Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML-Experten berichten

63rd ASH Meeting 2021

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

Prof. Dr. med. Peter Borchmann
Klinik I für Innere Medizin | Uniklinik Köln

Diffus großzelliges B-Zell-Lymphom (DLBCL)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2021 wird in Kooperation mit sechs unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Anstellungsverhältnis, Führungsposition	na
Beratungs-/ Gutachtertätigkeit	Novartis, Takeda, Celgene, MSD, Gilead, Oxford Therapeutics
Besitz von Geschäftsanteilen, Aktien oder Fonds	na
Patent, Urheberrecht, Verkaufslizenz	na
Honorare	Takeda, Novartis, Roche, MSD, BMS, Gilead, Incyte
Finanzierung wissenschaftlicher Untersuchungen	Novartis, Takeda, MSD
Andere finanzielle Beziehungen	nana
Immaterielle Interessenkonflikte	

Kapitel 1

Kann R-CHOP verbessert werden, indem Vincristin durch Polatuzumab Vedotin ersetzt wird?

LBA 1 – The POLARIX Study: Polatuzumab Vedotin with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (pola-R-CHP) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) Therapy in Patients with Previously Untreated Diffuse Large B-Cell Lymphoma

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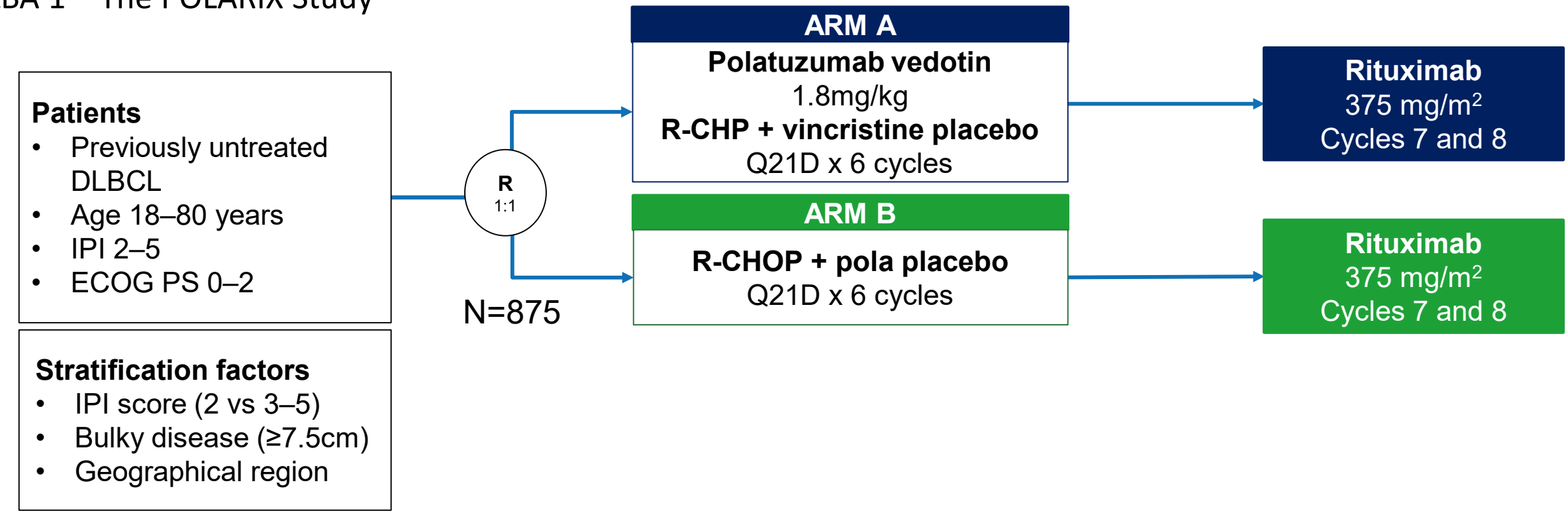
Hervé Tilly, MD1, Franck Morschhauser, MD, PhD2*, Laurie H. Sehn, MD3, Jonathan W. Friedberg, MD 4, Marek Trněny, MD5, Jeff P. Sharman, MD6, Charles Herbaux, MD7, John M. Burke, MD8, Matthew Matasar, MD9,10, Shinya Rai, MD, PhD11*, Koji Izutsu, MD, PhD12*, Neha Mehta-Shah, MD13, Lucie Oberic, D14*, Adrien Chauchet, MD15*, Wojciech Jurczak, PhD, MD16, Yuqin Song, MD17*, Richard Greil, MD18, Larysa Mykhalska, MD19*, Juan Miguel Bergua Burgues, MD20*, Matthew C. Cheung, MD21, Antonio Pinto, MD22*, Ho-Jin Shin, MD, PhD23*, Greg Hapgood, MD, PhD24*, Eduardo Munhoz, MD25*, Paul brisqueta Costa, MD, PhD26*, Jyh-Pyng Gau, MD27*, Jamie Hirata, PharmD28, Yanwen Jiang, PhD28*, Mark Yan, PhD29*, Calvin Lee, MD28, Christopher R. Flowers, MD30 and Gilles Salles, MD, PhD31

