMPLIFY: AV vs AVO vs CIT

Acalabrutinib-Venetoclax ± Obinutuzumab vs FCR oder BR

Most Common AEs (Any Grade)

Preferred Term	AV (n=291)
Neutropenia	90 (30.9)
Diarrhea	95 (32.6)
Headache	102 (35.1)
Nausea	43 (14.8)
Infusion-related reaction	0
COVID-19	55 (18.9)
Pyrexia	17 (5.8)
Contusion	40 (13.7)
Neutrophil count decreased	18 (6.2)
Thrombocytopenia	13 (4.5)
COVID-19 pneumonia	21 (7.2)
Febrile neutropenia	5 (1.7)
Anemia	20 (6.9)

Events

Any ECI
Cardiac e
Atrial fib
Ventricu
Hypertens
Hemorrhage

Major hemorrhage

Neutropenia (any)^b

Infections (any)

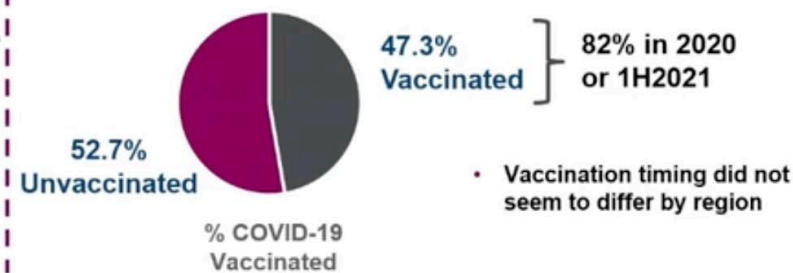
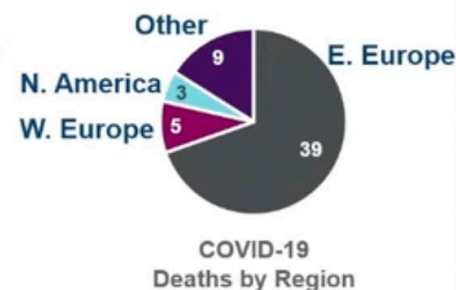
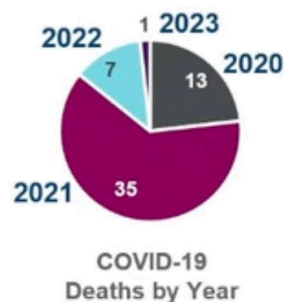
Second primary malignancies

Excl. non-melanoma skin

Tumor lysis syndrome

COVID-19 AEs, Treatment Discontinuations, and Deaths

	AV (n=291)	AVO (n=284)	FCR/BR (n=259)
Any confirmed/suspected COVID-19 AE	64 (22.0)	69 (24.3)	10 (3.9)
Any confirmed/suspected COVID-19 AE leading to discontinuation of any treatment	7 (2.4)	23 (8.1)	3 (1.2)
Deaths due to COVID-19*	10 (3.4)	25 (8.7)	21 (7.2)

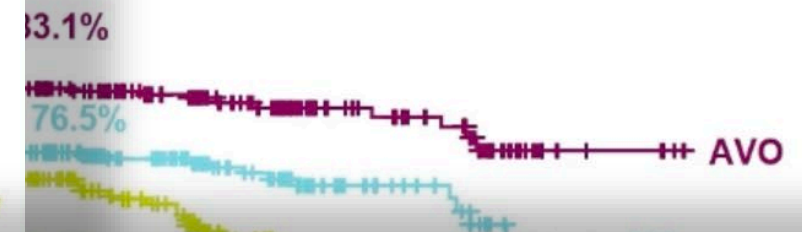
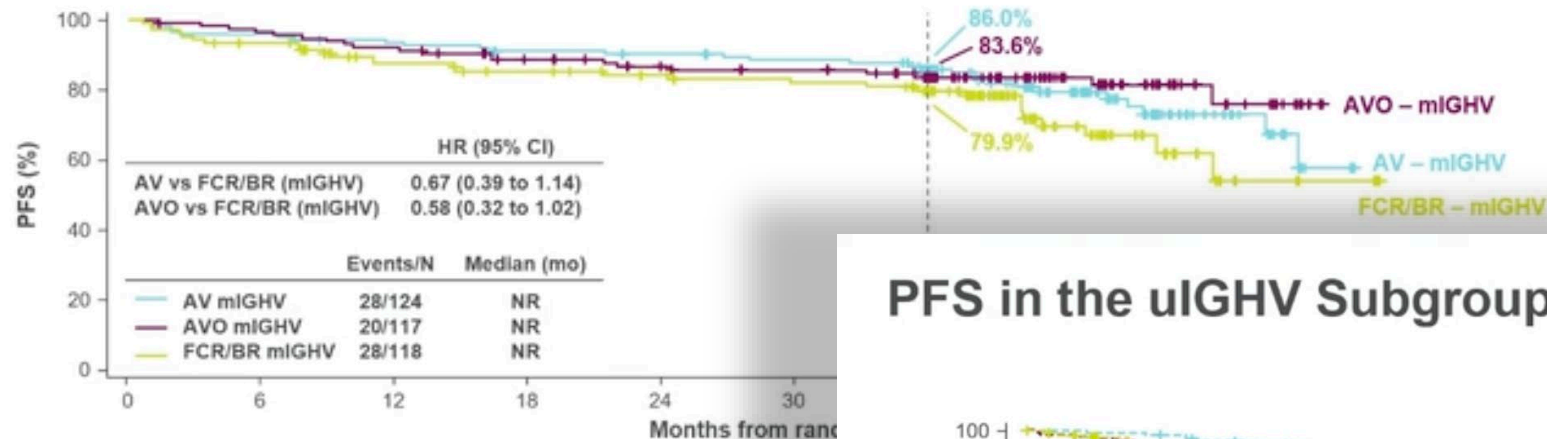


Major hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia (any) ^b	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infections (any)	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Second primary malignancies	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
Excl. non-melanoma skin	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

#1009 AMPLIFY: AV vs AVO vs CIT Erstline CLL

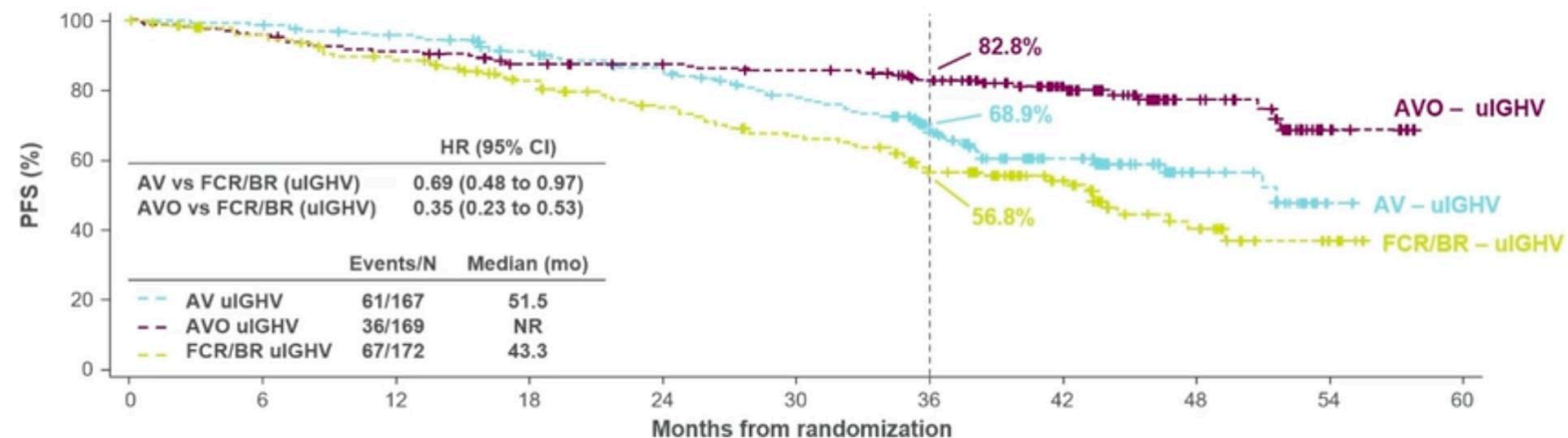
Acalabrutinib-Venetoclax $\pm$ Obinutuzumab vs FCR oder BR

PFS in the mIGHV Subgroup



Patients at risk						
AV mIGHV	124	119	114	110	108	105
AVO mIGHV	117	111	106	96	89	86
FCR/BR mIGHV	118	99	86	81	76	72

PFS in the uIGHV Subgroup

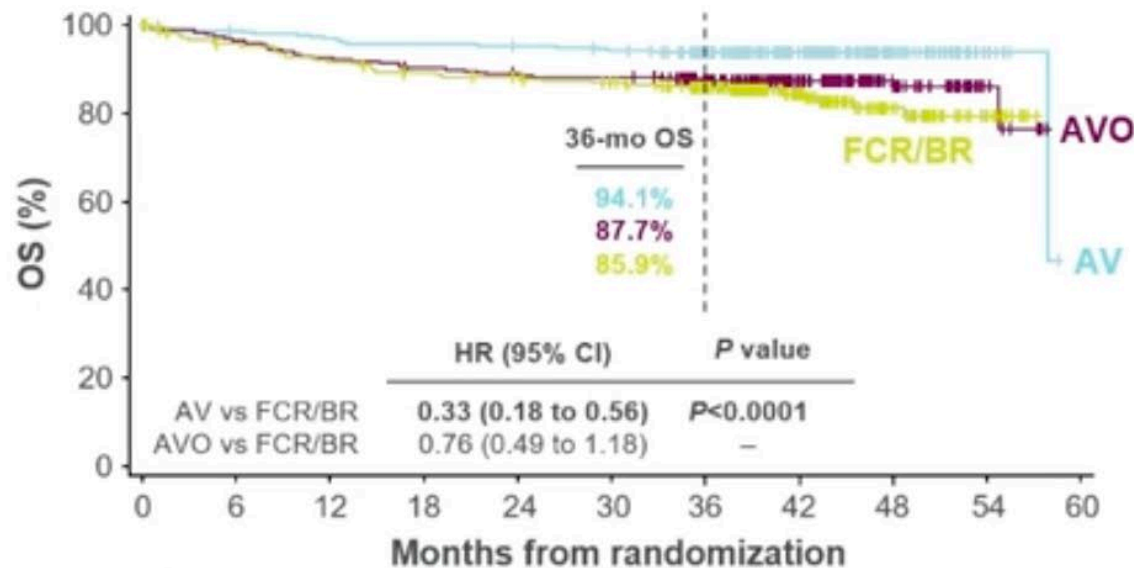


Patients at risk											
AV uIGHV	167	163	155	141	129	114	86	48	17	1	0
AVO uIGHV	169	161	152	141	136	133	118	75	36	7	0
FCR/BR uIGHV	172	137	122	108	94	82	62	38	19	4	0

