lymphoma connect®

POWERED BY COR2ED

RECENT DEVELOPMENTS IN THE TREATMENT OF DLBCL

Prof. Georg Lenz, MD
Department of Haematology, Oncology and Pneumology
University Hospital Münster, Germany

May 2020

DISCLAIMER AND DISCLOSURES

lymphoma connect®
POWERED BY COR2ED

LYMPHOMA CONNECT

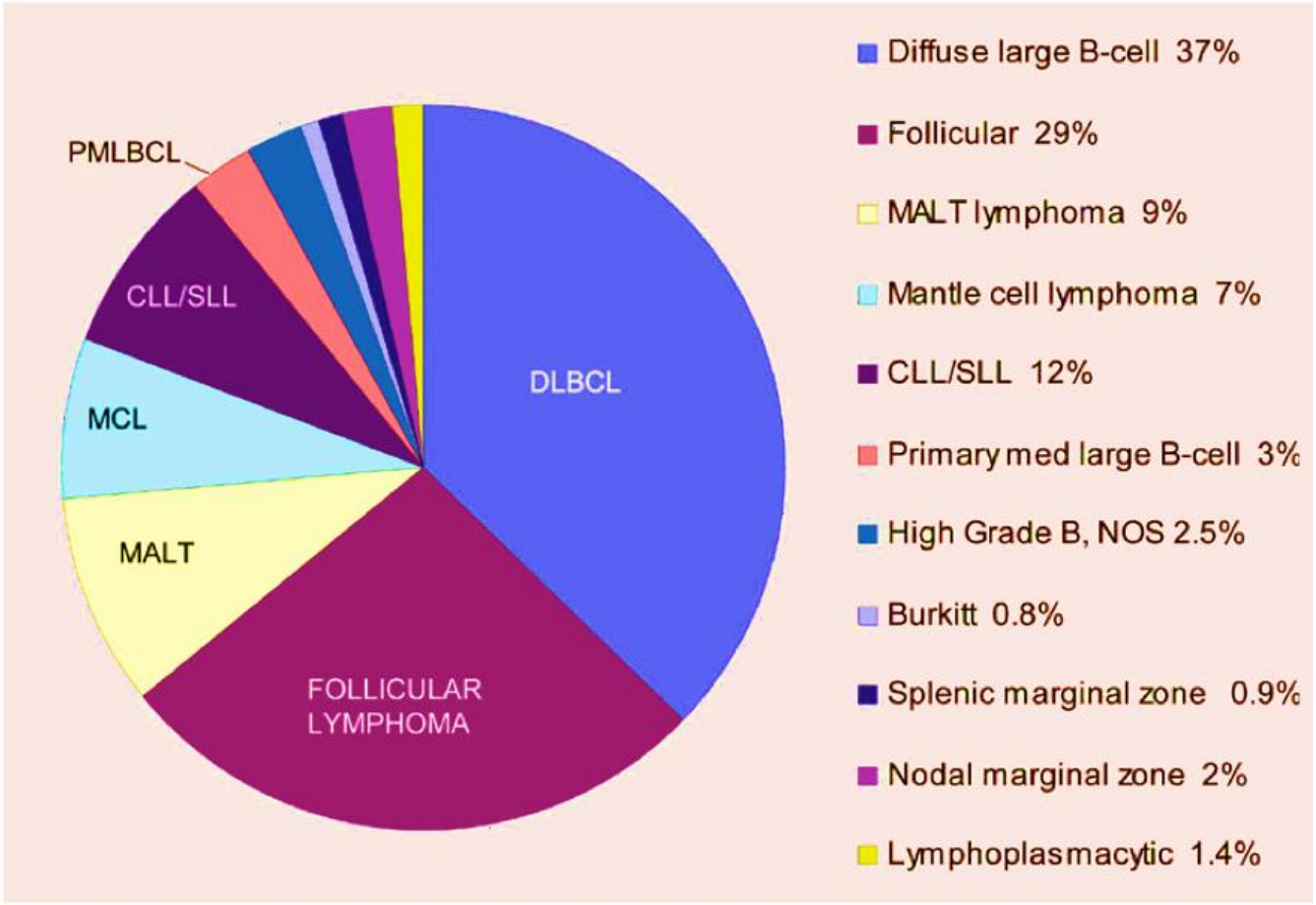
is supported by an Independent Educational Grant from Bayer

The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the authors' academic institutions or the rest of the LYMPHOMA CONNECT group

DISCLOSURES PROF. LENZ

Celgene, Janssen, Roche, Gilead, Bayer, BMS, Hexal, AstraZeneca, MorphoSys, NanoString, Takeda, Abbvie

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) REPRESENTS THE MOST FREQUENT LYMPHOMA SUBTYPE

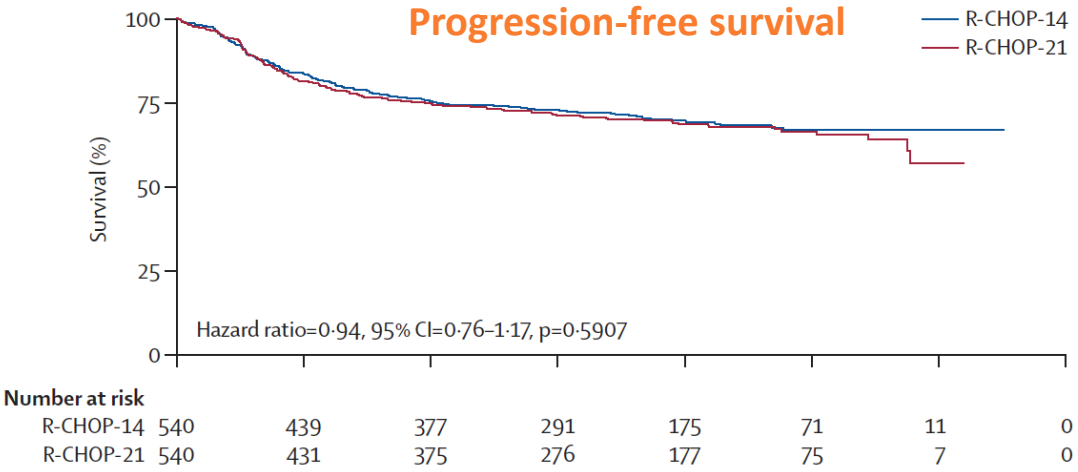


CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; MCL, mantle-cell lymphoma; NOS, not otherwise specified; PMLBCL, primary mediastinal large B-cell lymphoma; SLL, small lymphocytic lymphoma