Kann R-CHOP verbessert werden, indem Vincristin durch Polatuzumab Vedotin ersetzt wird?

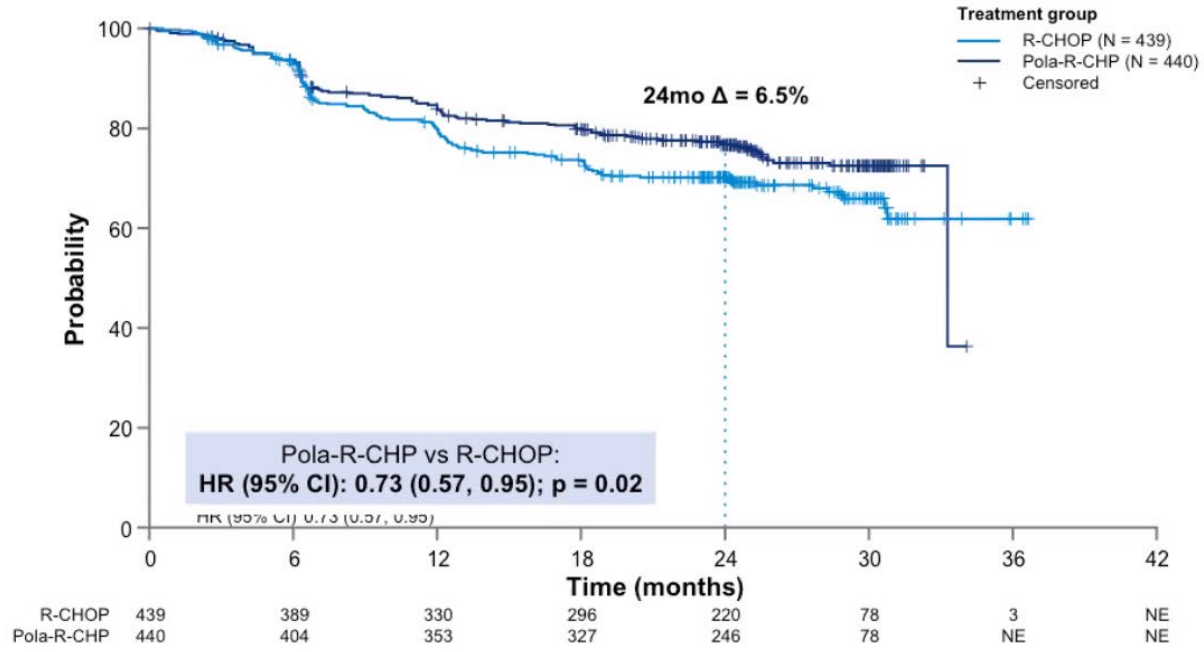
LBA 1 – The POLARIX Study



Study population	R-CHOP	Pola-R-CHP	Total
Intention-to-treat (as randomised population)	439	440	879
Safety evaluable (as treated population)	438**	435	873

Polarix Primary Endpoint PFS

Investigator-assessed PFS – ITT population



At the CCOD of June 28 2021, 241 PFS events were observed

- Minimum follow up: 24 months
- Median duration on study: 27.9 months

Gesamtüberleben

Pola+R-CHP vs R-CHOP:
Number of events: 53 (12%) vs 57 (13%)
HR (95% CI): 0.94 (0.65, 1.37); p = 0.75