#1009 AMPLIFY: AV vs AVO vs CIT Erstline CLL

Acalabrutinib-Venetoclax $\pm$ Obinutuzumab vs FCR oder BR

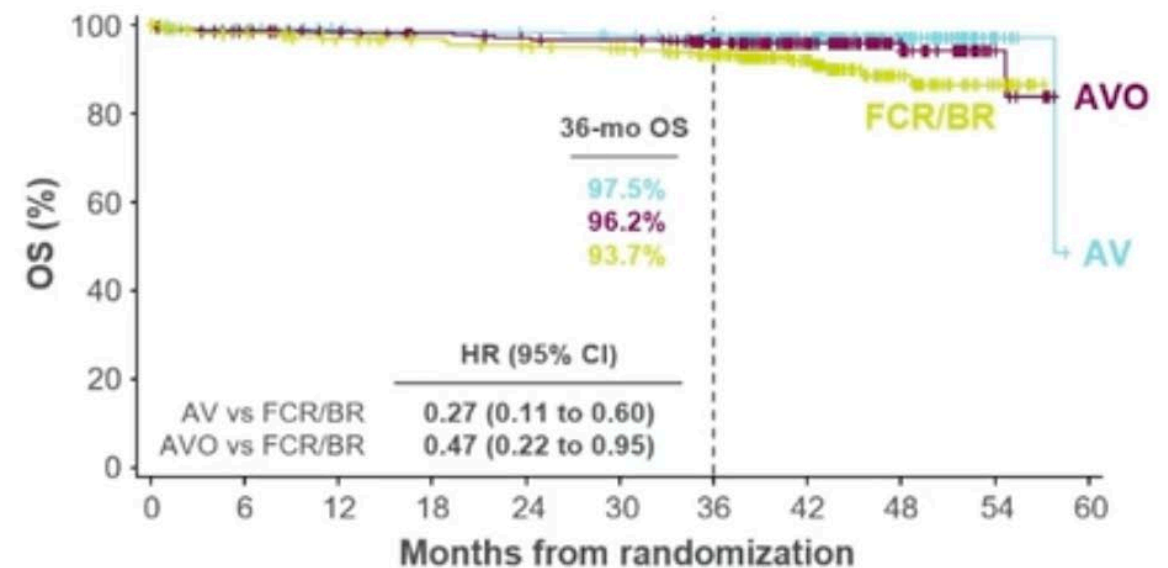
OS Prolonged
With AV vs FCR/BR



Patients at risk

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

OS Prolonged With AV and AVO vs FCR/BR
(COVID-19 Deaths Censored)



Patients at risk

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)



#883 Epcoritamab Monotherapy in Patients (Pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): Results from CLL Expansion and Optimization Cohorts of Epcore CLL-1

Epcoritamab in R/R CLL

Study Design: EPCORE® CLL-1 Expansion and C1 Optimization

Key inclusion criteria

- CD20+ R/R CLL
- ≥2 prior lines of systemic therapy
- ECOG PS 0–2
- Measurable disease with ≥5×10⁹/L B lymphocytes (expansion only)
- No prior allogeneic HSCT

CRS prophylaxis

- Prednisone

Step-up dose 1 (C1D1): 0.16 mg

Step-up dose 2 (C1D8): 0.8 mg

Data cutoff: May 28, 2024

Median follow-up: 22.8 months

• **Primary endpoint (EXP):** Overall response rate

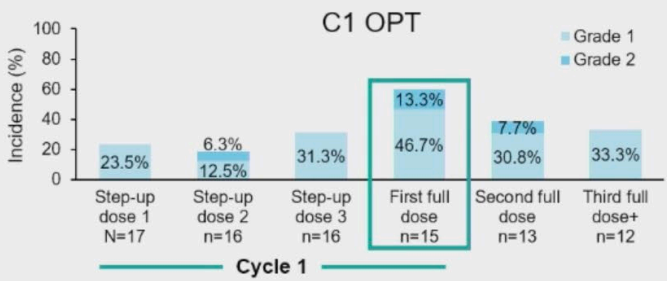
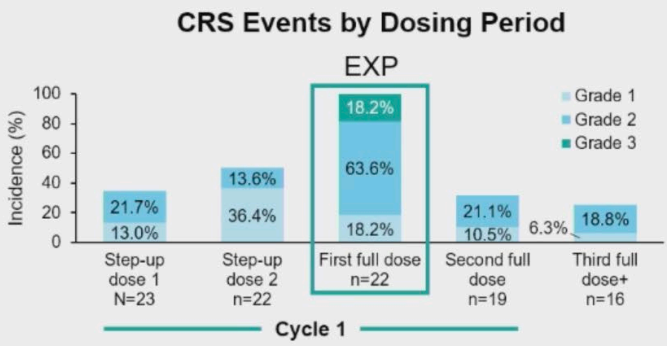
• **Primary endpoint (C1 OPT):** Incidence and severity of CRS, ICANS, and clinical TLS

• **Key secondary endpoints (EXP):** CR rate, time to response, MRD (PBMCs using the clonoSEQ® assay), and safety/tolerability

ClinicalTrials.gov: NCT04623541; EudraCT: 2023-504828-25.

C1 OPT Mitigated Adverse Events of Interest Including ICANS and Clinical TLS

	EXP N=23	C1 OPT N=17
CRS, n (%)	22 (96)	14 (82)
Grade 1	2 (9)	12 (71)
Grade 2	16 (70)	2 (12)
Grade 3	4 (17)	0
Treated with tocilizumab, n (%)	20 (87)	6 (35)
Leading to treatment discontinuation, n (%)	0	0
CRS resolution, n/n (%)	22/22 (100)	14/14 (100)
Median time to resolution, days (range)	3 (1–16)	3.5 (1–7)
ICANS, n (%)	3 (13)	0
Grade 1	1 (4)	0
Grade 2	2 (9)	0
Clinical TLS, n (%)	1 (4)	0
Grade 2	1 (4)	0



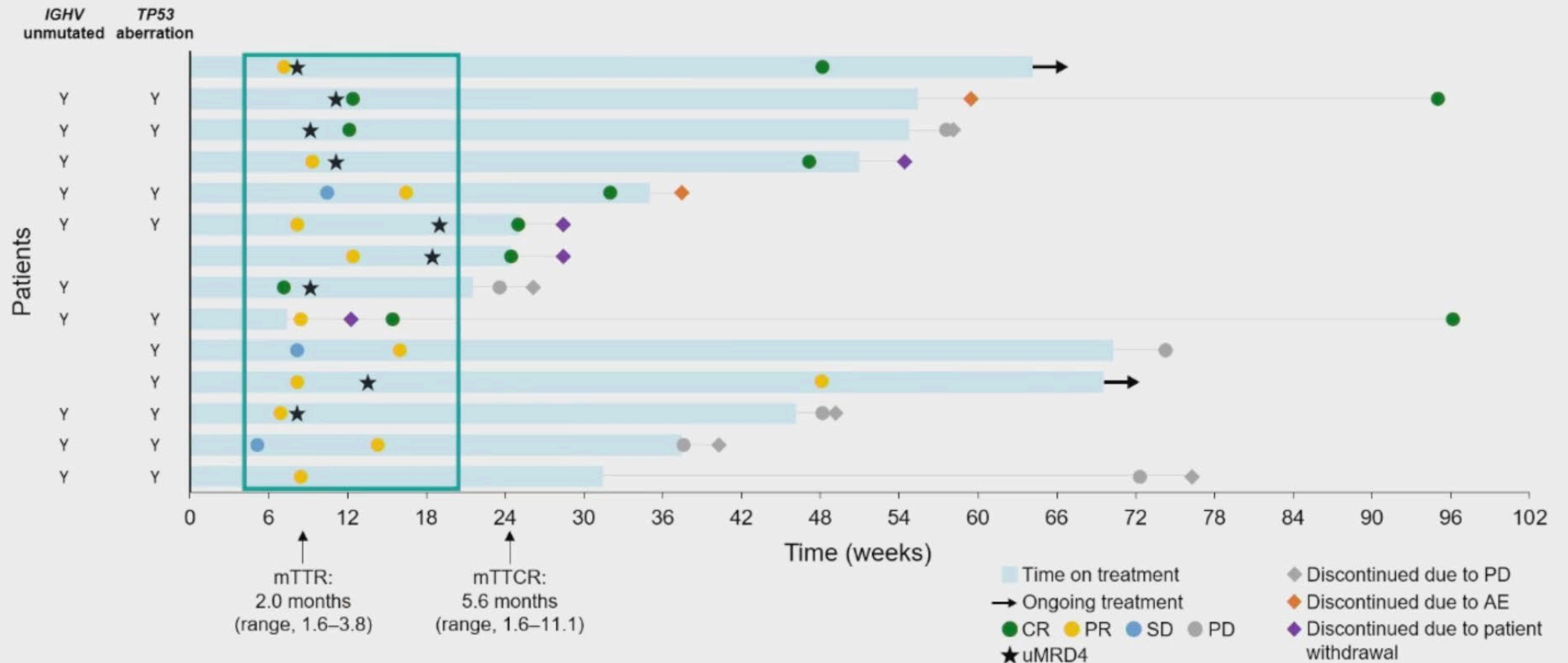
#883 Epcoritamab Monotherapie bei in R/R CLL

