Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

61. ASH Annual Meeting
7. – 10. Dezember 2019

KML-Experten berichten vom ASH 2019 aus Orlando

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Prof. Dr. med. Georg Lenz

Aggressive Lymphome

Direktor der Medizinischen Klinik A (Hämatologie, Hämostaseologie, Onkologie und Pneumologie) des Universitätsklinikums Münster | Mitglied im Kompetenznetz Maligne Lymphome e.V.

Offenlegung potentieller Interessenskonflikte

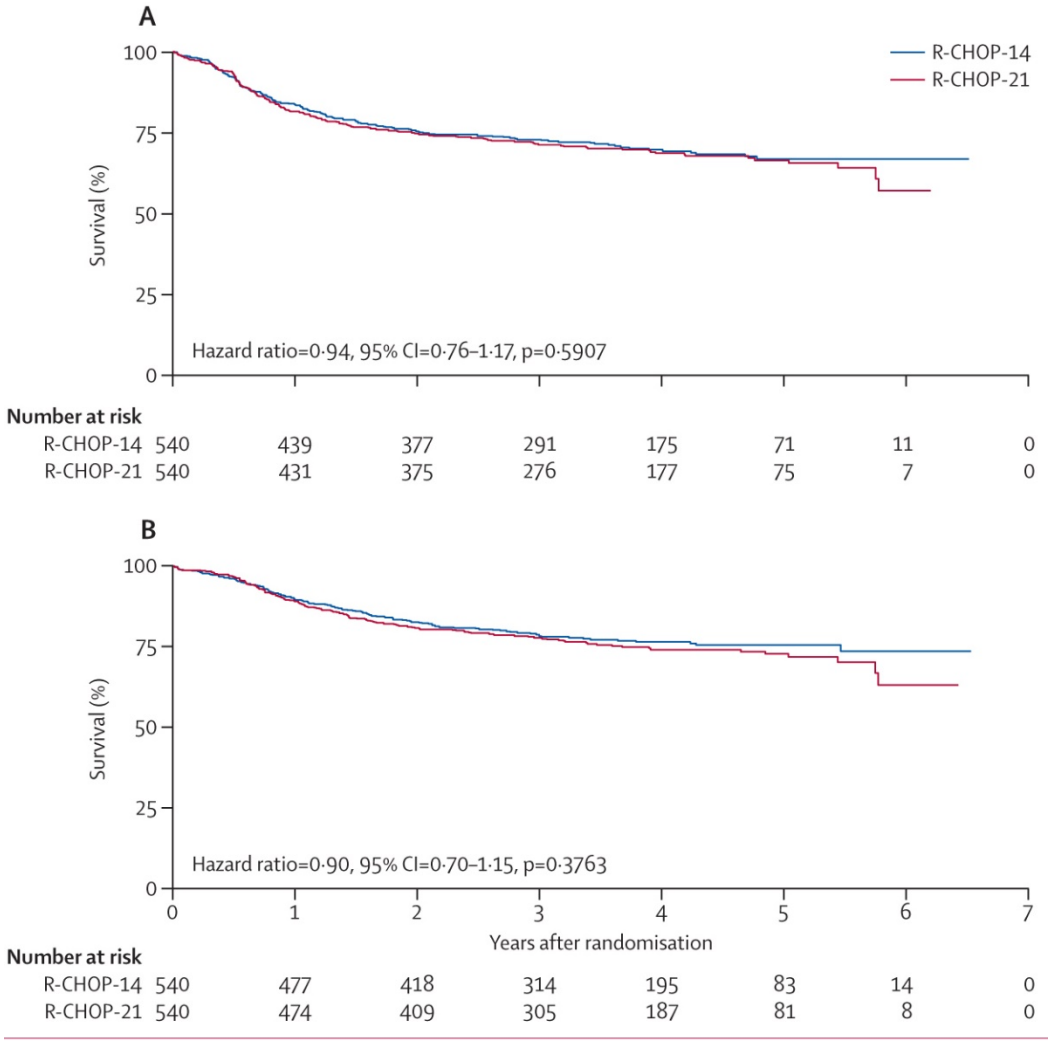
LymphomKompetenz KOMPAKT – ASH2019 wird in Kooperation mit vier unterstützenden Firmen durchgeführt. Diese Firmen haben keinen Einfluss auf die Inhalte dieses Vortrags. Meine weiteren Disclosures betreffen:

Unternehmen	Interessenskonflikt
Roche	Advisory Board, invited speaker, research support
Gilead	Advisory Board, research support
Janssen	Advisory Board, invited speaker, research support
Bayer	Advisory Board, invited speaker, research support
Celgene	Advisory Board, invited speaker, research support
Novartis	Advisory Board, research support
AstraZeneca	Advisory Board, research support
Takeda	Advisory Board
BMS	Advisory Board
NanoString	Advisory Board
Abbvie	Invited speaker

Kapitel 1

Aggressive NHL
Erstlinientherapie

Aggressive NHL

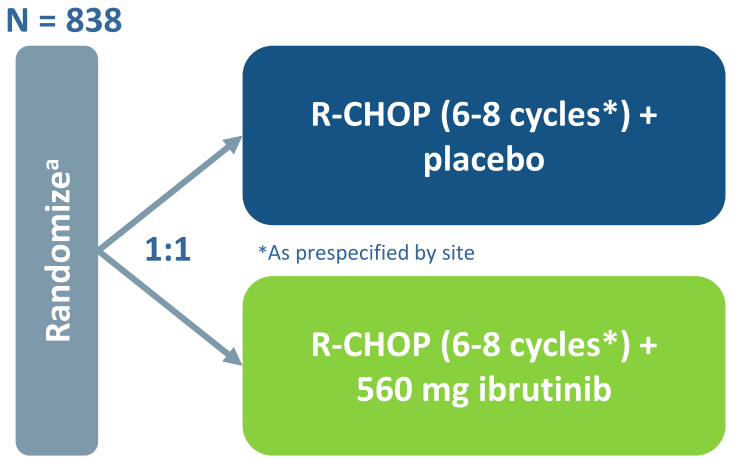


Cunningham et al., Lancet, 2013

PHOENIX Studie

Study Design: Double-Blind, Placebo-Controlled Study

PHOENIX PCI-32765DBL3001



[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.

Key eligibility criteria
- Untreated non-GCB DLBCL
  - Determined by Hans-based IHC at a central laboratory
  - Retrospectively analyzed for ABC subtype using GEP
- Stage II to IV measureable 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[1]

1. Cheson BD, et al. *J Clin Oncol*. 2007;25:579-586.

American Society of Hematology 60th Annual Meeting and Exposition, Younes A, et al. Abstract 784.