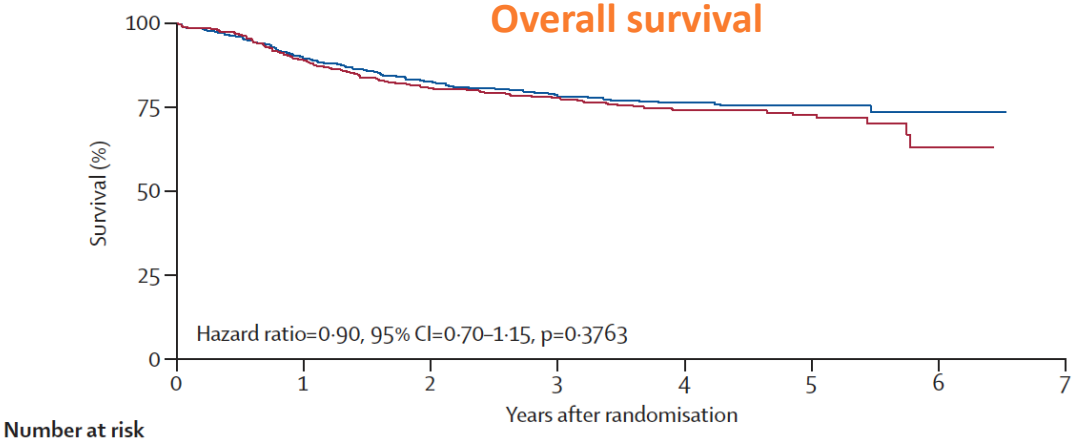
Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th Edition, volume 2. 2008.

ROUGHLY 70% OF DLBCL PATIENTS CAN BE CURED WITH R-CHOP

lymphoma connect®
POWERED BY COR2ED



Number at risk								
R-CHOP-14	540	439	377	291	175	71	11	0
R-CHOP-21	540	431	375	276	177	75	7	0



Number at risk								
R-CHOP-14	540	477	418	314	195	83	14	0
R-CHOP-21	540	474	409	305	187	81	8	0

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine-prednisolone

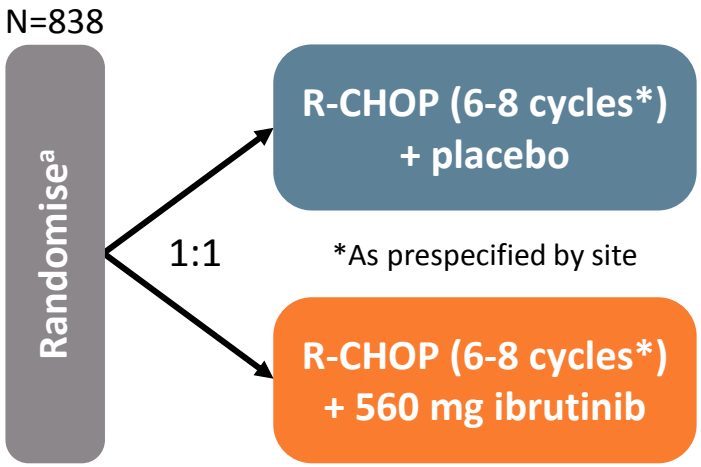
Cunningham D, et al. Lancet 2013; 381:1817-26

PHOENIX TRIAL

R-CHOP + IBRUTINIB VS R-CHOP + PLACEBO IN PREVIOUSLY UNTREATED NON-GCB DLBCL

PHOENIX: DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY[1]

STUDY DESIGN



Key eligibility criteria

- Untreated non-GCB DLBCL
  - Determined by Hans-based IHC at a central laboratory
  - Retrospectively analysed for ABC subtype using GEP
- Stage II to IV measurable disease
- R-IPI ≥1
- ECOG performance status ≤2

End points

- Primary end point: EFS[†] in ITT (non-GCB) and ABC subgroup
- Secondary end points: PFS, CR rate, OS, safety
  - Response assessed per Revised Response Criteria for Malignant Lymphoma[2]

[a]Stratified by R-IPI, region, and number of prespecified treatment cycles (6 vs 8 cycles)

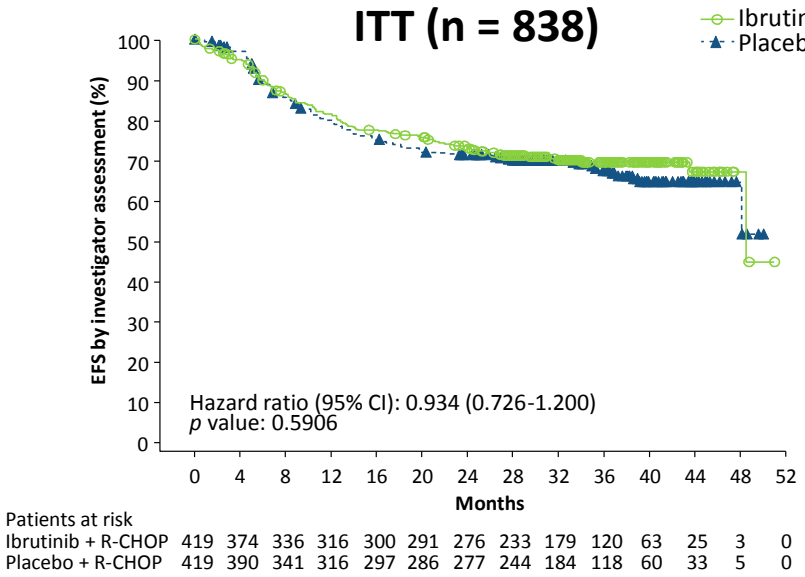
- Prophylactic antibiotics and G-CSF were not mandated but were permitted at the investigator's discretion per local or other standard guidelines