Response, n (%)	EXP mFU: 22.8 months					C1 OPT mFU: 2.9 months
	Full Analysis Set	Response Evaluable	TP53 Aberration	IGHV Unmutated	Double Exposed ^a	Response Evaluable

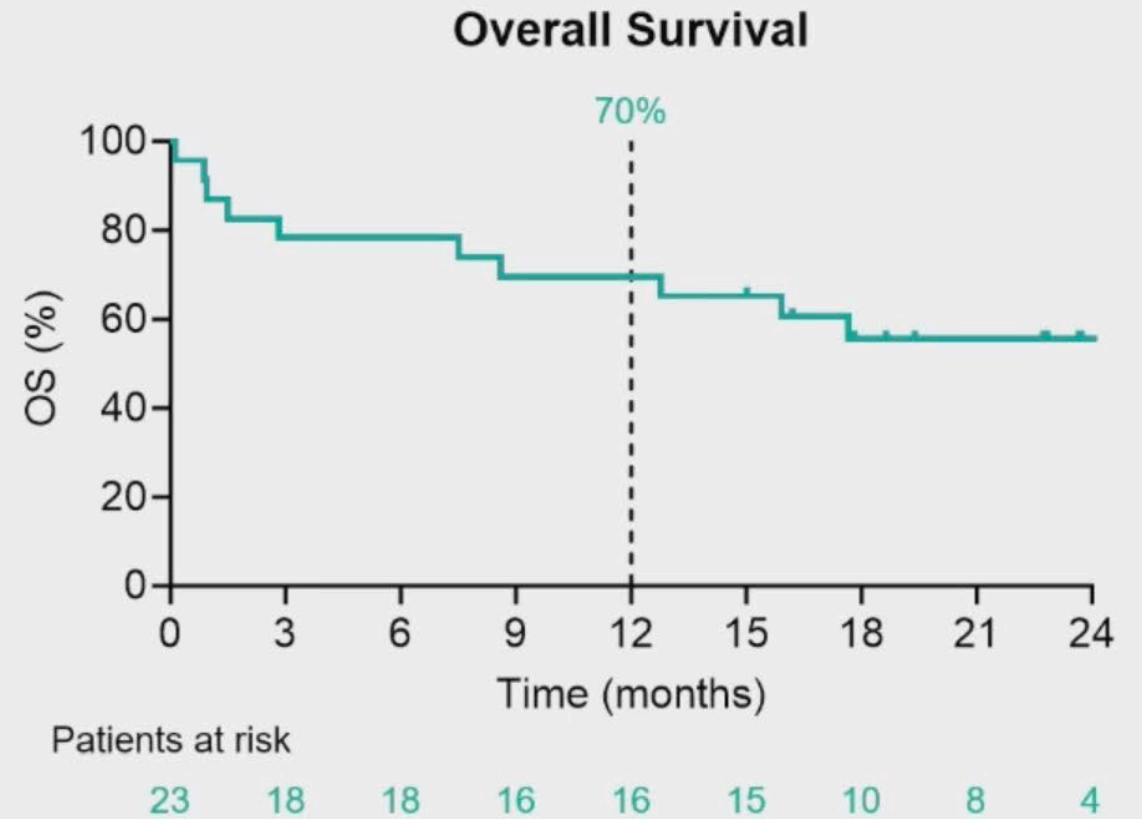
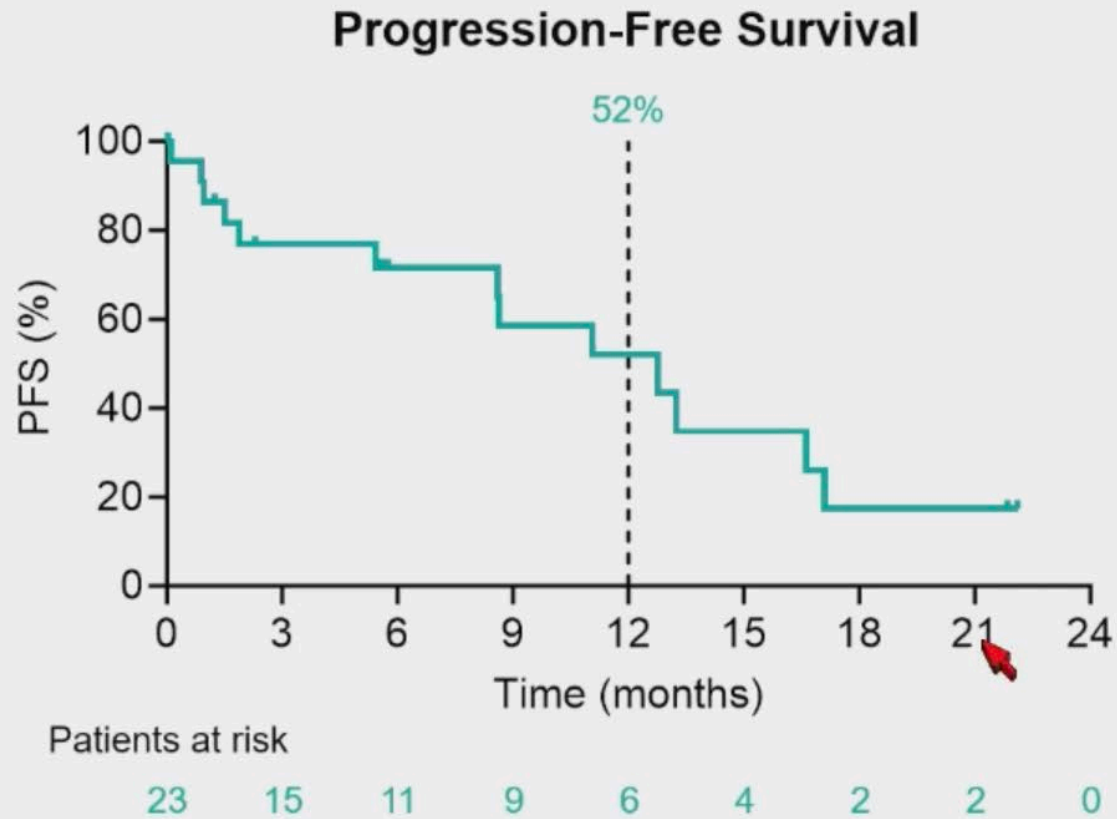
Overall response^b

Complete response
Partial response
Stable disease
Progressive disease

- With limited follow-up, it does not appear to affect overall survival
- uMRD4 in PBM responders, including those who were tested for uMRD4



#883 Epcoritamab Monotherapie bei R/R CLL



- Median PFS was 12.8 months (95% CI, 5.4–17.1); median OS was not reached (95% CI, 8.6 months–NR)

Mantelzell-Lymphom



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#235 Ibrutinib-Rituximab Is Superior to Rituximab-Chemotherapy in Previously Untreated Older Mantle Cell Lymphoma Patients: Results from the International Randomised Controlled Trial, Enrich

Trial design

Inclusion criteria

- 60 years or older
- Pathologically confirmed MCL, including either cyclin D1 overexpression or t(11;14)(q13;q32)
- Previously untreated, measurable (>1.5cm), stage II-IV MCL in need of treatment
- ECOG 0-2

Exclusion criteria

- Considered fit for stem cell transplantation
- CNS involvement
- Known serological positivity for HBC/HCV/HIV

Rituximab 375mg/m²

Ibrutinib - 560mg od

Bendamustine 90mg/m² D1+D2 of 28 day cycle

CHOP - (Cyclophosphamide 750mg/m², Doxorubicin 50mg/m², Vincristine 1.4mg/m², Prednisolone 100mg *5 days) 21 day cycle

Maintenance rituximab - 1400mg sc every 56 days

ENRICH

Choice of
immunochemotherapy (R-
Chemo)