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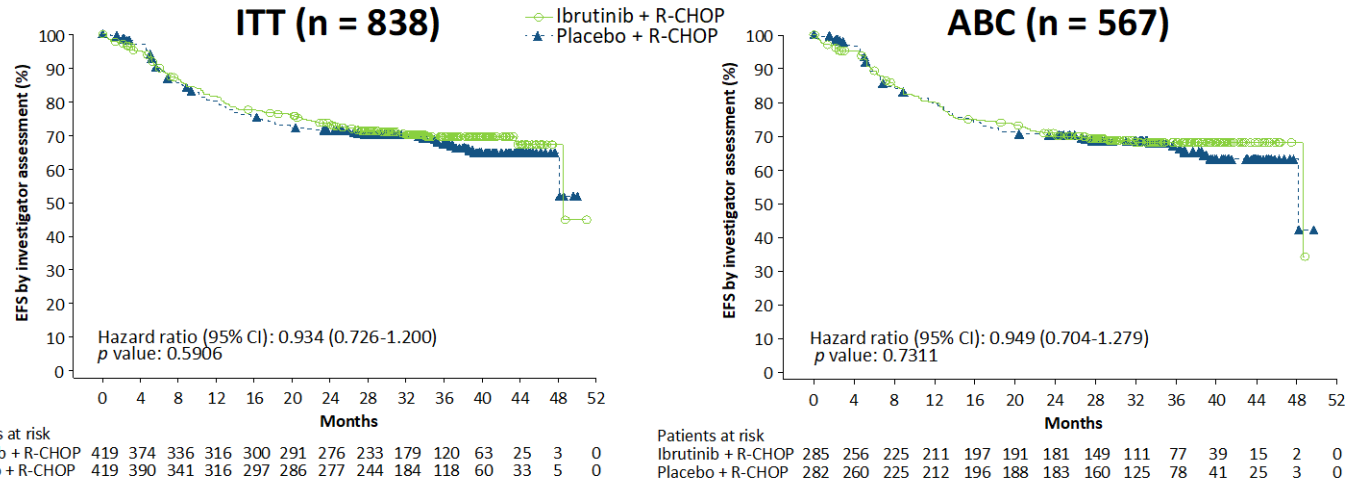
Younes et al., JCO, 2019

PHOENIX Studie

Primary End Point: EFS in the ITT and ABC Population

PHOENIX PCI-32765DBL3001



- 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: 10 (2.4%) vs 16 (3.8%) patients in the ibrutinib + R-CHOP and placebo + R-CHOP arms

American Society of Hematology 60th Annual Meeting and Exposition, Younes A, et al. Abstract 784.

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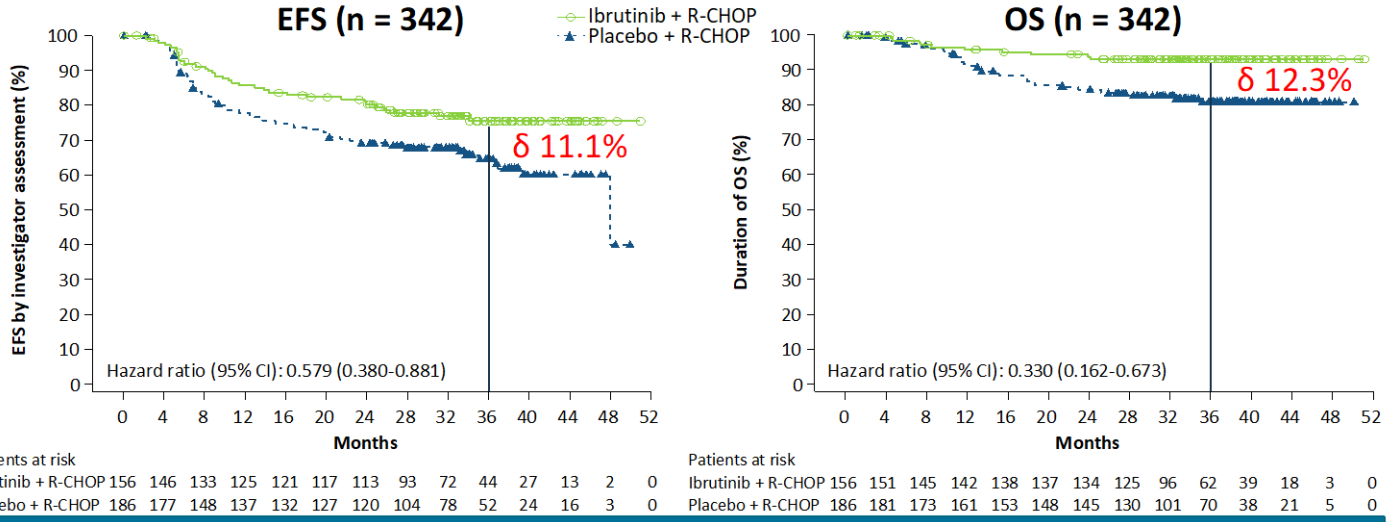
Younes et al., JCO, 2019

PHOENIX Studie

EFS and OS in Patients < 60 Years



- 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 (25.2% vs 33.5%)

American Society of Hematology 60th Annual Meeting and Exposition, Younes A, et al. Abstract 784.

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Younes et al., JCO, 2019

#354

CLINICAL IMPACT OF IBRUTINIB WITH R-CHOP IN UNTREATED NON-GCB DLBCL CO-EXPRESSING BCL2 AND MYC GENES IN THE PHASE 3 PHOENIX TRIAL

Peter Johnson, MD, FRCP[1], Sriram Balasubramanian[2], Brendan Hodkinson[3], Michael Schaffer[3], Lori Parisi[4*], S. Martin Shreeve[2*], Steven Sun[3*], Jessica Vermeulen[5], Laurie H Sehn, MD[6], Louis Staudt, MD[7], Anas Younes, MD[8] and* ***Wyndham Wilson, MD***[9]

[1]*Cancer Research UK Clinical Centre, University of Southampton, Southampton, United Kingdom*