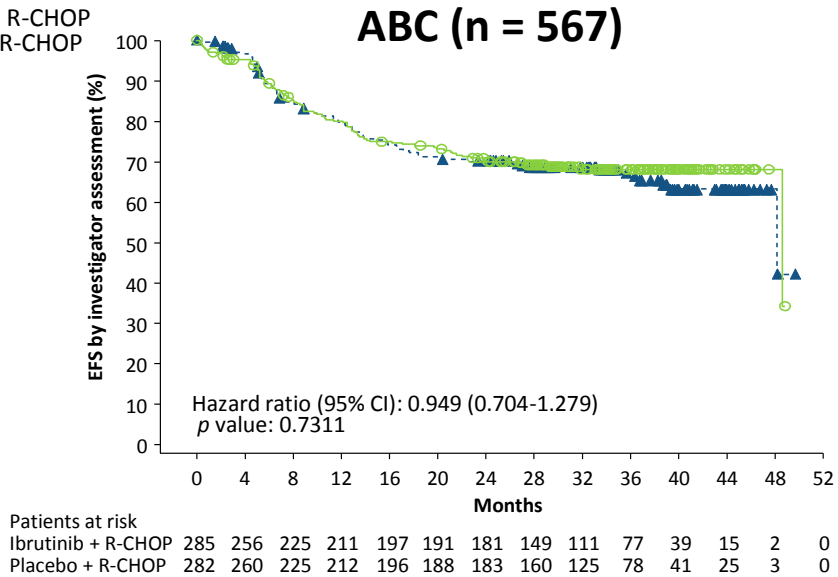
[†]EFS: time from randomization to PD, relapse from CR, initiation of subsequent disease-specific therapy for PET-positive or biopsy-proven residual disease after ≥6 cycles of R-CHOP, or any-cause death

ABC, activated B-cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; GCB, germinal centre B cell-like; GEP, gene expression profiling; G-CSG, granulocyte colony stimulating factor; IHC, immunohistochemistry; ITT, intent-to-treat; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; R-CHOP, rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine-prednisolone; R-IPI, revised International Prognostic Index

1. Younes A, et al. J Clin Oncol 2019; 37; 1285-95. 2. Cheson BD, et al. J Clin Oncol 2007;25:579-86

PHOENIX PRIMARY END POINT:
EFS IN THE ITT AND ABC POPULATION





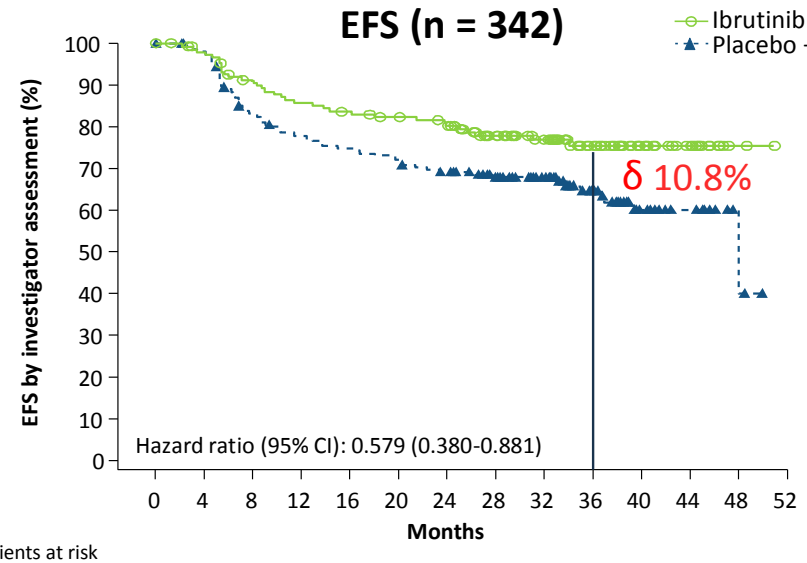
- **Overall response** (89.3% vs 93.1%) **and CR rates** (67.3% vs 68.0%) **were similar** in the ibrutinib + R-CHOP and placebo + R-CHOP arms in the ITT population
- **CNS progression** was observed in 10 (2.4%) vs 16 (3.8%) patients in the ibrutinib + R-CHOP and placebo + R-CHOP arms

ABC, activated B-cell; CI, confidence interval; CNS, central nervous system; CR, complete response; EFS, event-free survival; ITT, intent-to-treat; R-CHOP, rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine-prednisolone

Younes A, et al. J Clin Oncol 2019; 37; 1285-95

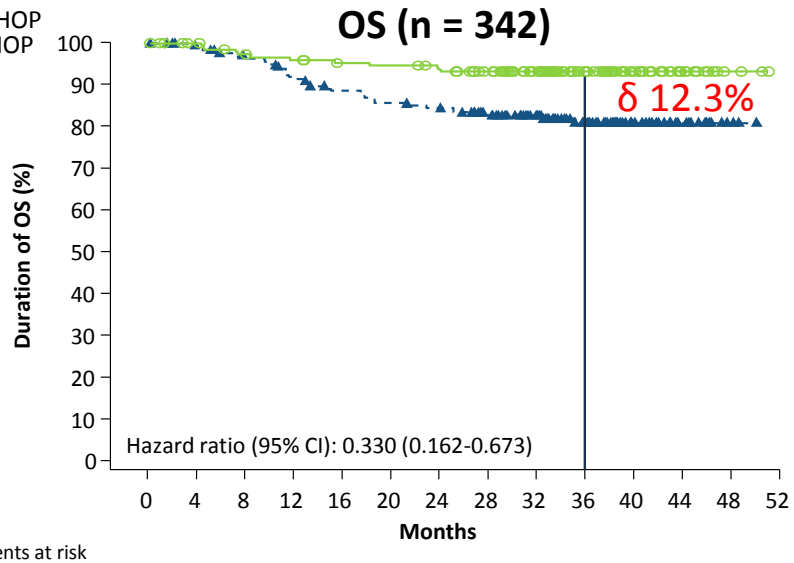
PHOENIX

EFS AND OS IN PATIENTS <60 YEARS (ITT POPULATION)