Bendam

R-Chemo
da

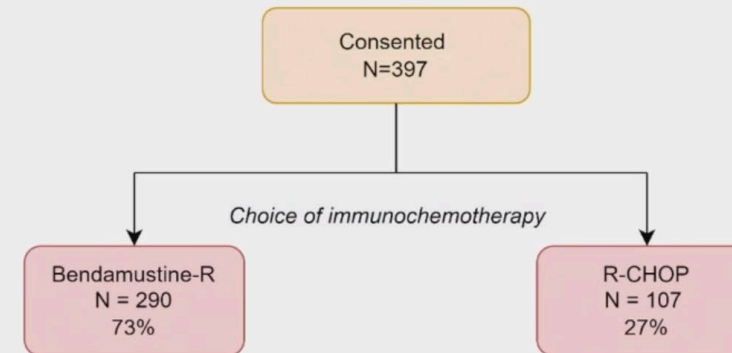
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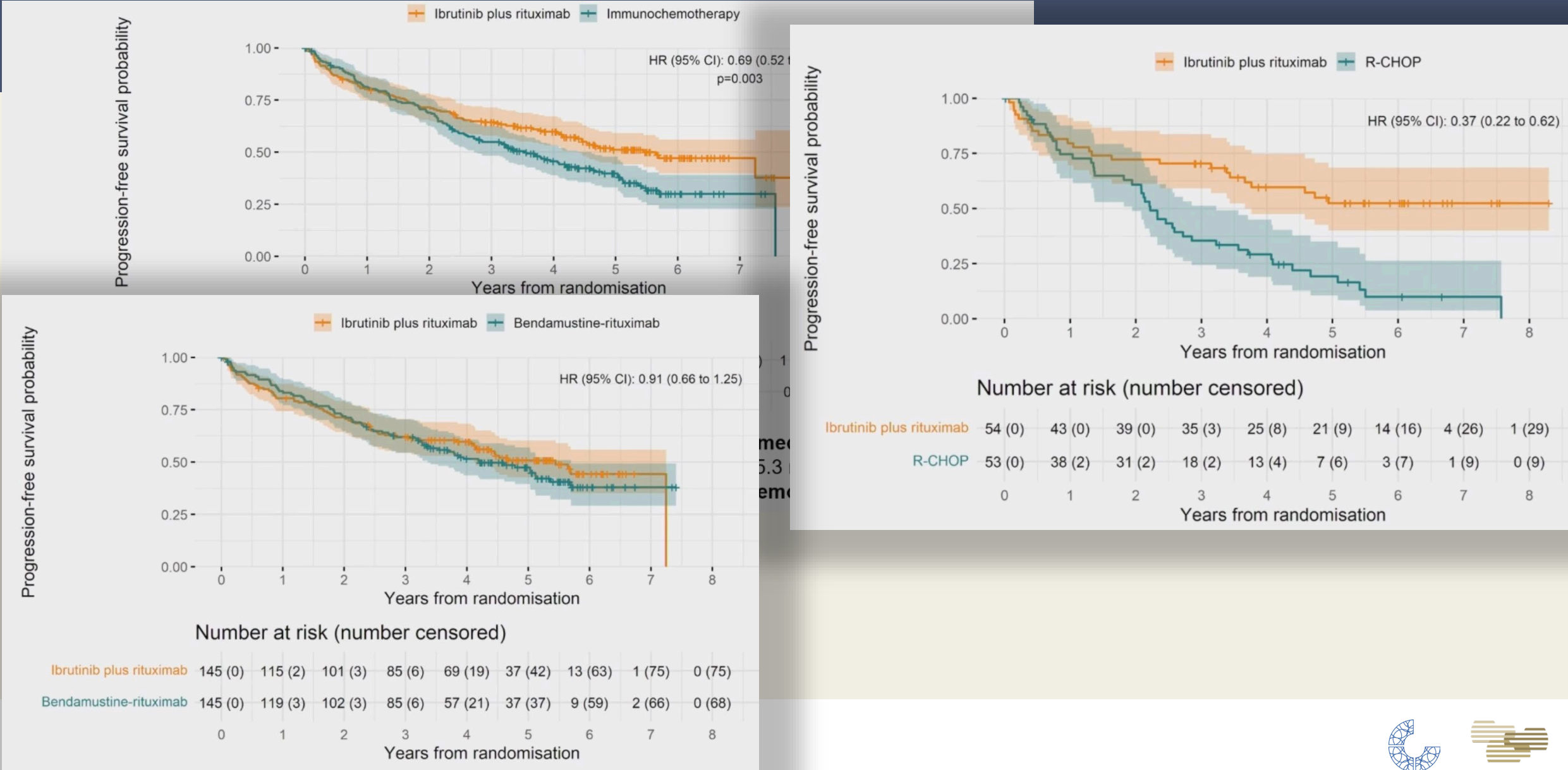
Patients

ENRICH

- Recruitment open December 2015 - June 2021
- Patients from 66 sites in UK, Sweden, Norway, Finland and Denmark



#235 ENRICH: Erstlinie MCL, Ibrutinib+Rituximab vs CIT

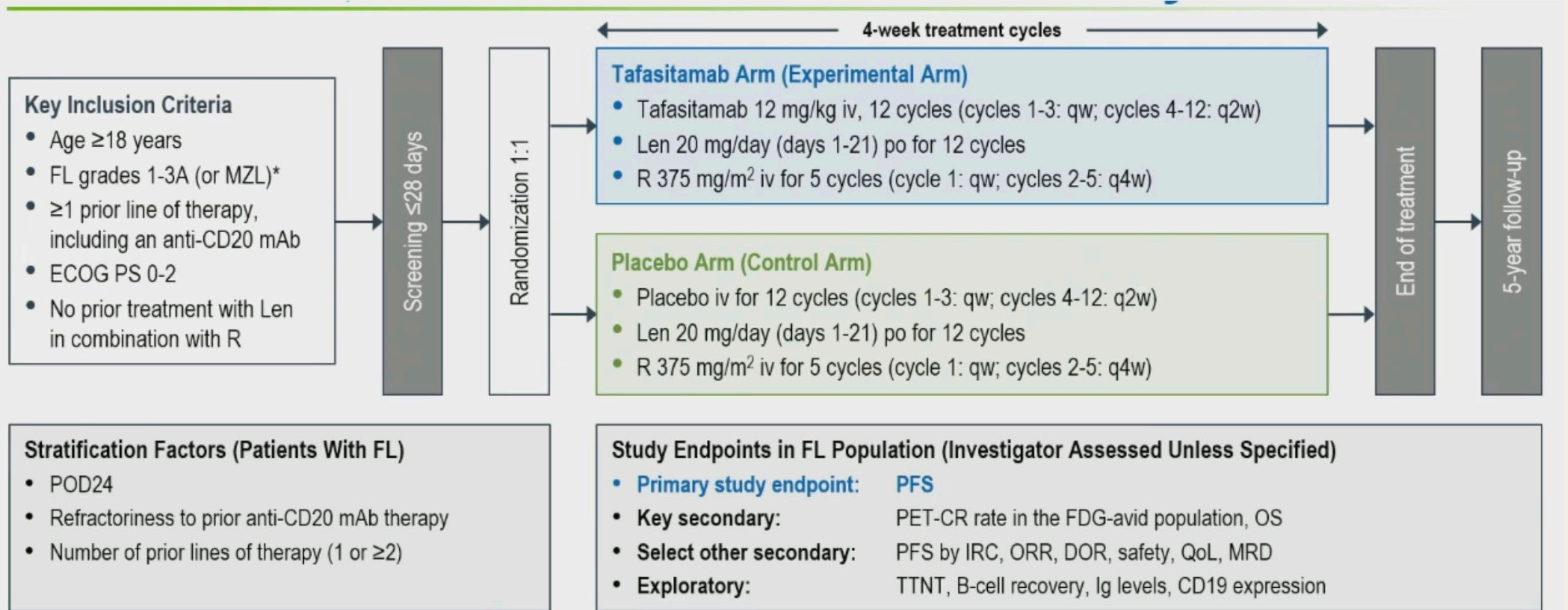


Folikuläres Lymphom



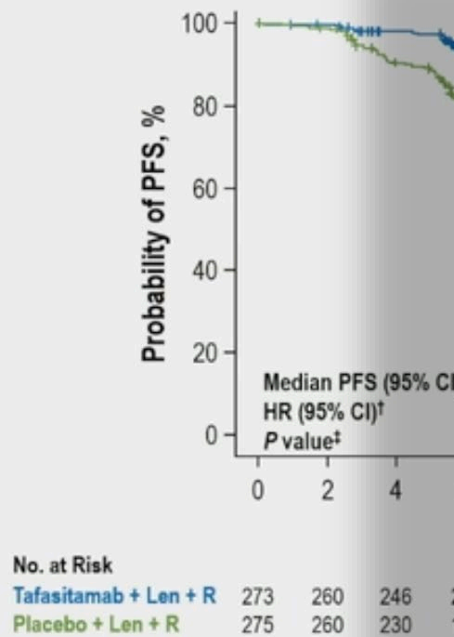
**Universitätsklinikum
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LBA-1 Tafasitamab Plus Lenalidomide and Rituximab for Relapsed or Refractory Follicular Lymphoma: Results from a Phase 3 Study (inMIND)