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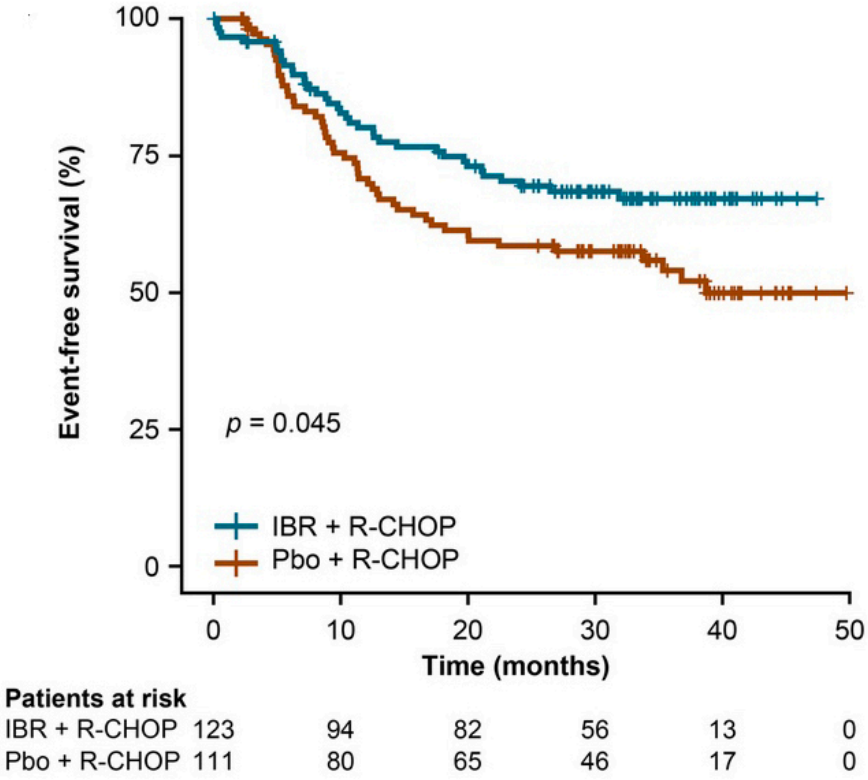
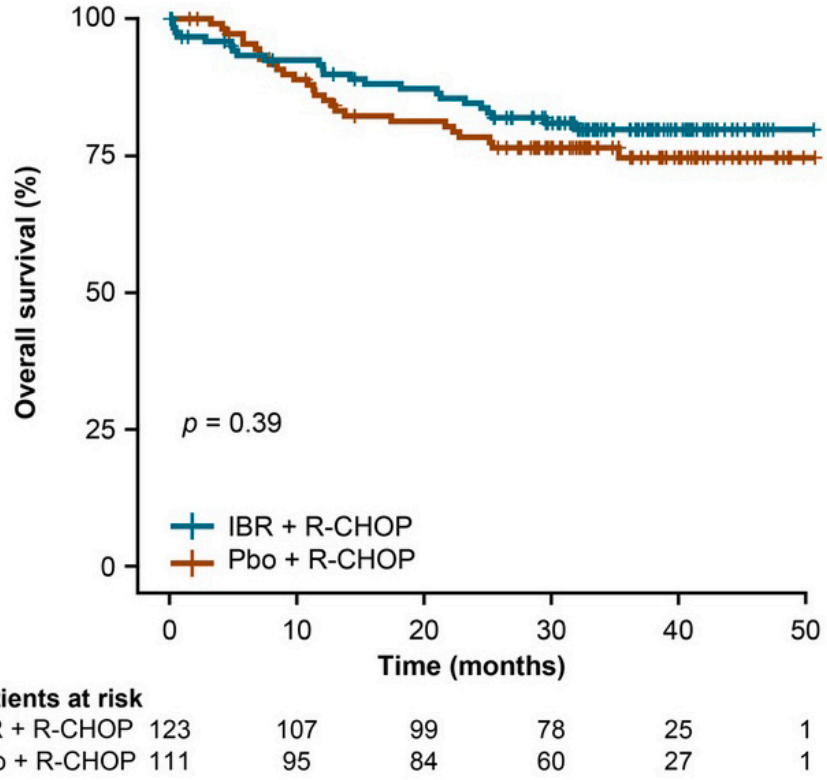
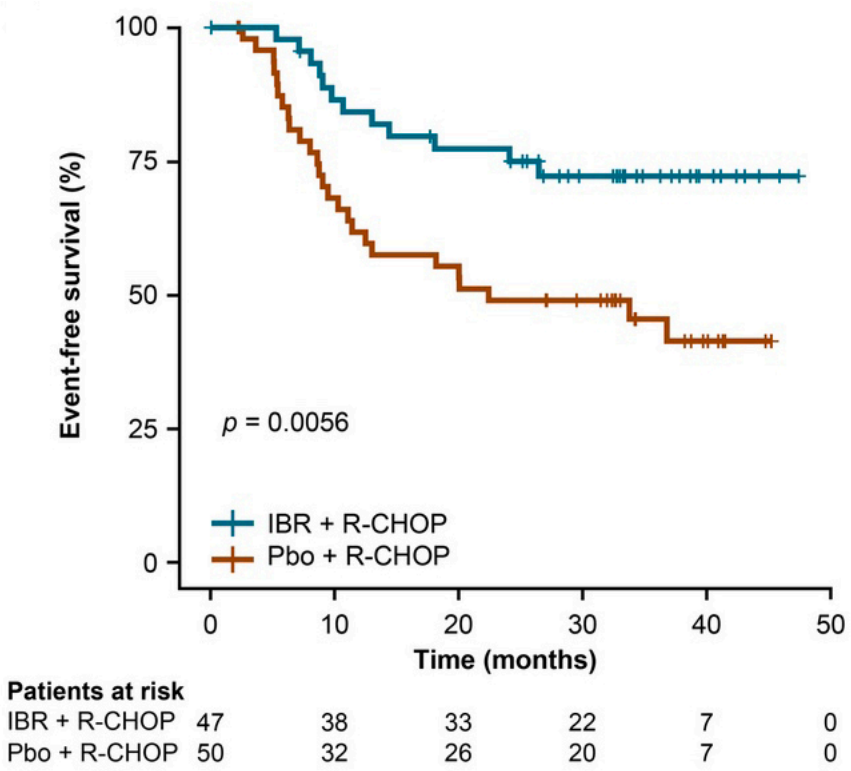
PHOENIX Studie – Einfluss von MYC und BCL2 Expression