Patients at risk

Ibrutinib + R-CHOP	156	146	133	125	121	117	113	93	72	44	27	13	2	0
Placebo + R-CHOP	186	177	148	137	132	127	120	104	78	52	24	16	3	0



Patients at risk

Ibrutinib + R-CHOP	156	151	145	142	138	137	134	125	96	62	39	18	3	0
Placebo + R-CHOP	186	181	173	161	153	148	145	130	101	70	38	21	5	0

- Ibrutinib + R-CHOP improved EFS and OS vs placebo + R-CHOP in patients <60 years of age
- Subgroup analyses showed that EFS benefit was consistent across most subgroups for baseline factors
- A similar trend with age was seen in patients with the ABC subtype (HR [95% CI]: 0.532 [0.307-0.922] for EFS; HR [95% CI]: 0.345 [0.138-0.862] for OS)
- More patients on the placebo + R-CHOP arm received subsequent antilymphoma therapy (16.2% vs 21.6%)

ABC, activated B-cell; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival; R-CHOP, rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine-prednisolone

Younes A, et al. J Clin Oncol 2019; 37; 1285-95

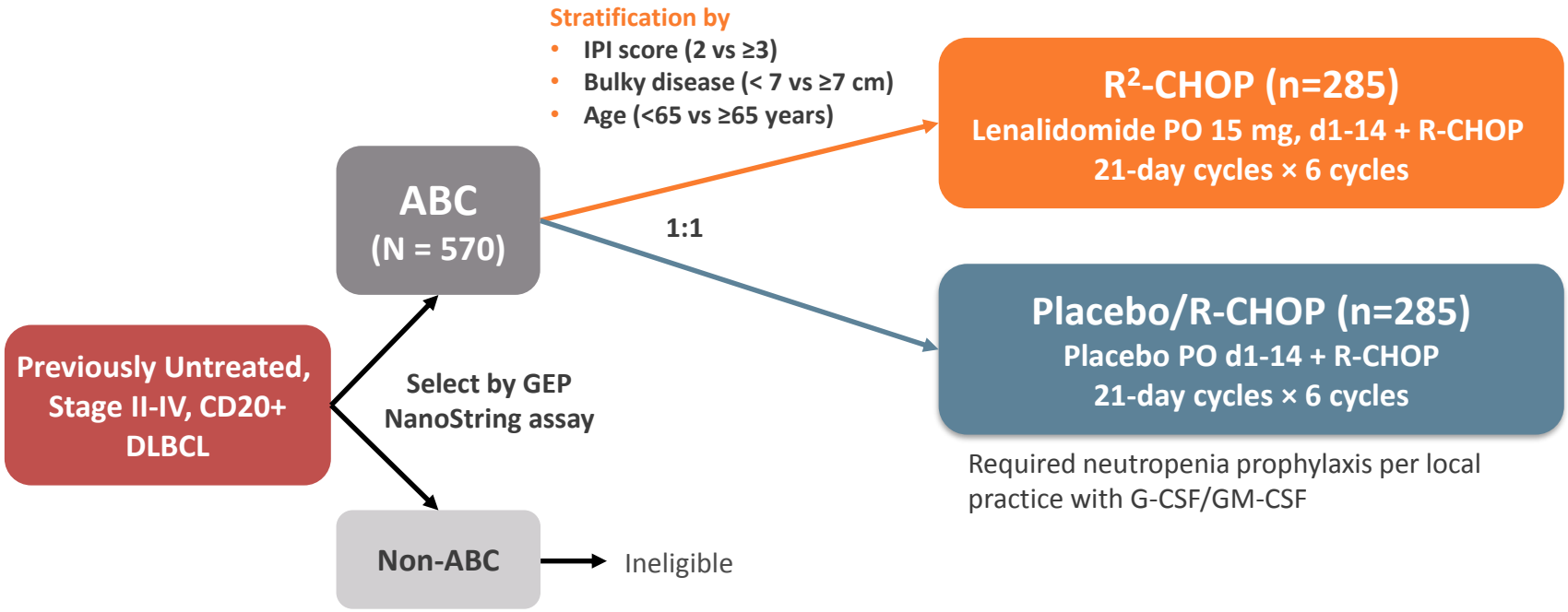
ROBUST TRIAL

R^2-CHOP VS PLACEBO/R-CHOP IN PREVIOUSLY UNTREATED ABC-TYPE DLBCL

ROBUST: PHASE 3 STUDY

STUDY DESIGN

- Multicentre, randomised, double-blind, placebo-controlled, phase 3 study in 282 global sites[1,2]
- Primary endpoint: PFS by central review (per 2014 IWG)[1,3]
- Secondary endpoints: EFS (key secondary), OS, ORR, CR rate, DOR, and safety[1]