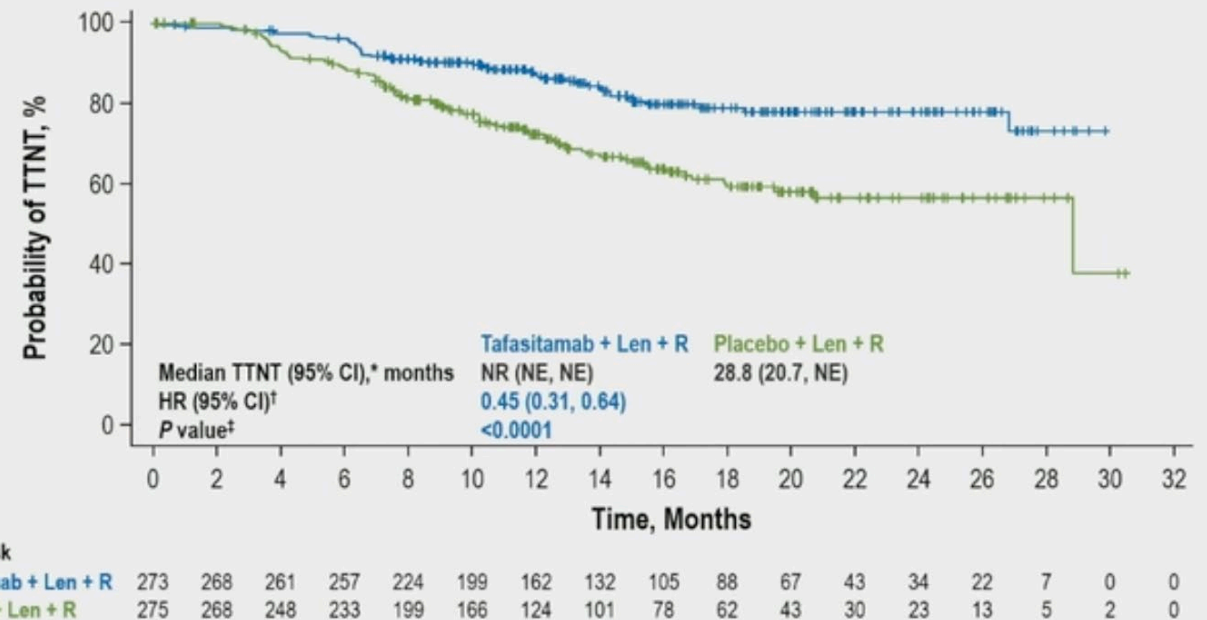


R² ± Tafasitamab bei R/R follikulärem Lymphom

PFS by Independent Review Committee



Time to Next Treatment



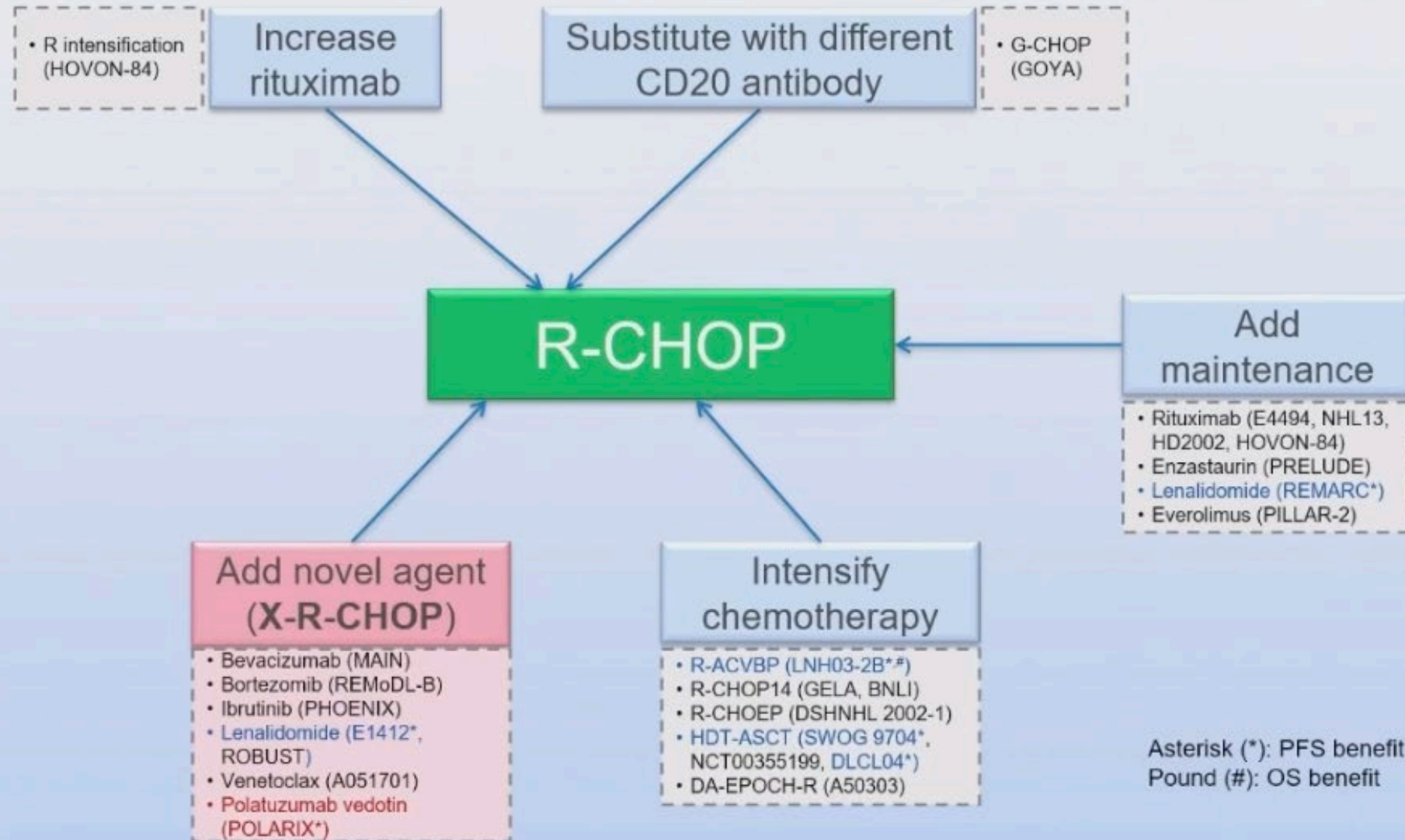
Large B cell lymphoma – LBCL

- DLBCL



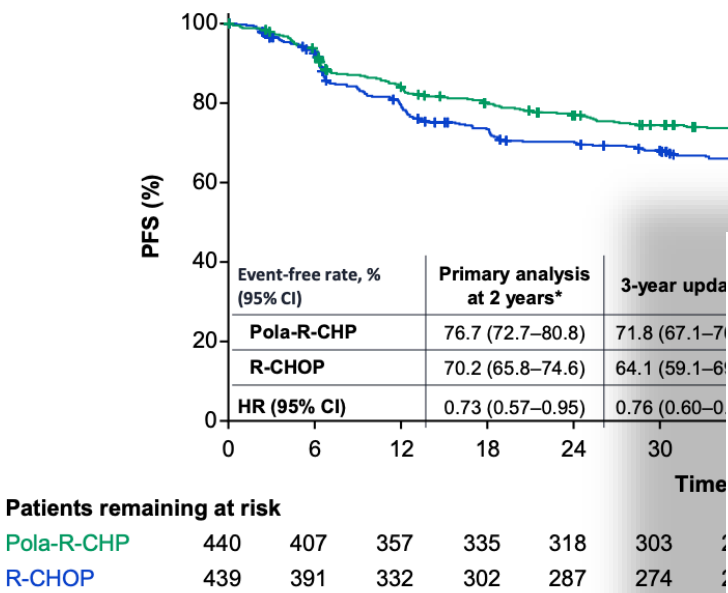
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R-CHOP + X

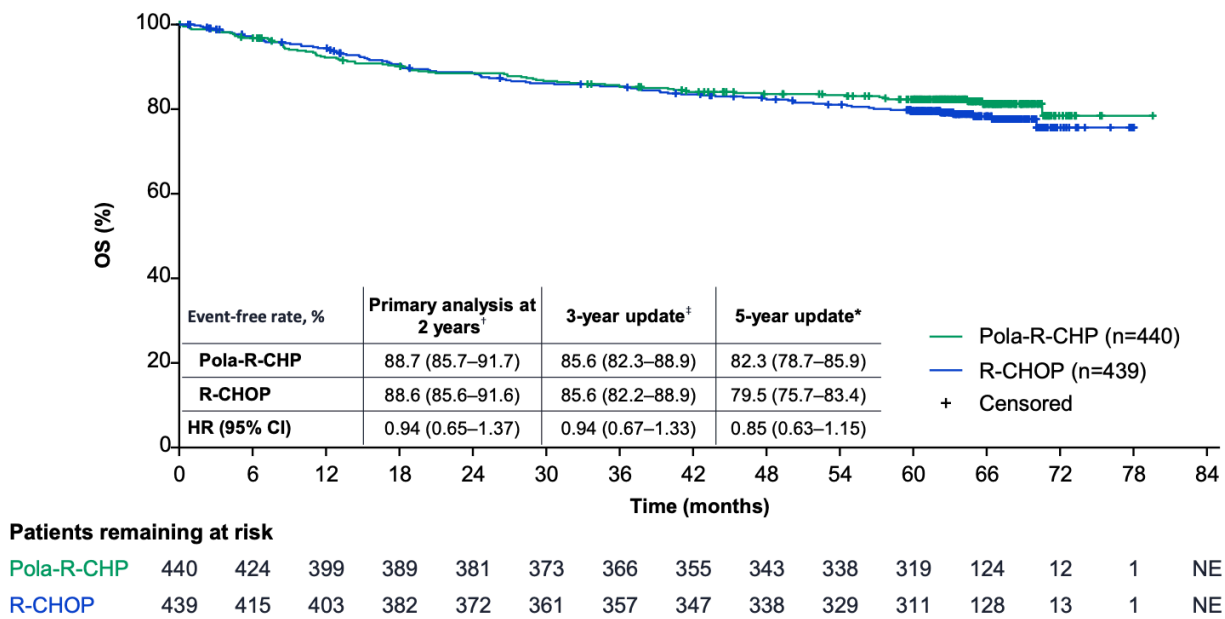


#469 Five-year analysis of the POLARIX study: Prolonged follow-up confirms positive impact of polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) on outcomes

PFS in the global ITT population



OS in the global population*



Deaths, n§	Pola-R-CHP (n=440)	R-CHOP (n=439)
Primary analysis at 2 years†	53	57
5-year update*	79	91



#582 A Randomized Phase 2, IIT of Glofitamab-R-CHOP or Glofitamab-Pola-R-CHP (COALITION) in ...High-Risk LBCL Demonstrates Safety, Uncompromised Chemotherapy Intensity, a High Rate of Durable Remissions, and Unique FDG-PET Response Characteristics