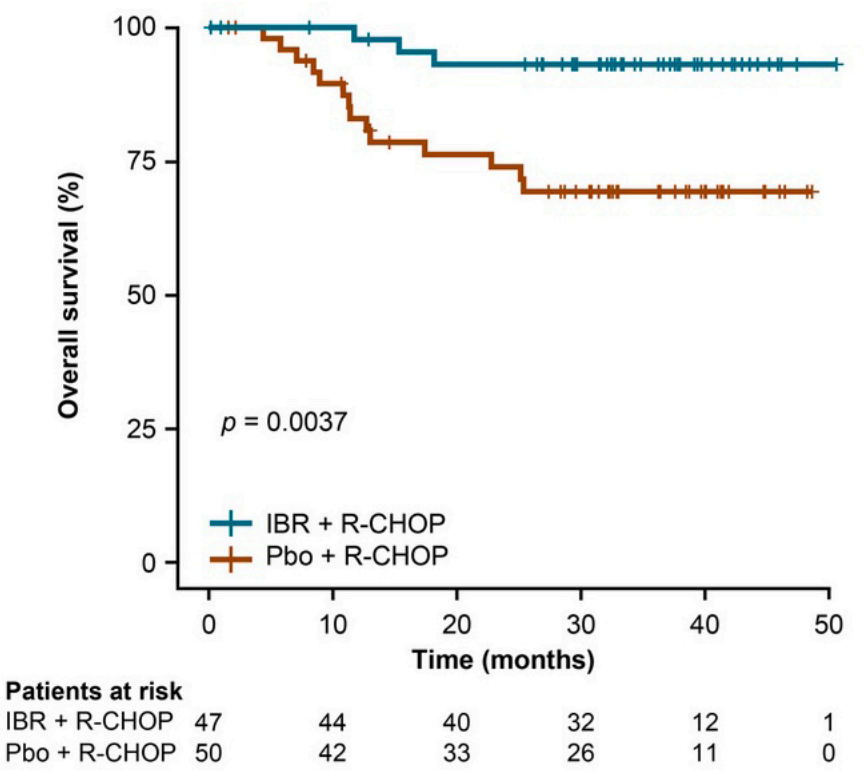




Johnson et al., ASH, Abstract # 354

PHOENIX Studie – Einfluss von MYC und BCL2 Expression





Johnson et al., ASH, Abstract # 354

#352

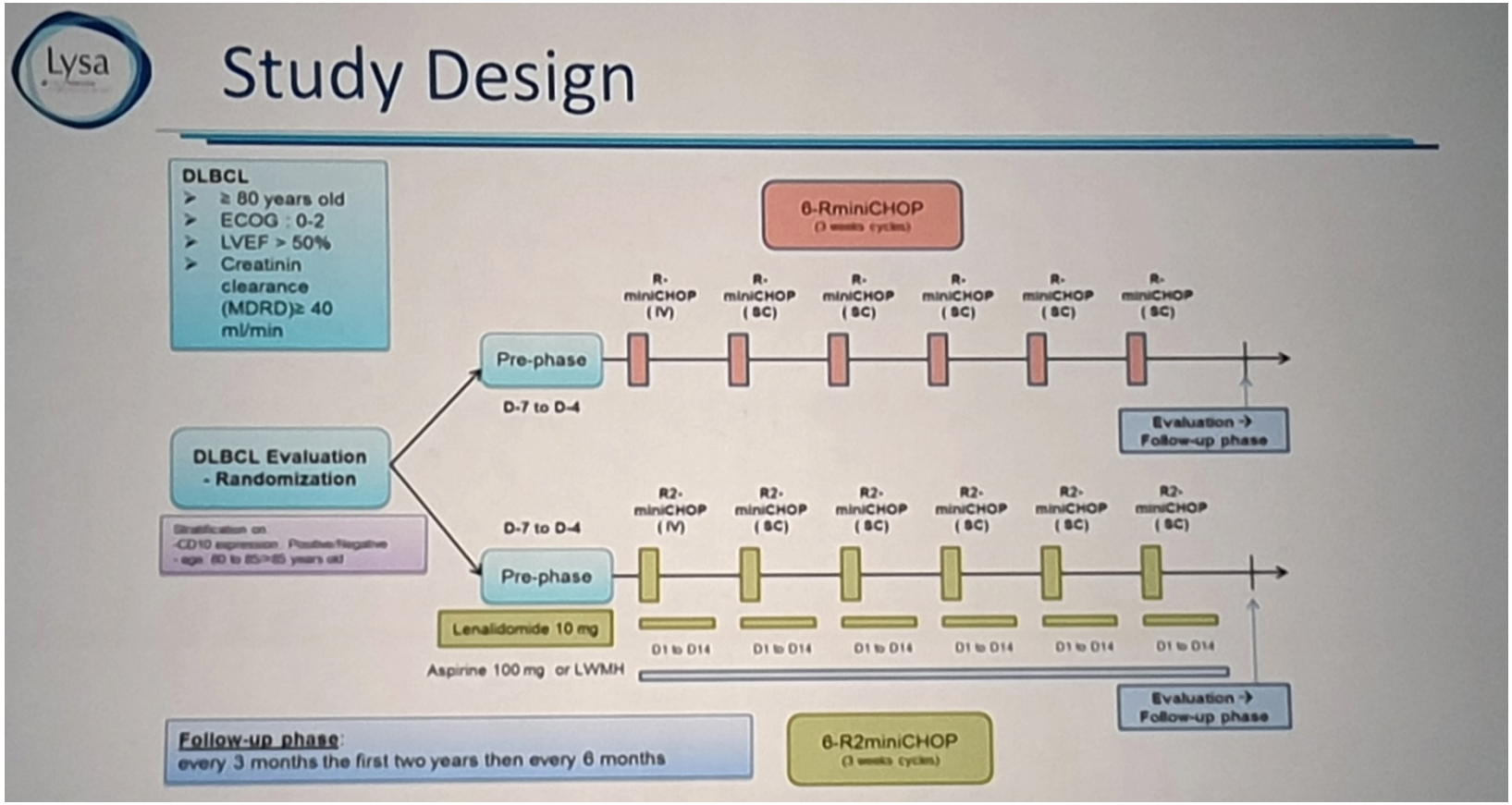
SUB-CUTANEOUS RITUXIMAB-MINICHOP VERSUS SUB-CUTANEOUS RITUXIMAB-MINICHOP + LENALIDOMIDE (R2-MINICHOP) IN DIFFUSE LARGE B CELL LYMPHOMA FOR PATIENTS OF 80 YEARS OLD OR MORE (SENIOR STUDY). A MULTICENTRIC RANDOMIZED PHASE III STUDY OF THE LYSA

Lucie Oberic, MD[1*], Mathieu Puyade, MD[2*], Frederic Peyrade, MD[3*], Herve Maisonneuve, MD[4], Julie Abraham[5*], Pierre Feugier, MD[6*], Catherine Thieblemont, MD PhD[7], Gilles A. Salles, MD, PhD[8], Fontanet Bijou, MD[9], Gian-Matteo Pica, MD[10*], Philippe Ruminy, PhD[11*], Peggy Dartigues-Cuillères, MD[12*], Gandhi Damaj, MD, PhD[13], Philippe Gaulard, MD-PHD[14*], Jean-François Emile, MD, PhD[15*], Bettina Fabiani[16*], Herve Tilly, MD, PhD[17], Corinne Haioun, MD PhD[18] and Fabrice Jardin[19*]

[1]Department of Hematology, Institut Universitaire Cancerologie Toulouse-Oncopole, Toulouse, France