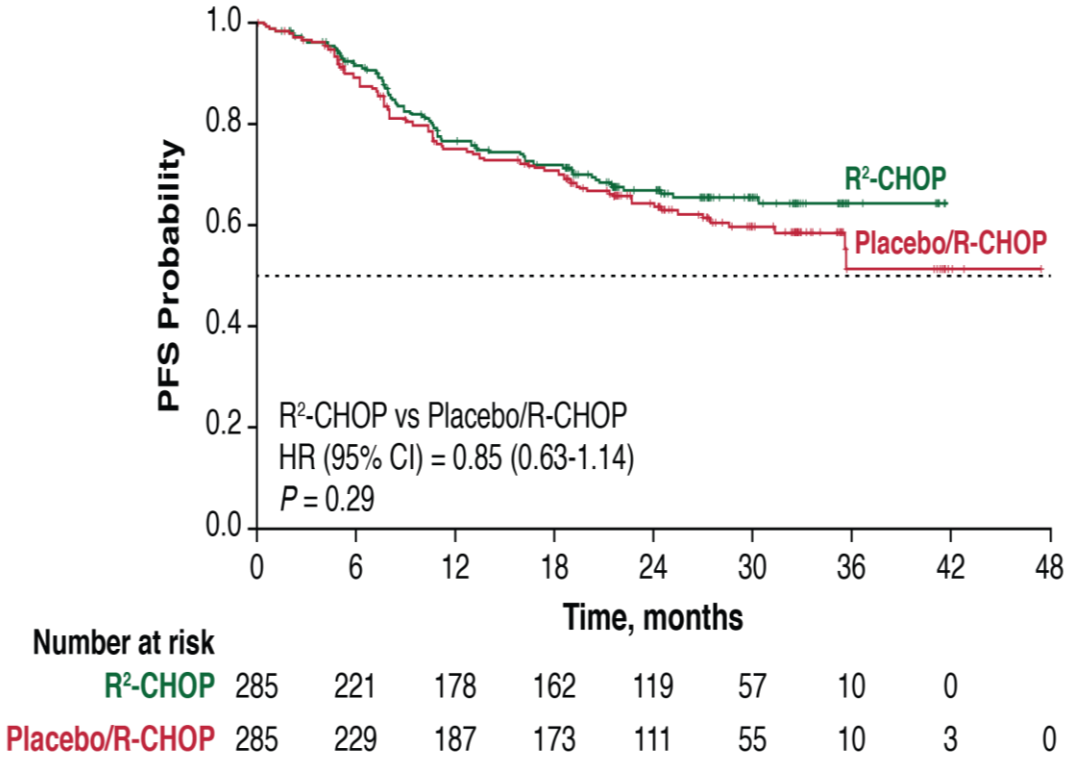


ABC, activated B-cell; CR, complete response; d, day; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EFS, event-free survival; GEP, gene expression profiling; HR, hazard ratio; IPI, International Prognostic Index; IWG, International Working Group; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; PO, oral administration; R-CHOP, rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine-prednisolone; R^2-CHOP, lenalidomide/R-CHOP

1. Vitolo U, et al. Hematol Oncol 2019;37(S2):36-7; 2. Clinicaltrials.gov NCT02285062 3. Cheson BD, et al. J Clin Oncol 2014;32:3059-68

ROBUST PRIMARY ENDPOINT

PROGRESSION-FREE SURVIVAL (ITT, IRAC)



PFS Rates	R²-CHOP (n = 285)	Placebo/ R-CHOP (n = 285)
1 year	77%	75%
2 year	67%	64%

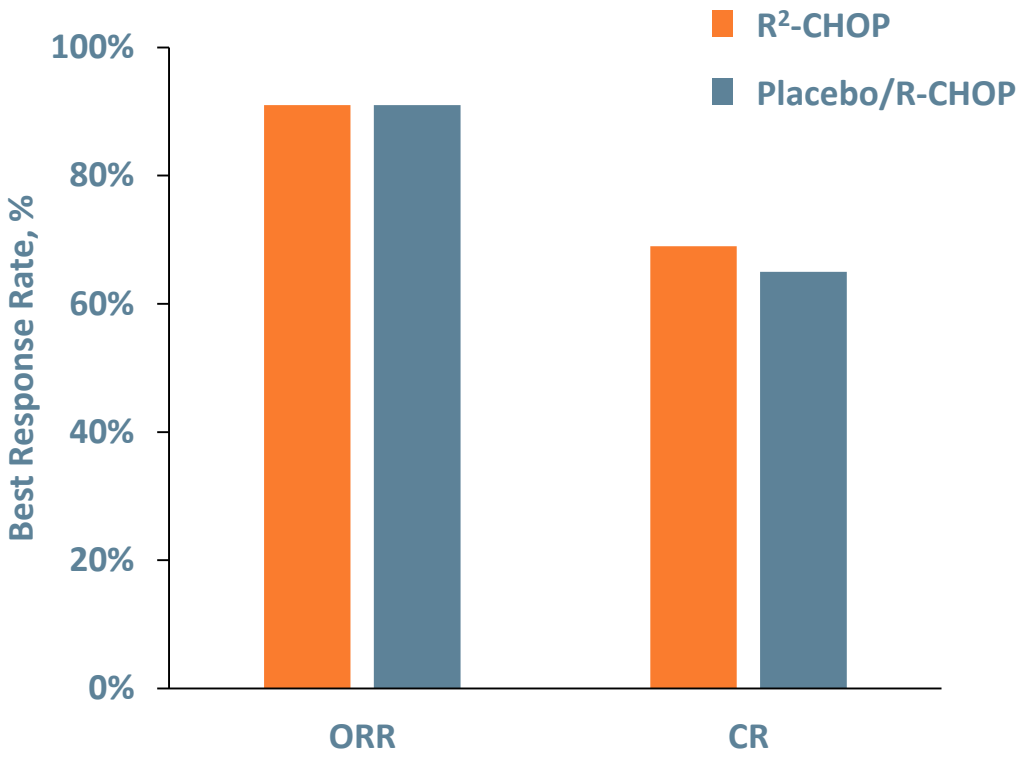
- At a median follow-up of 27.1 months (range 0–47), the primary endpoint of PFS was not met (medians not reached)
- Median PFS improved from 24 months with R-CHOP to 38 months with R²-CHOP in ABC-DLBCL (192 events with 90% power; HR = 0.625)

CI, confidence interval; HR, hazard ratio; IRAC, independent response adjudication committee; ITT, intent-to-treat; PFS, progression-free survival; R-CHOP, rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine-prednisolone; R²-CHOP, lenalidomide/R-CHOP

Data cut-off 15 Mar 2019.