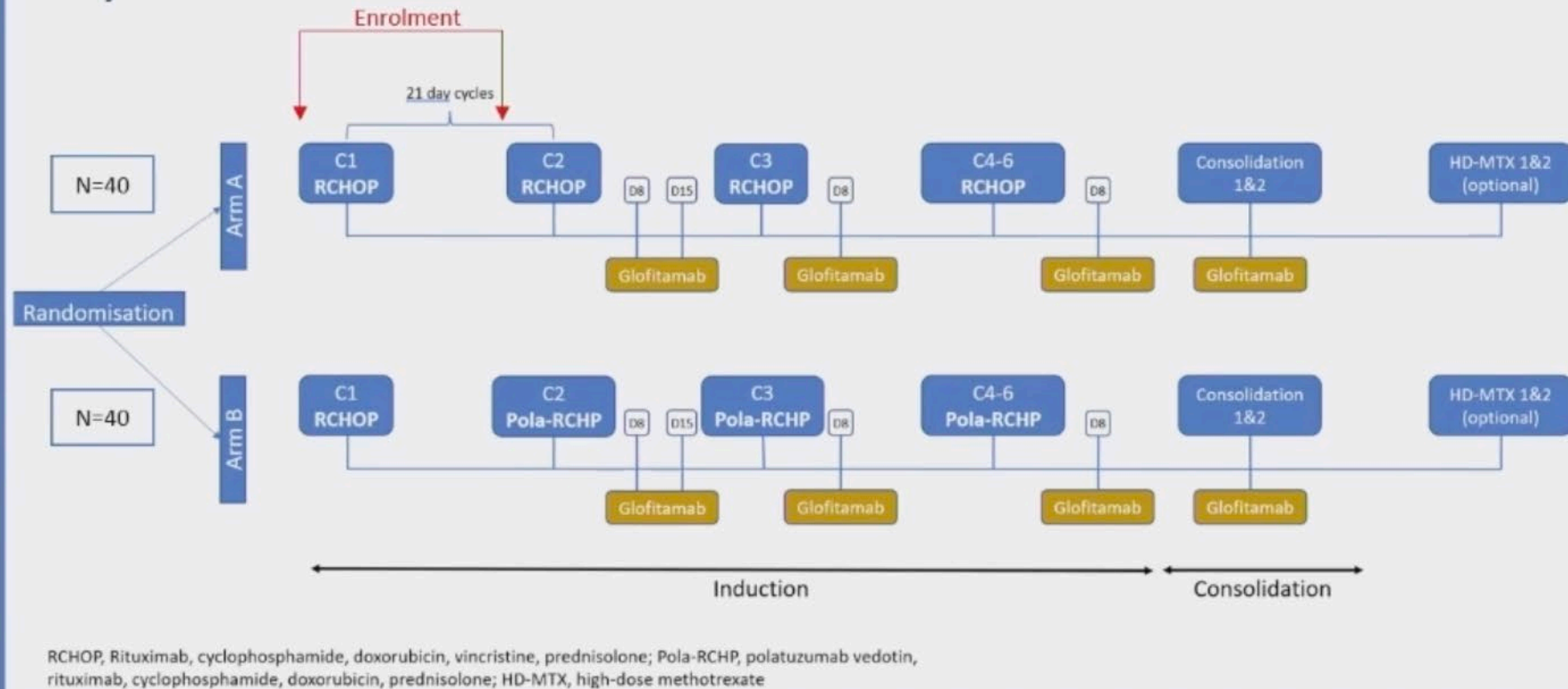
Key inclusion criteria:

- Newly diagnosed DLBCL or HGBL
- Age 18-65
- At least one H-R feature
 - IPI ≥ 3
 - NCCN-IPI ≥ 4
 - *MYC* and *BCL2* and/or *BCL6* rearrangements
- ECOG 0-3 prior to cycle 1 or 0-1 prior to cycle 2

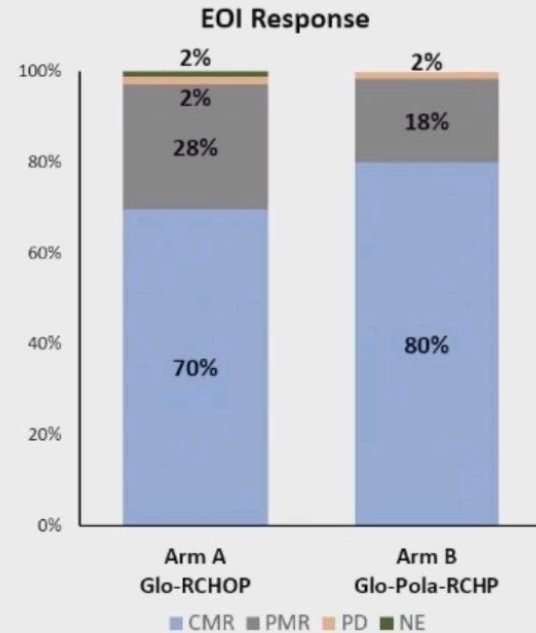
Key exclusion criteria:

- CNS involvement
- Prior treatment of indolent lymphoma

Study Schema:



#582 Phase II Glofitamab-R-CHOP or Glofitamab-Pola-R-CHP (COALITION)

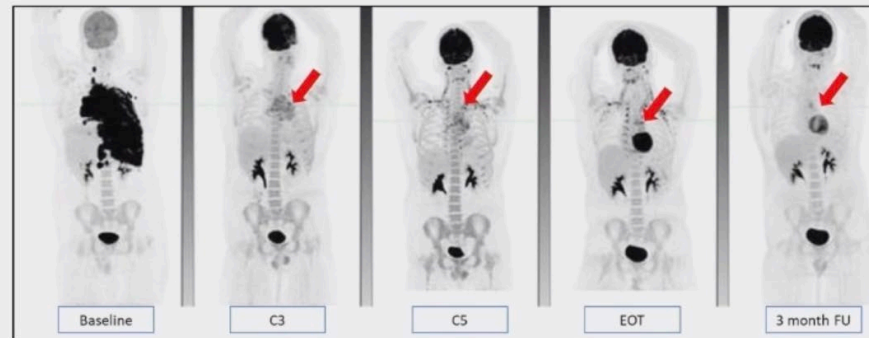


The rate of CR at EOI was 75% overall



All patients

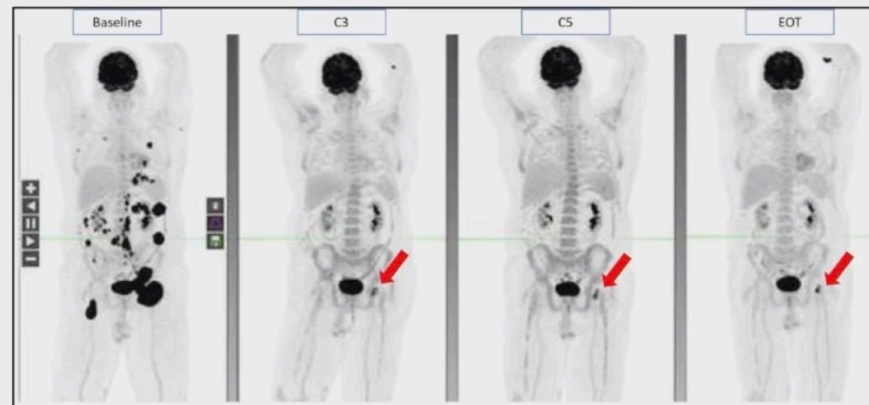
Responses: PRs may represent inflammatory response



Eventual resolution of FDG avidity

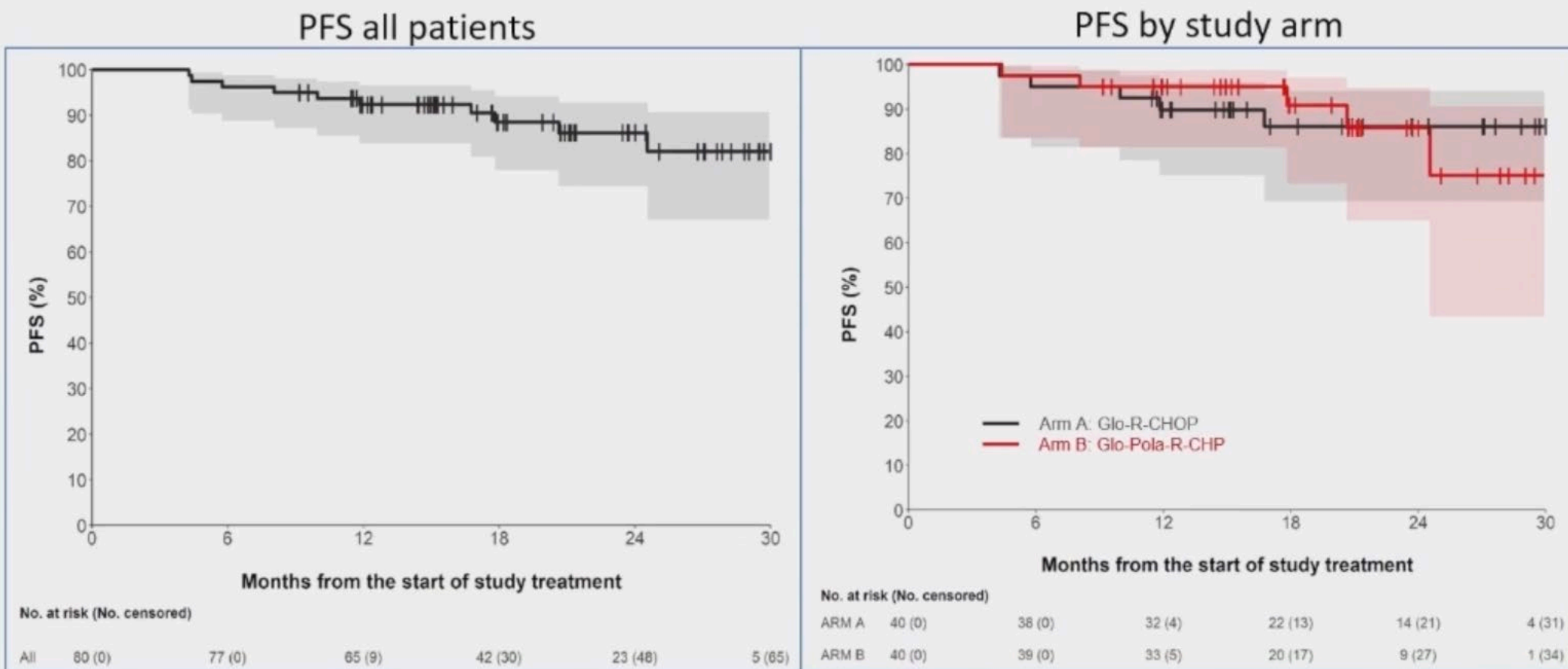
Pattern of gradual resolution at sites of bulk