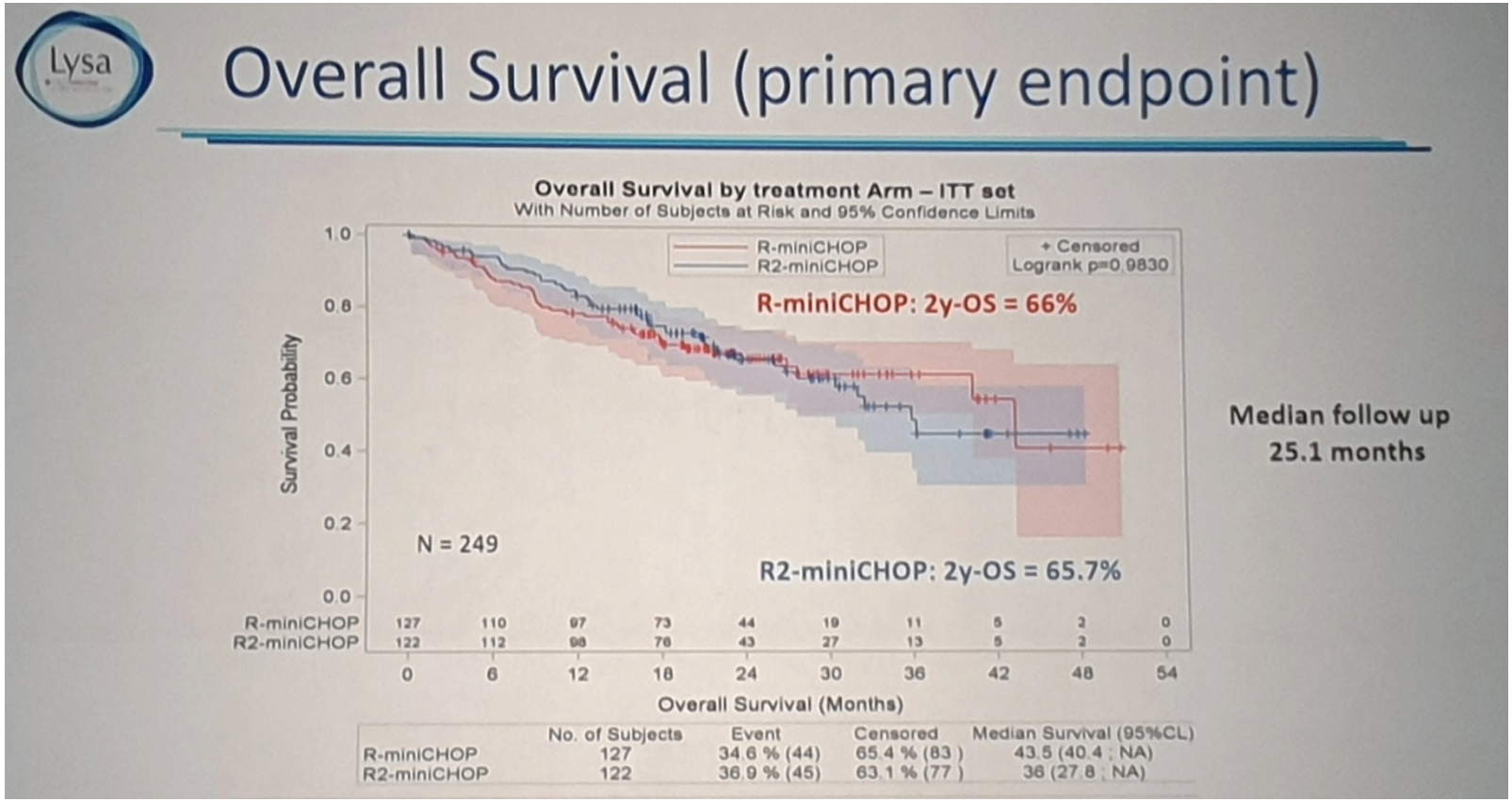
Aggressive NHL

Behandlung älter Patienten - SENIOR Studie



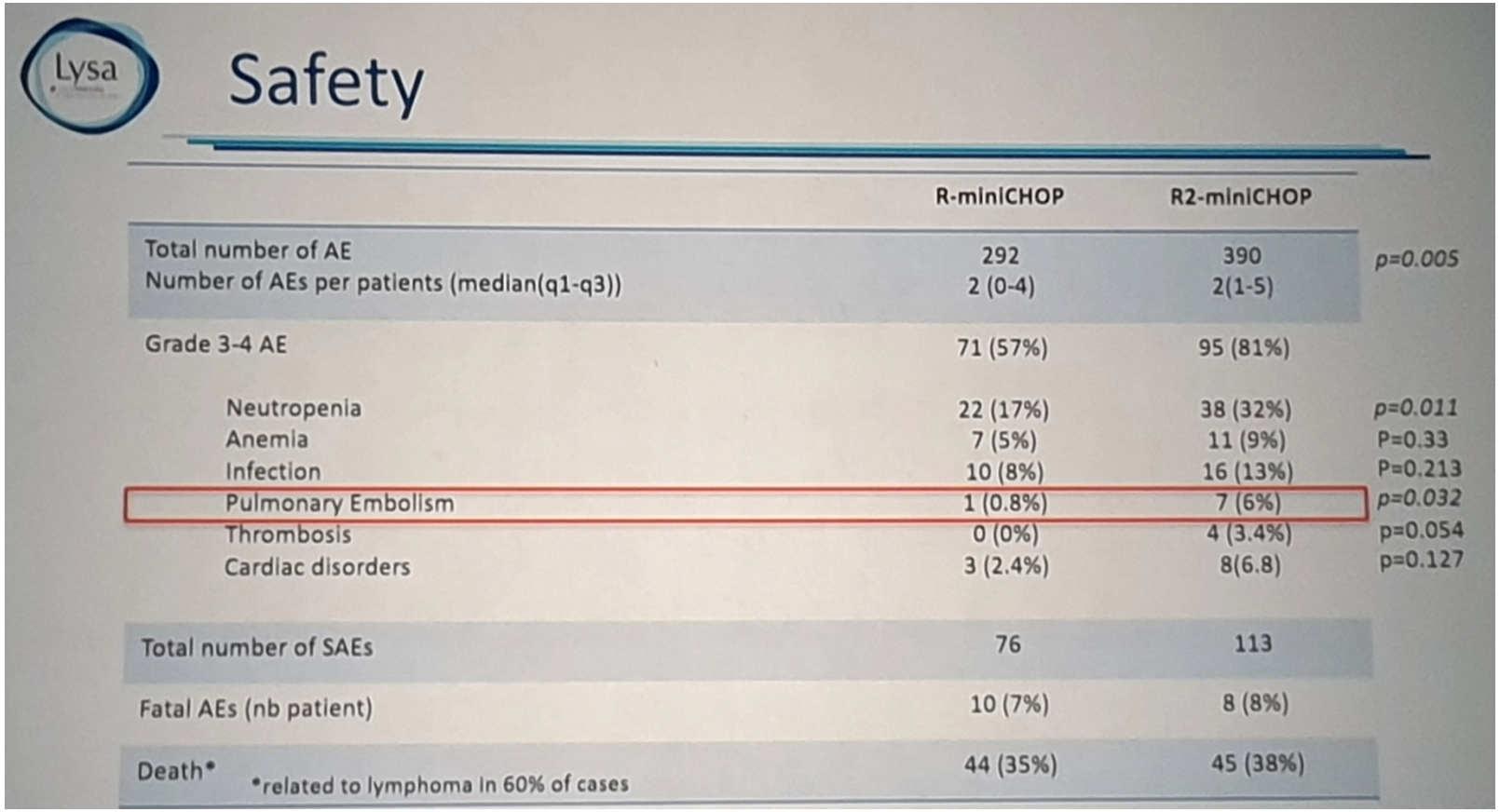
Oberic et al., ASH, Abstract # 352

Behandlung älter Patienten - SENIOR Studie



Oberic et al., ASH, Abstract # 352

Behandlung älter Patienten - SENIOR Studie



Lysa

Safety

	R-miniCHOP	R2-miniCHOP	
Total number of AE	292	390	p=0.005
Number of AEs per patients (median(q1-q3))	2 (0-4)	2(1-5)	
Grade 3-4 AE	71 (57%)	95 (81%)	
Neutropenia	22 (17%)	38 (32%)	p=0.011
Anemia	7 (5%)	11 (9%)	P=0.33
Infection	10 (8%)	16 (13%)	P=0.213
Pulmonary Embolism	1 (0.8%)	7 (6%)	p=0.032
Thrombosis	0 (0%)	4 (3.4%)	p=0.054
Cardiac disorders	3 (2.4%)	8(6.8)	p=0.127
Total number of SAEs	76	113	
Fatal AEs (nb patient)	10 (7%)	8 (8%)	
Death*	44 (35%)	45 (38%)	

*related to lymphoma in 60% of cases

Oberic et al., ASH, Abstract # 352

Kapitel 2

Aggressive NHL
Neue therapeutische Ansätze

#6

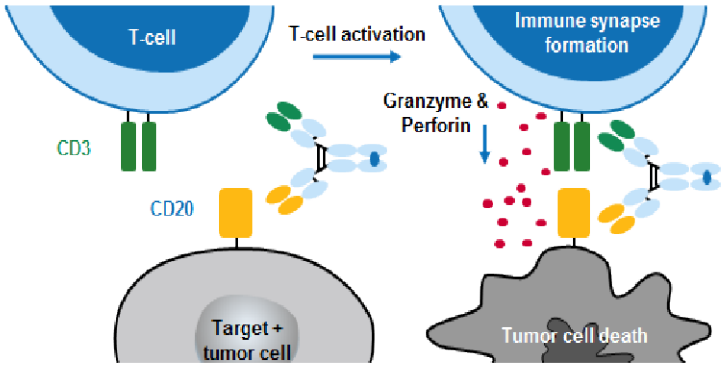
MOSUNETUZUMAB INDUCES COMPLETE REMISSIONS IN POOR PROGNOSIS NON-HODGKIN LYMPHOMA PATIENTS, INCLUDING THOSE WHO ARE RESISTANT TO OR RELAPSING AFTER CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPIES, AND IS ACTIVE IN TREATMENT THROUGH MULTIPLE LINES