Vitolo U, et al. Hematol Oncol 2019;37(S2):36-7

ROBUST
RESPONSE



- ORR and CR rates were high in both arms
- **Median time from diagnosis to treatment was 31 days for each arm**

CR, complete response; ORR, objective response rate; R-CHOP, rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine-prednisolone; R2-CHOP, lenalidomide/R-CHOP

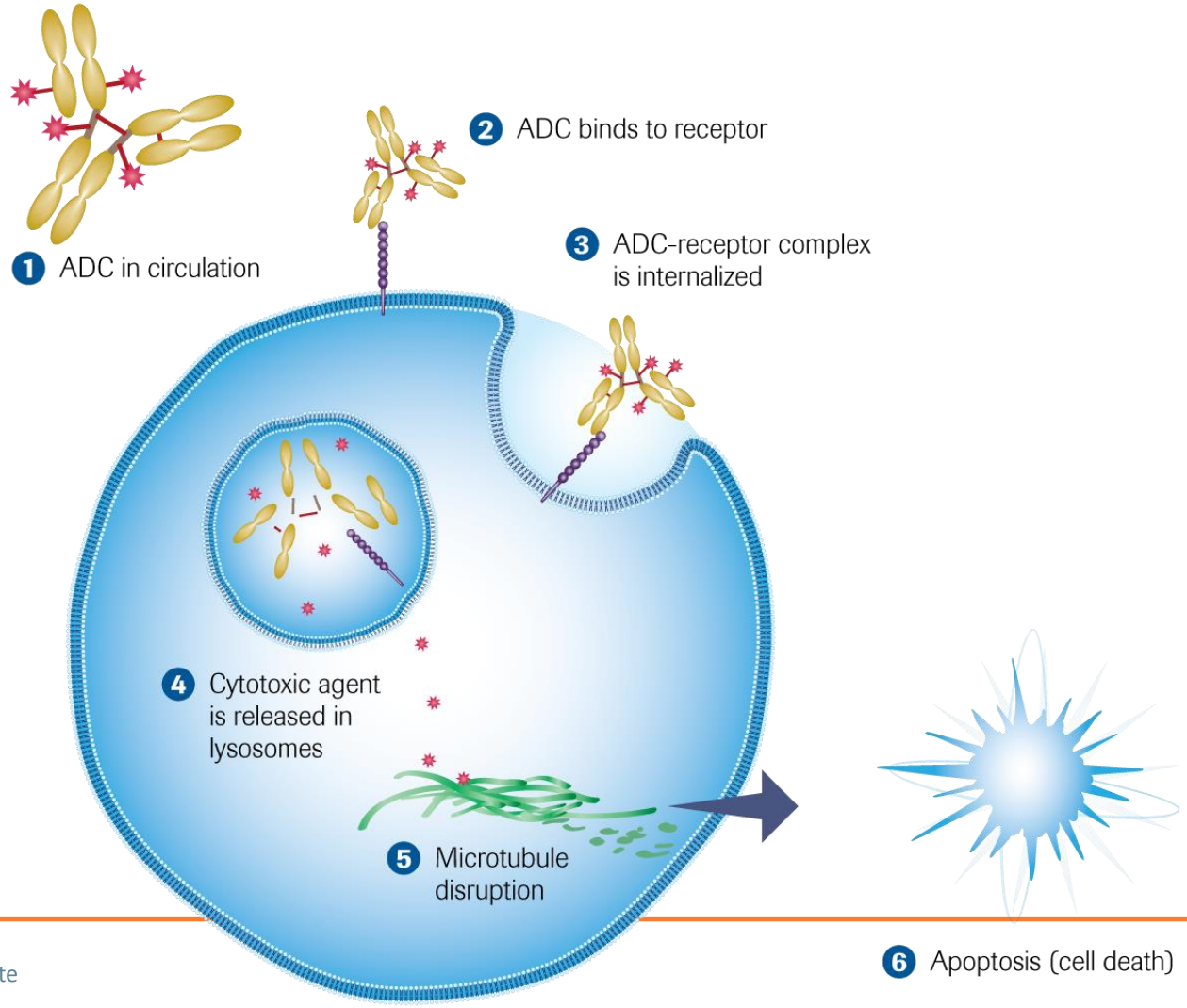
Data cut-off 15 Mar 2019. CR was assessed by 2014 IWG criteria with CT-PET (Cheson BD, et al. J Clin Oncol. 2014;32:3059-3068)

Vitolo U, et al. Hematol Oncol 2019;37(S2):36-7

POLATUZUMAB

POLATUZUMAB VEDOTIN IS AN ANTIBODY-DRUG CONJUGATE (ADC)