Where biopsies performed, they have demonstrated inflammatory reactions (3/18)



Biopsy demonstrated histiocytic inflammatory reaction

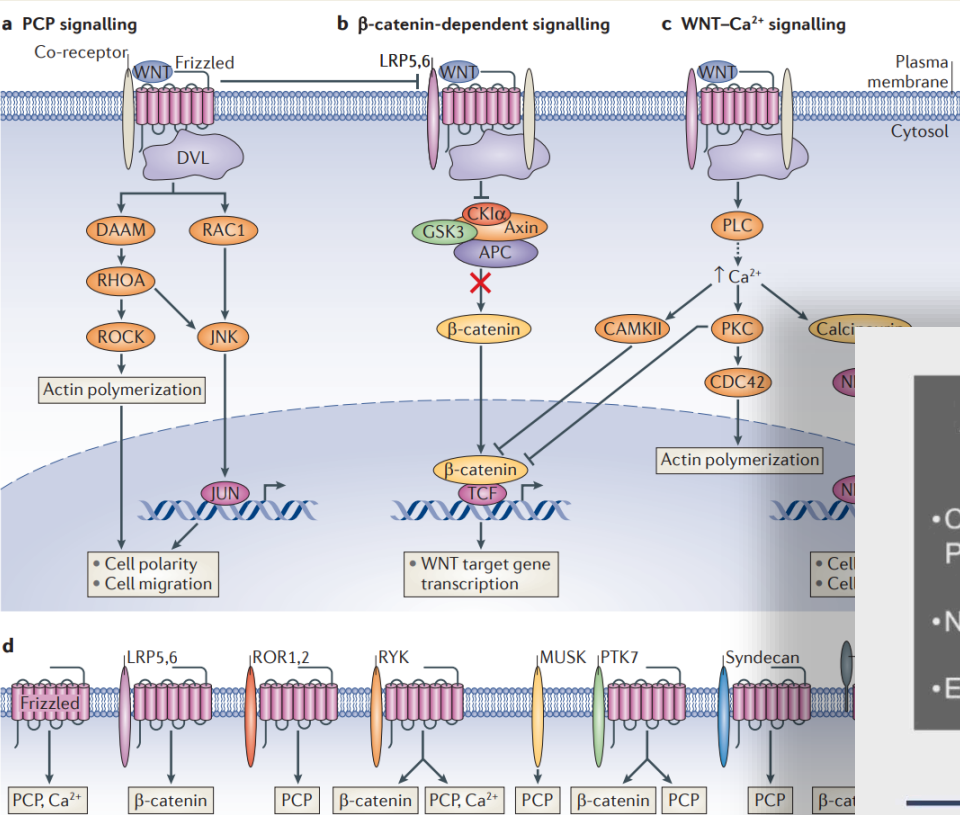
#582 Phase II Glofitamab-R-CHOP or Glofitamab-Pola-R-CHP (COALITION)



PFS estimate	Arm A Glo-R-CHOP (n=40)	Arm B Glo-Pola-R-CHP (n=40)	All patients (n=80)
12-month PFS, % (95% CI)	90% (75%-96%)	95% (81%-99%)	92% (84%-97%)
24-month PFS, % (95% CI)	86% (69%-94%)	86% (65%-95%)	86% (75%-93%)

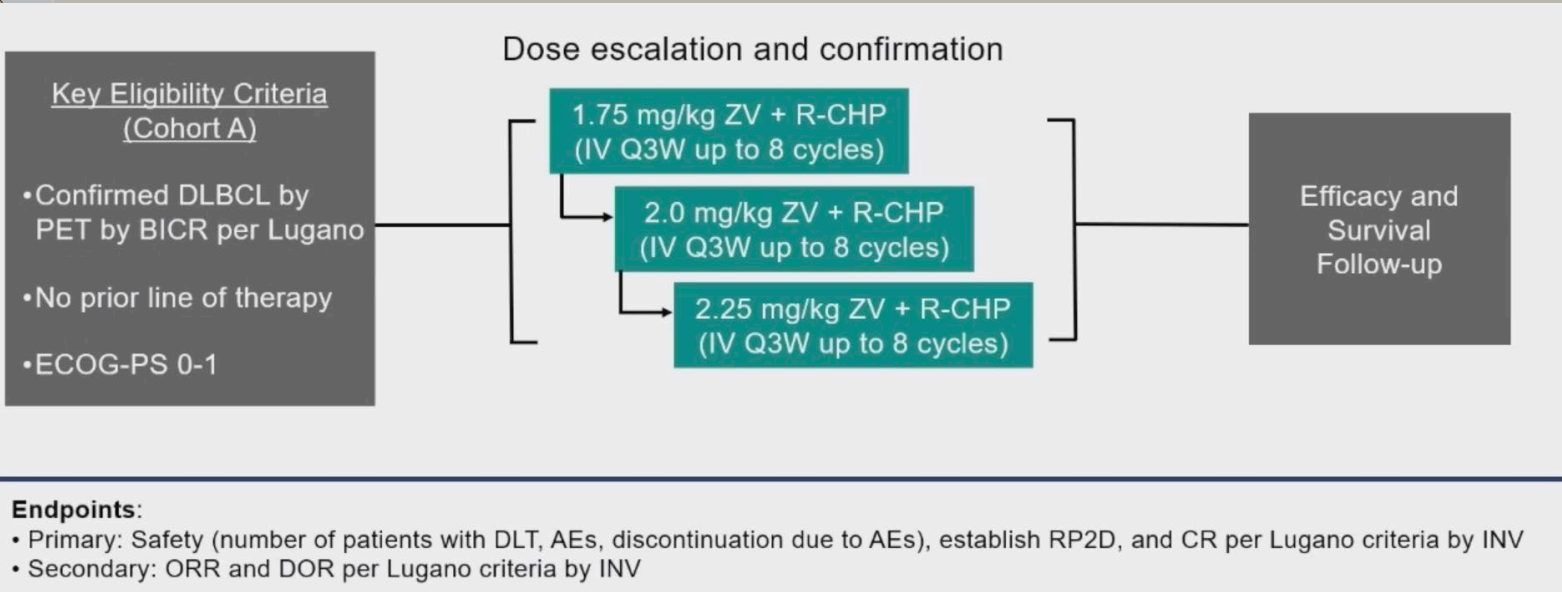


#578 Waveline-007: Dose Escalation and Confirmation, and Efficacy Expansion Trial of Zilovertamab Vedotin in Combination with R-CHP in Patients with Diffuse Large B Cell Lymphoma



Wang et al., NEJM 2022

- Phase I, Monotherapie
- R/R B-NHL
 - MCL and DLBCL vielversprechend



Zilovertamab-Vedotin, anti-ROR1-ADC

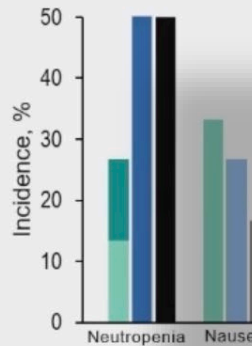


#578 Waveline-007: Zilovertamab-Vedotin-R-CHP

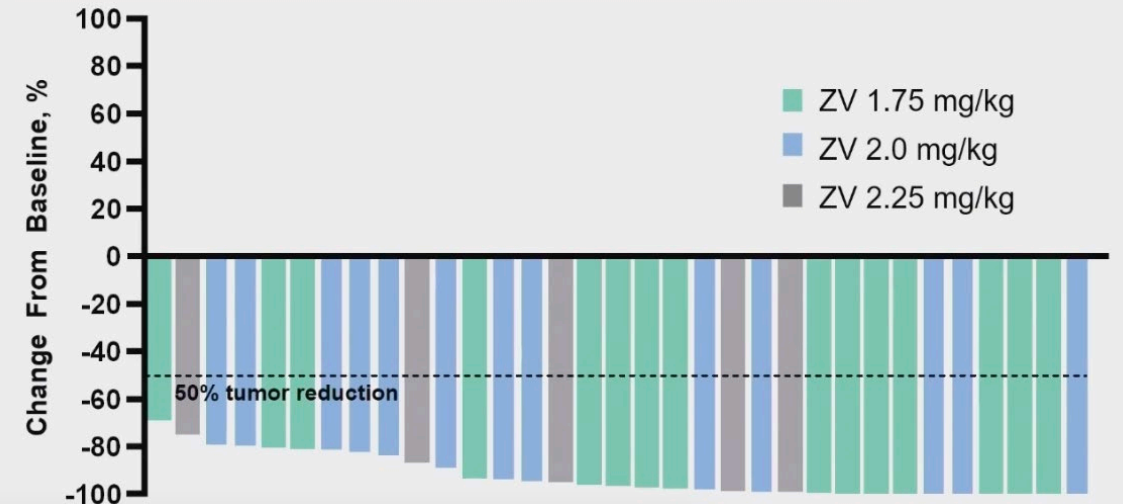
Summary of Adverse Events

Adverse events, n (%)	zilovertamab vedotin +		
	ZV 1.75 mg/kg N = 15	ZV 2.0 mg/kg N = 15	ZV 2.25 mg/kg N = 6
All cause	15 (100)	15 (100)	6 (100)
Drug-related adverse events	15 (100)	15 (100)	6 (100)
Serious	1 (7)	1 (7)	2 (33)
Grade 3-4	5 (33)	11 (73)	5 (83)
Drug-discontinued ^a	0	1 (7)	0
Death	0	0	0