Stephen J Schuster, MD[1], *Nancy L Bartlett, MD*[2*], *Sarit Assouline, MD*[3], *Sung-Soo Yoon, MD, PhD*[4], *Francesc Bosch, MD, PhD*[5], *Laurie H Sehn, MD*[6], *Chan Y. Cheah*[7], *Mazyar Shadman, MD, MPH*[8*], *Gareth P Gregory, MBBS (Hons), PhD, FRACP, FRCPA*[9], *Matthew Ku, MBBS, FRACP, FRCPA, PhD*[10*], *Michael C Wei, MD, PhD*[11], *Shen Yin, PhD*[11], *Antonia Kwan, MD, PhD, MRCPCH*[11*], *Kasra Yousefi, MSc*[12*], *Genevive Hernandez, PhD*[11*], *Chi-Chung Li, PhD*[11*], *Carol O'Hear, MD, PhD*[11*] *and Lihua E Budde, MD, PhD*[13]

[1]*Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background

- Mosunetuzumab (RG7828; BTCT4465A)
  - Full-length, fully humanized IgG1 bispecific antibody[1]
  - Redirects T cells to engage and eliminate B cells; T-cell activation, cytokine elevation and increase in TILs observed (**Hernandez et al. ASH 2019 P-1585**)
  - No ex-vivo T cell manipulation required ('off-the-shelf' and no delay in treatment)



- GO29781
  - Phase I/Ib dose-escalation and expansion study in heavily pre-treated R/R B-cell NHL
  - Cycle 1 step-up dosing: mitigates CRS, allowing dose escalation to maximize therapeutic potential[2,3]
- We report data for 270 R/R B-cell NHL pts, including 30 pts with prior CAR-T

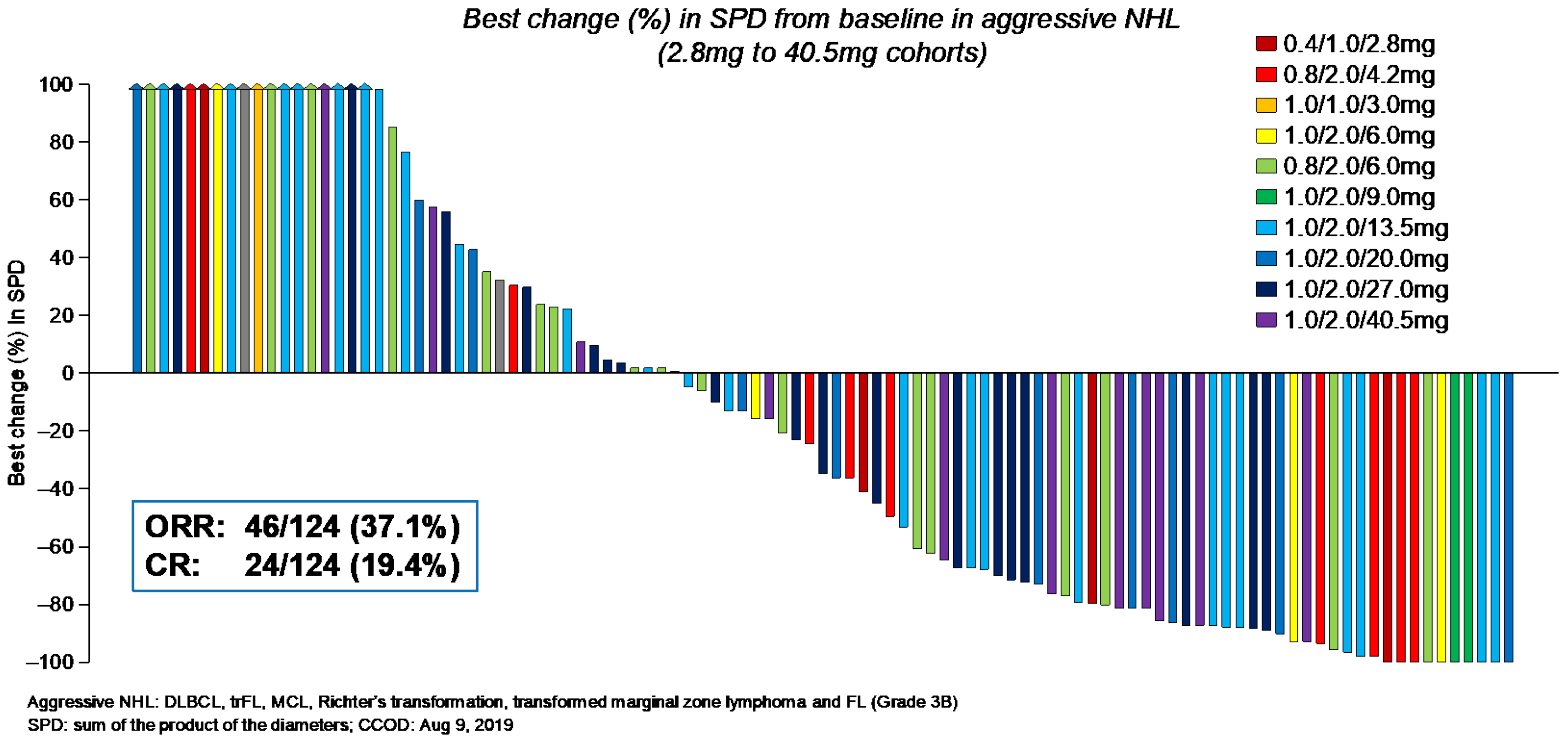
Registry number: NCT02500407

CRS, cytokine release syndrome; NHL, non-Hodgkin lymphoma; pts, patients; R/R, relapsed or refractory; TILs, tumor-infiltrating lymphocytes

1. Sun et al. Sci Transl Med 2015
2. Budde et al. ASH 2018; 3 Bartlett et al. ASCO 2019

Schuster et al., ASH, Abstract # 6

Objective response rate in aggressive NHL



Aggressive NHL: DLBCL, trFL, MCL, Richter's transformation, transformed marginal zone lymphoma and FL (Grade 3B)
SPD: sum of the product of the diameters; CCOD: Aug 9, 2019