MECHANISM OF ACTION

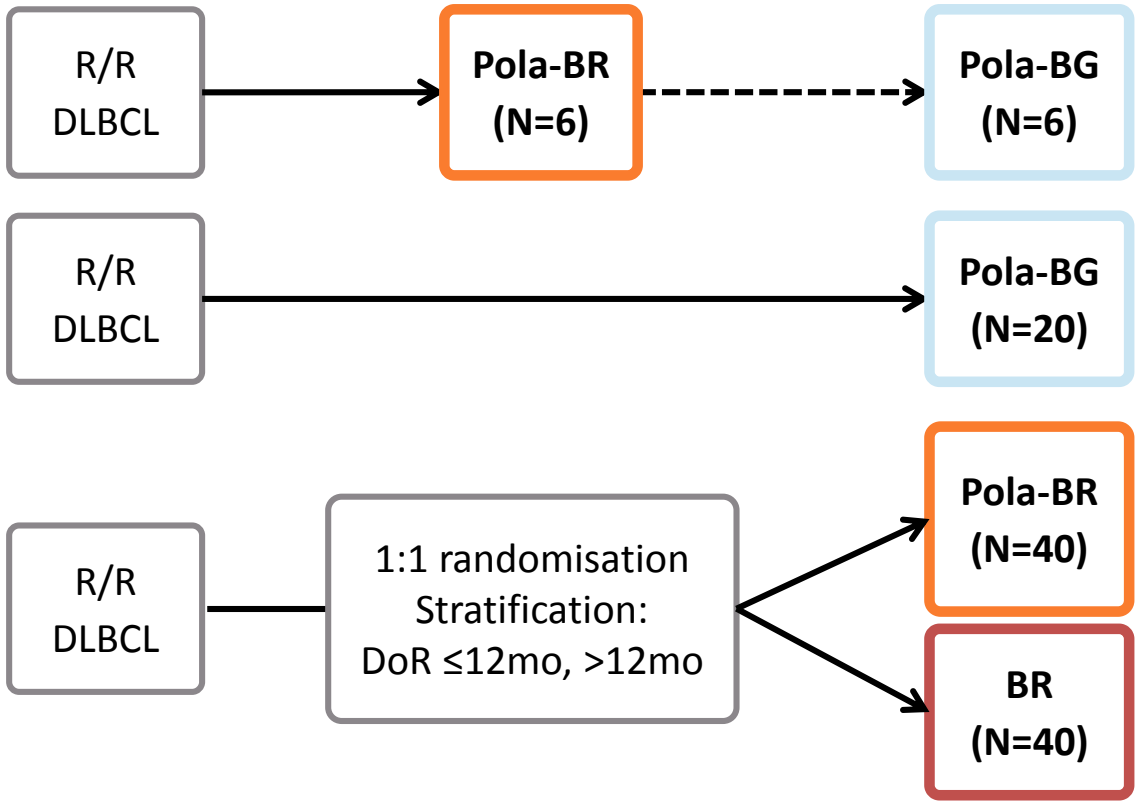


ADC, antibody-drug conjugate

Sharman J, et al. EHA 2015

POLATUZUMAB PHASE 1/2 STUDY IN DLBCL

STUDY DESIGN



Treatment administered every 21 days x 6 cycles:

- Polatuzumab vedotin: 1.8 mg/kg, C1D2, then D1 for C2+
- Bendamustine (B): 90 mg/m^2, C1D2/3, then D1/2 for C2+
- Obinutuzumab (G): 1000 mg, C1D1/8/15, then D1 for C2+
- Rituximab (R): 375 mg/m^2, D1 for C1+

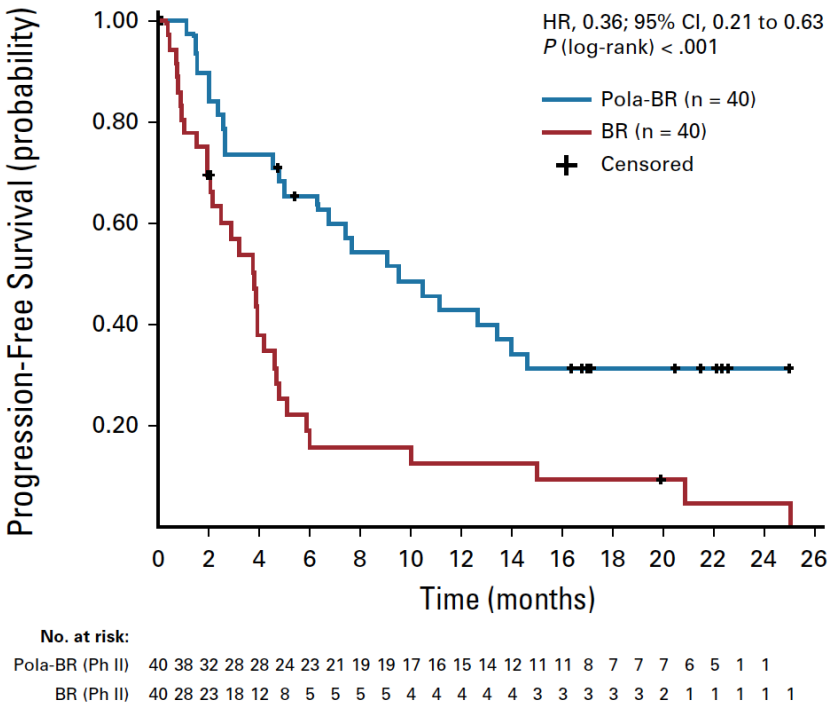
B, bendamustine; C, cycle; D, day; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; G, obinutuzumab; mo, months; pola, polatuzumab; R, rituximab; R/R, relapsed/refractory

Sehn L, et al. J Clin Oncol. 2020;38:155-65; Clinicaltrials.gov NCT02257567

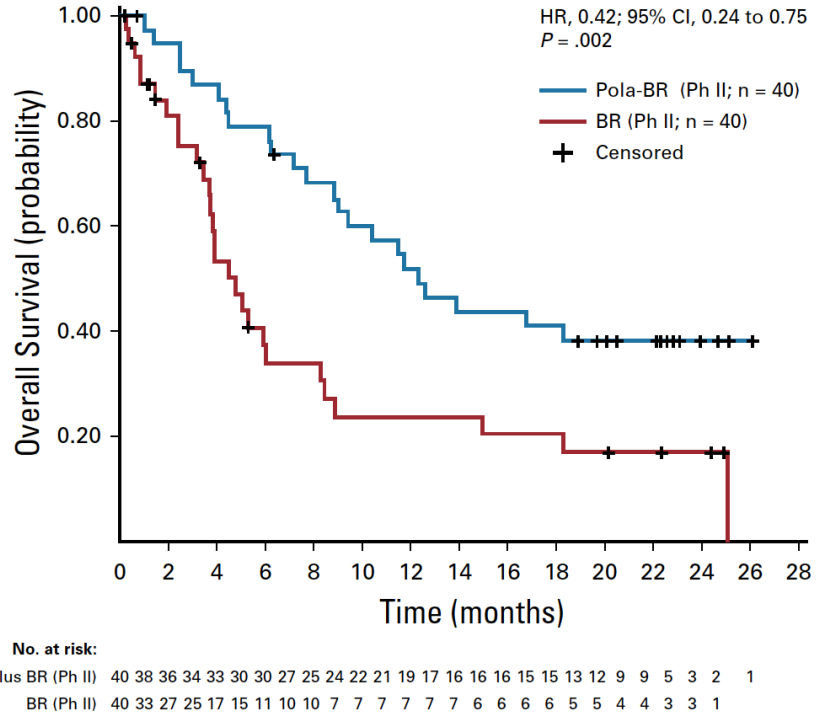
POLATUZUMAB IS ACTIVE IN DLBCL

lymphoma connect® POWERED BY COR2ED

Progression-free Survival (IRC)