Treatment-Related Adverse Events With Incidence



Best Percentage Change From Baseline in Target Lesion Size

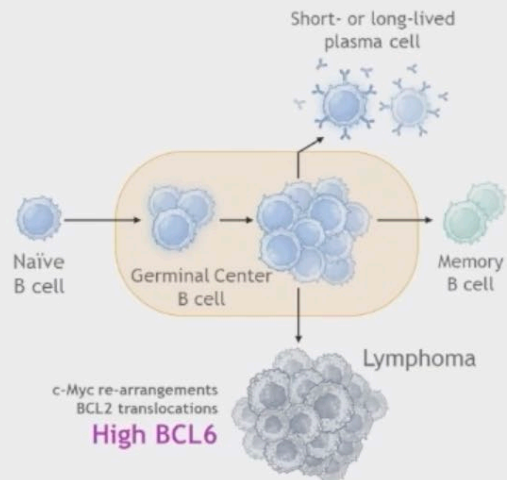


Best Response and Duration of Response

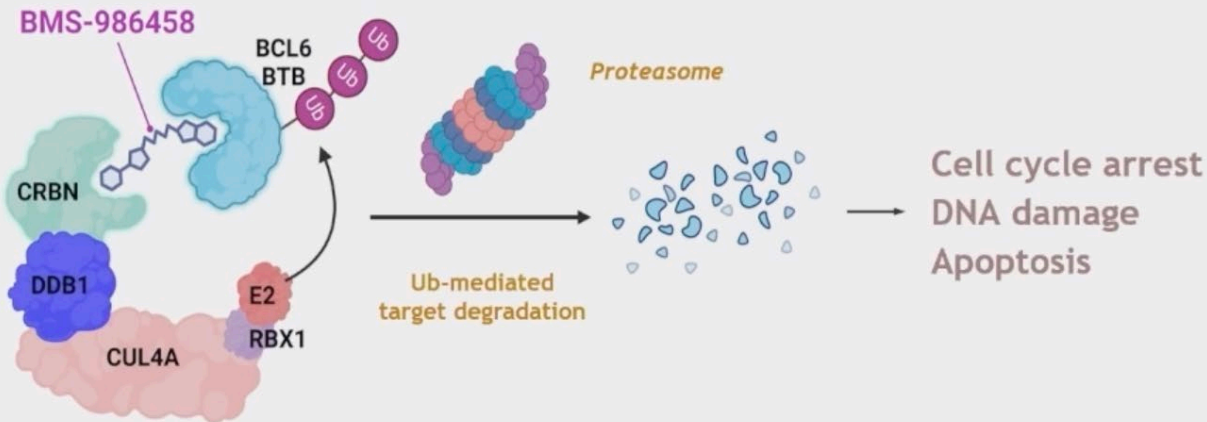
	zilovertamab vedotin + R-CHP			
	ZV 1.75 mg/kg N = 15	ZV 2.0 mg/kg N = 15	ZV 2.25 mg/kg N = 6	Total N = 36
Objective Response ^a , % (95% CI)	15 100% (78.2-100.0)	14 ^b 93.3% (68.1-99.8)	6 100% (54.1-100.0)	35 97.2% (85.5-99.9)
Partial response	0	0	0	0
Complete response	15 (100%)	14 (93.3%)	6 (100%)	35 (97.2%)
Median DOR (range), months	NR (2.4+-20.2+)	NR (1.3+-19.7+)	NR (13.8-16.9+)	NR (1.3+-20.2+)
12-month DOR rate	91.7%	92.3%	100%	93.5%

#957 BMS-986458 a Potential First-in-Class, Highly Selective, Potent and Well Tolerated BCL6 Ligand Directed Degradar (LDD) Demonstrates Multi-Modal Anti-Tumor Efficacy for the Treatment of B-Cell Non-Hodgkin's Lymphoma

Using ligand directed degraders (LDDs) to target the “undruggable”



- BCL6 is a transcriptional repressor required for tolerance of Ig hypermutation and normal B-cell maturation¹
- Along with BCL2 and c-Myc, BCL6 is one of the most frequent genetically misregulated proteins in DLBCL (~20%)¹
- As a sequence-specific transcription factor, BCL6 was once considered “undruggable”²



PROTACs

BTK-degrader

- #884 NX-5948 BTKi-degrader
Phase 1b expansion
- #885 BGB-16673 BTK-degrader,
CaDAnCe-101



#957 BMS-986458, BCL6-degrader

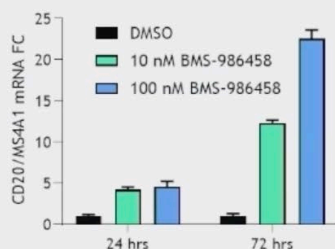
- immunomodulatory effects

Enhancement of CD20 expression following BMS-986458 treatment leads to synergy with standard of care agents

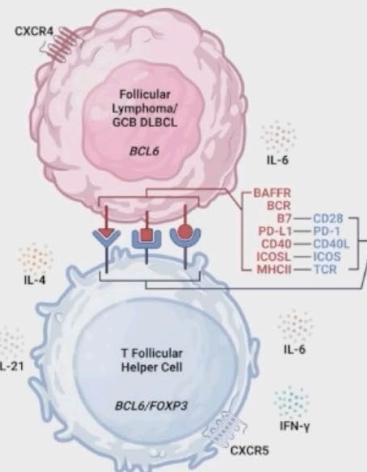
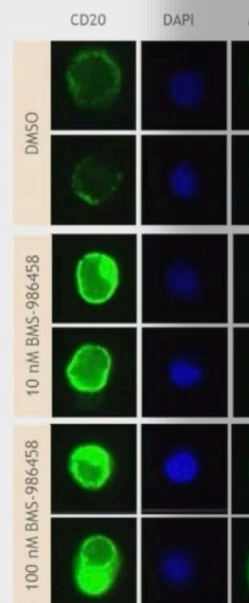
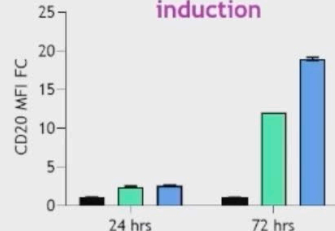
BMS-986458 exhibits immunomodulatory properties that may drive an antitumor response independent from tumor-intrinsic BCL6 expression

In follicular diseases such as GCB-DLBCL and FL, Tfh are believed to provide critical proliferative support to malignant B cells

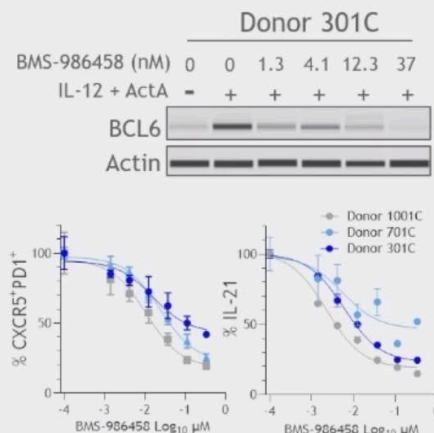
Transcript induction



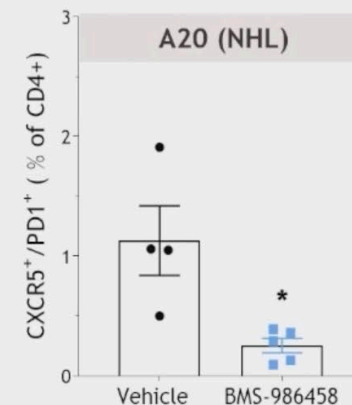
Cell surface CD20 protein induction



In vitro Tfh differentiation



In vivo Tfh assessment in syngeneic models



* $P \leq 0.5$, ** $P \leq 0.01$.
ADCC, antibody-dependent cellular cytotoxicity; DMSO, dimethyl sulfoxide; FC, fold change; MFI, median fluorescence intensity; Grocock L, et al. ASH 2024

* $P \leq 0.5$.
ActA, Activin A; BAFFR, B-cell activating factor receptor; BCL6, B-cell lymphoma 6; BCR, B-cell receptor; CD40, cluster of differentiation 40; CD40L, CD40 ligand; CXCR, C-X-C chemokine receptor; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell; ICOS(L), inducible T-cell costimulator (ligand); IFN, interferon; IL, interleukin; MHCII, major histocompatibility complex II; NHL, non-Hodgkin lymphoma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TCR, T-cell receptor; Tfh, T-follicular helper cell.

Grocock L, et al. ASH 2024 [Abstract #957]

Zusammenfassung

Klassisches Hodgkin-Lymphom

BrECADD bei älteren Pat mit sehr guter Wirksamkeit. Hämatologische Toxizität relevant. Vergleich zu Nivo-AVD?

Im Rezidiv: Pembro-GVD mit Pembro-Erhaltung bei erreichter CR eine Alternative zu autoSCT – spätere Salvage gut möglich

Chronische lymphatische Leukämie

Erstlinientherapie mit 2nd-Generation BTKi in Kombination mit Venetoclax +/- Obinutuzumab, fixed-duration

Vorteil PFS, relevante COVID-Infektionen – anti-CD20-assoziiert

Bispezifischer CD20-CD3-Antikörper, Epcoritamab bei R/R CLL wirksam und durchführbar – bisher kurzes PFS

Mantelzell-Lymphom

Ibrutinib + Rituximab gegenüber R-CHOP überlegen und gleichwertig zu BR, Subgruppen?

Folikuläres Lymphom

Im Rezidiv ist Tafasitamab – Rituximab – Lenalidomid ein neuer Standard

Large B cell lymphoma – LBCL

Pola-R-CHP im 5-Jahres follow-up weiterhin im PFS überlegen

CD20-CD3-bispezifischer Antikörper, Glofitamab, in der Erstlinie in Kombination R-CHOP – Phase III?

anti-ROR1-ADC, Zilovetamab-Vedotin, Phase III bei DLBCL und MCL

PROTACs target the undruggable – BCL6

und am Ende....

**Vielen Dank für
Ihre Aufmerksamkeit**