Schuster et al., ASH, Abstract # 6

Response rates and duration in aggressive NHL

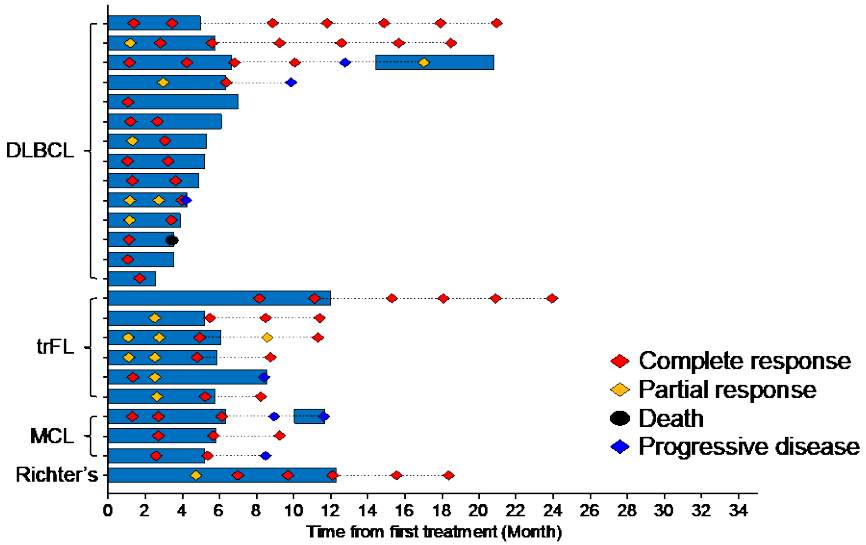
Investigator-assessed best objective response (pooled data from 2.8mg to 40.5mg cohorts)

	N*	ORR, n (%)	CR, n (%)
Aggressive NHL	124	46 (37.1%)	24 (19.4%)
DLBCL/trFL	98	37 (37.8%)	20 (20.4%)
• Refractory to anti-CD20	88/98	32 (36.4%)	18 (20.5%)
• With prior auto SCT	32/98	17 (53.1%)	11 (34.3%)

- Dose optimization is ongoing
- Increased efficacy in pts with higher exposure to mosunetuzumab, as measured by CD20 receptor occupancy (RO%)

Li et al. ASH 2019 P-1285

Time on treatment and duration of response among aggressive NHL complete responders



- **17 CR pts (70.8%) remain in remission (up to 16 months off treatment)**

*efficacy-evaluable pts: pts who were enrolled for at least 3 months, or had response data available at any time, or discontinued treatment for any cause; CCOD: Aug 9, 2019

Schuster et al., ASH, Abstract # 6

CRS adverse events

	CRS[1]	
	Safety evaluable pts (N=270)	*Prior CAR-T pts (n=30)*
Any Grade	78 (28.9%)	8 (26.7%)
Gr 1	54 (20.0%)	6 (20.0%)
Gr 2	21 (7.8%)	1 (3.3%)
Gr 3	3 (1.1%)	1 (3.3%)
Use of tocilizumab for CRS	8 (3.0%)	1 (3.3%)
AE characteristics	• Median onset of first CRS event: Day 4 (range 1–43) • Median duration: 2 days (range 1–59) • 96.6% of CRS events resolved by the clinical cut-off date	

CCOD: Aug 9, 2019

1. Lee et al. Blood 2014

Schuster et al., ASH, Abstract # 6

Neurological adverse events (CTCAE v4.0)

	NAEs	
	Safety evaluable pts (N=270)	*Prior CAR-T pts (n=30)*
Any Grade	118 (43.7%)	13 (43.3%)
Gr 1	74 (27.4%)	7 (23.3%)
Gr 2	34 (12.6%)	3 (10.0%)
Gr 3	10 (3.7%)	3 (10.0%)
Related Gr 3	3 (1.1%)	1 (3.3%)
ICANS-like NAE	3 (1.1%)	0
Gr 1	2 (0.7%)	0
Gr 2	1 (0.4%)	0
AE characteristics	• Most common NAEs: headache (15.6%), insomnia (9.3%), dizziness (9.3%) • ICANS-like	

Diefenbach et al. ASH 2019 P-4728 (Mon, Dec 9, 2019; 18:00–20:00)

NAE, neurological adverse event, defined as any Preferred Term from the Nervous System Disorders and Psychiatric Disorders System Organ Classes; ICANS, immune effector cell-associated neurotoxicity syndrome[1]; CCOD: Aug 9, 2019

1. Lee et al. Biol Blood Marrow Transplantation 2019

Schuster et al., ASH, Abstract # 6

Kapitel 3

Aggressive NHL
CAR-T Zell Therapien

#241

PIVOTAL SAFETY AND EFFICACY RESULTS FROM TRANSCEND NHL 001, A MULTICENTER PHASE 1 STUDY OF LISOCABTAGENE MARALEUCEL (LISO-CEL) IN RELAPSED/REFRACTORY (R/R) LARGE B CELL LYMPHOMAS

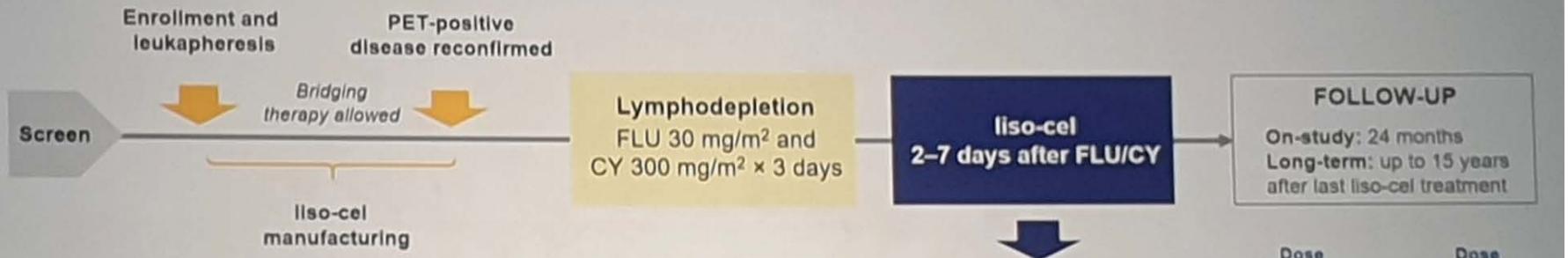
Jeremy S. Abramson, MD, MMSc[1], *Maria Lia Palomba, MD*[2], *Leo I. Gordon, MD*[3], *Matthew A. Lunning, DO, FACP*[4], *Michael L. Wang, MD*[5], *Jon E. Arnason, MD*[6], *Amitkumar Mehta, MD*[7], *Enkhtsetseg Purev, MD, PhD*[8], *David G. Maloney, MD PhD*[9], *Charalambos Andreadis, MD, MSCE*[10*], *Alison R. Sehgal, MD*[11], *Scott R. Solomon, MD*[12], *Nilanjan Ghosh, MD, PhD*[13], *Tina Albertson, MD*[14], *Jacob Garcia, MD*[14], *Ana Kostic*[14*], *Daniel Li, PhD*[14*], *Yeonhee Kim*[14*] *and Tanya Siddiqi, MD*[15*]

[1]*Massachusetts General Hospital Cancer Center, Boston, MA*

Aggressive NHL

TRANSCEND NHL 001 (NCT02631044)

Pivotal Phase 1, Multicenter, Seamless Design Study



Patient Eligibility

- LBCL after ≥2 lines of therapy
  - DLBCL NOS (de novo)
  - DLBCL NOS (transformed from FL, CLL, MZL, or other)
  - HGBCL (double/triple hit)
  - PMBCL
  - FL3B
- Prior HSCT allowed (auto/allo)
- ECOG PS of 0–2
- Patients with secondary CNS lymphoma were eligible
- CrCl >30 mL/min/1.73 m²
- LVEF ≥40%
- No lower threshold for ALC, ANC, platelets, or hemoglobin