Overall Survival



B, bendamustine; CI, confidence interval; HR, hazard ratio; pola, polatuzumab; R, rituximab

Sehn L, et al. J Clin Oncol. 2020;38:155-65

CLINICAL IMPLICATIONS

lymphoma connect®
POWERED BY COR2ED

Standard of care

- **R-CHOP** remains the first-line standard of care in DLBCL

No benefit of adding ibrutinib or lenalidomide

- The **PHOENIX and ROBUST trials** did not show clinically meaningful improvement of adding ibrutinib or lenalidomide to R-CHOP
- However, the PHOENIX trial showed an interesting signal in patients <60 years, indicating that adding a BTK inhibitor might improve outcomes in this group

Promising novel agents

- Antibody-drug conjugates, such as polatuzumab vedotin
- CAR T-cells
  - CAR T-cells have been approved for use in the R/R setting
- Bispecific antibodies

REACH LYMPHOMA CONNECT VIA TWITTER, LINKEDIN, VIMEO & EMAIL OR VISIT THE GROUP'S WEBSITE

http://www.lymphomaconnect.info

Follow us on Twitter
@lymphoma_connec

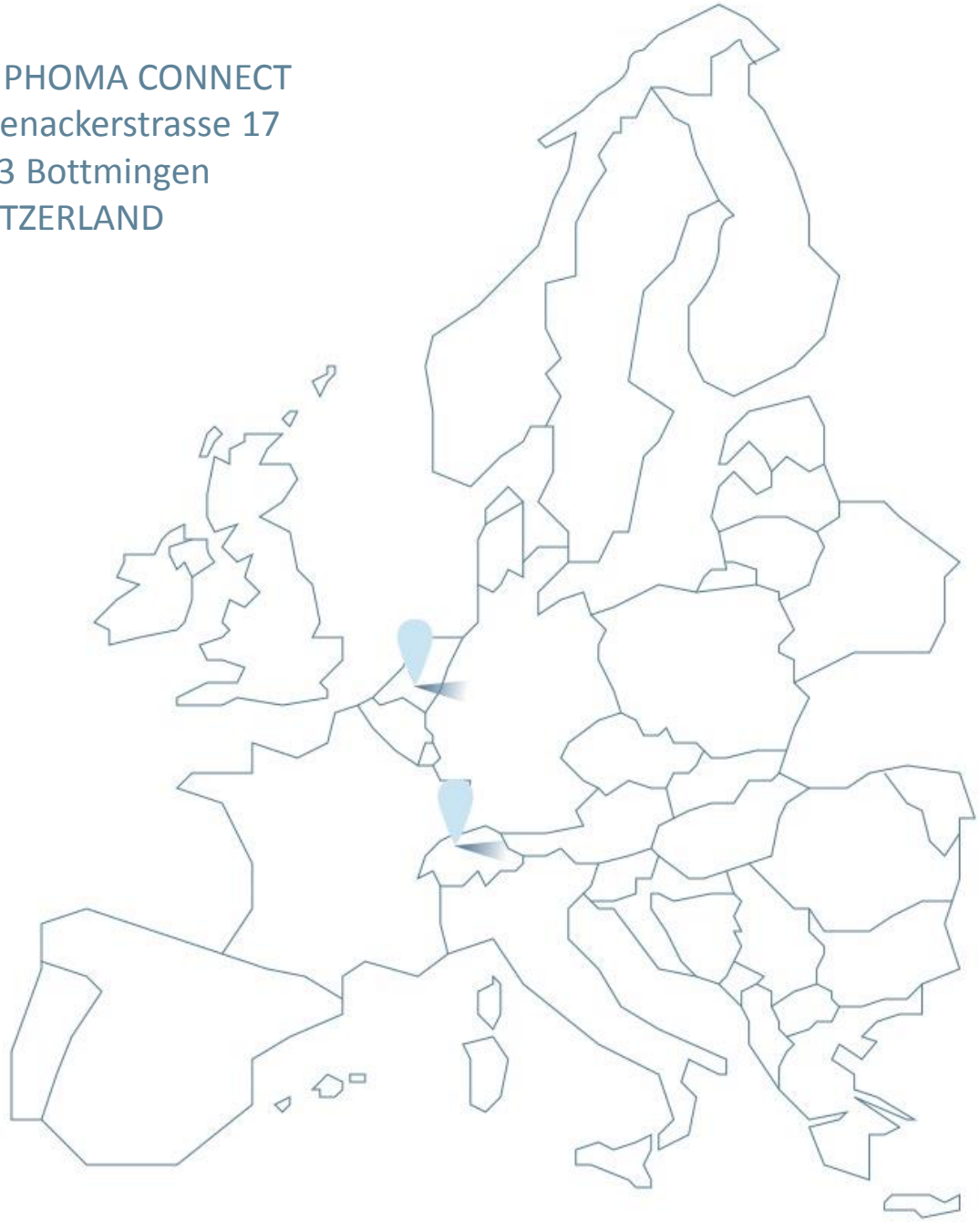
Follow the
LYMPHOMA CONNECT
group on LinkedIn

Watch us on the
Vimeo Channel
LYMPHOMA CONNECT

Email
froukje.sosef
@cor2ed.com

lymphoma connect®
POWERED BY COR2ED

LYMPHOMA CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND



Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com