End Points

Primary

- Adverse events, ORR by IRC

Secondary

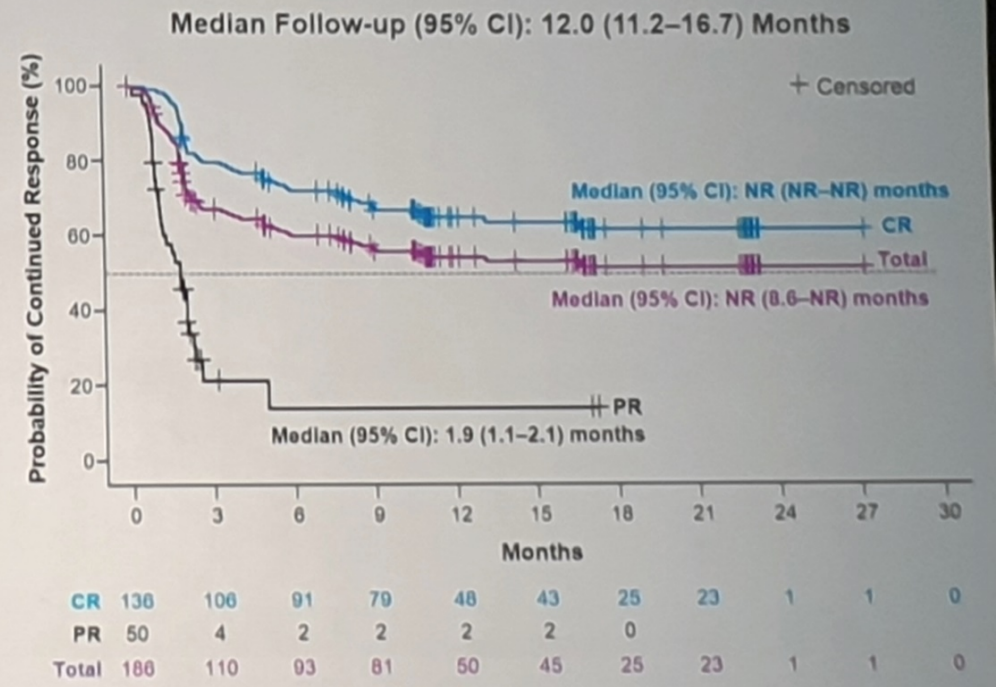
- CR rate by IRC, duration of response, PFS, OS, PK

Abramson et al., ASH, Abstract # 241

Aggressive NHL

Response and Durability by IRC Assessment

Efficacy-Evaluable Patients (N=256)	
ORR (95% CI)	73% (67–78)
CR rate (95% CI)	53% (47–59)
Time to first CR or PR, median (range), months	1.0 (0.7–8.9)
DOR at 6 months (95% CI), %	60.4 (52.6–67.3)
DOR at 12 months (95% CI), %	54.7 (46.7–62.0)



Efficacy among patients who received nonconforming product (n=25) was similar to those who received liso-cel

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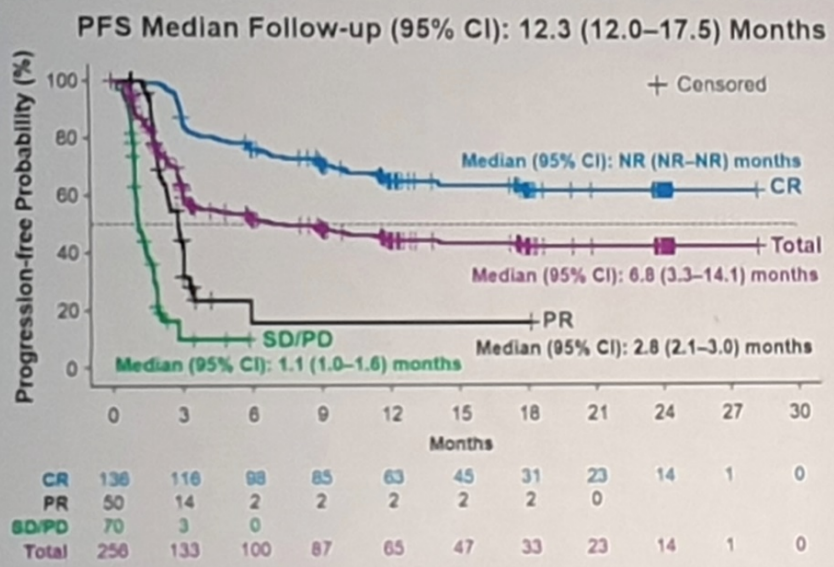
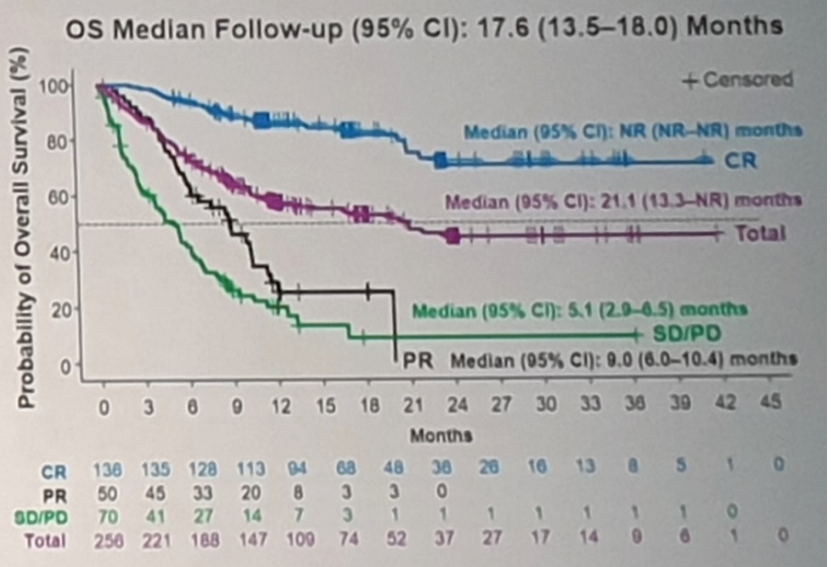
CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PR, partial response.

Abramson et al., ASH, Abstract # 241

Aggressive NHL

PFS and OS by Objective Response





6-month PFS (95% CI), %	
All patients	51.4 (44.6–57.7)
Patients with BOR of CR	76.1 (67.9–82.4)
12-month PFS (95% CI), %	
All patients	44.1 (37.3–50.7)
Patients with BOR of CR	65.1 (56.1–72.7)

6-month OS (95% CI), %	
All patients	74.7 (68.9–79.6)
Patients with BOR of CR	94.1 (88.6–97.0)
12-month OS (95% CI), %	
All patients	57.9 (51.3–63.8)
Patients with BOR of CR	85.5 (78.2–90.5)

CI, confidence interval; CR, complete response; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Abramson et al., ASH, Abstract # 241

Zusammenfassung

- R-CHOP bzw. R-CHOP-ähnliche Regime bleiben der Standard in der Erstlinientherapie bei Patienten mit DLBCL
- Vielversprechende Ergebnisse durch bispezifsche Antikörper bei Patienten mit rezidivierter/refraktärer Erkrankung
- Vielsprechende Ergebnisse durch ein neues CAR T-Zell Produkt zur Behandlung von Patienten mit rezidiviertem/refraktärem DLBCL

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2019

Für den Inhalt verantwortlich:

Prof. Dr. med. Georg Lenz

Direktor der Medizinischen Klinik A • Universitätsklinikum Münster

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