Polarix Safety

Adverse event (AE) summary, n (%)	R-CHOP (N = 438)	Pola-R-CHP (N = 435)
Any grade AE	431 (98.4)	426 (97.9)
Grade 3–4 AE	252 (57.5)	251 (57.7)
Grade 5 AE	10 (2.3)	13 (3.0)
Serious AE	134 (30.6)	148 (34.0)
Related to any study drug	86 (19.6)	112 (25.7)
AE leading to treatment discontinuation		
Any study treatment	29 (6.6)	27 (6.2)
Polatuzumab vedotin/vincristine	22 (5.0)	19 (4.4)
AE leading to dose reduction		
Any study treatment	57 (13.0)	40 (9.2)
Polatuzumab vedotin/vincristine	45 (10.3)	24 (5.5)
AE leading to dose interruption		
Any study treatment	111 (25.3)	103 (23.7)
Polatuzumab vedotin/vincristine	60 (13.7)	61 (14.0)

- *Pola-R-CHP is comparable with R-CHOP*
- *Fewer dose reductions were observed in the pola-R-CHP arm*

Authors' Conclusion:

"The pola-R-CHP combination demonstrated a 27% reduction in the relative risk of disease progression, relapse, or death compared with R-CHOP, with a similar safety profile in the first-line treatment of patients with DLBCL."

Kapitel 2

Ist die intravenöse HD-MTX Prophylaxe für Hochrisiko-DLCBL Patienten eigentlich wirksam und sicher?

Ist die intravenöse HD-MTX Prophylaxe für Hochrisiko-DLCBL Patienten eigentlich wirksam und sicher?

181 – High-Dose Methotrexate Is Not Associated with Reduction in CNS Relapse in Patients with Aggressive B-Cell Lymphoma: An International Retrospective Study of 2300 High-Risk Patients

Katharine Louise Lewis, BMBS, FRCPath, MRCPath1,2, Lasse H. Jakobsen, MSc, PhD3*, Diego Villa, M PH, FRCPC4, Sabela Bobillo, MD, PhD5*, Karin Ekstroem Smedby, MD, PhD6*, Kerry J. Savage, MD, MSc, FRCPC4, Toby A. Eyre7*, Kate Cwynarski8*, Paris L Caporn, BBiomedSc9*, Joan Van Zyl, BBioMedSc9*, Magdalena Klanova, MD, PhD10,11*, Marek Trněný, MD, Prof12,13, Robert Puckrin, MD FRCPC14*, Douglas A. Stewart, MD, FRCPC15,16, Mark J Bishton, MB ChB, PhD17*, Christopher P. Fox17*, Aung M Tun, MD18*, Gita Thanarajasingam, MD18, Faouzi Djebbari19*, Erel Joffe, MD, MSc20, Sandra Eloranta, PhD21*, Sara Harrysson, MD21*, Laurie H. Sehn, MD22, Seth M Maliske, MD23, Kittika Poonsombudlert, MD24, Xiao Guo, MD25*, Greg Hapgood, MD, PhD25*, Kate Manos26*, Eliza Hawkes, MD27, Jahanzaib Khwaja28*, Adrian Minson, MBBS29*, Michael Dickinson, MBBS29,30, Andreas Kiesbye Øvlisen, MD3*, Gareth P Gregory, MBBS PhD31, Michael Gilbertson, MBBS (Hons) FRACP FRCPA32*, Isaac T Streit, MSc4*, Hamish W Scott33*, Matthew Ku34,35, Sanjay de Mel, BSc (Hons) BM (Hons), MRCP(UK), FRCPath36*, Kar Ying Yong, MBBS, MRCP37*, Liu Xin, M.A. in Counselling and Guidance, MSc in Biomedical Engineering37*, Mridula Mokoonlall, MBBS38*, Dipti Talaulikar, PhD, FRACP, FRCPA, MBBS38, Nicholas L McVilly, MBBS39*, Anna Johnston, MBBS, FRACP, FRCPA39,40*, Matthew J Brunner, MD41*, Priyanka A Pophali, MD42,43, Matthew Maurer, MS, DMSc44*, Tarec Christoffer El-Galaly, MD3 and Chan Yoon Cheah2,9,45

Ist die intravenöse HD-MTX Prophylaxe für Hochrisiko-DLCBL Patienten eigentlich wirksam und sicher?

181 – High-Dose Methotrexate Is Not Associated with Reduction in CNS Relapse in Patients with Aggressive B-Cell Lymphoma: An International Retrospective Study of 2300 High-Risk Patients

	Alle Patienten (n = 2300)		CR Patienten (n = 1455)	
	Kein HD-MTX (n = 1890)	HD-MTX (n = 410)	Kein HD-MTX (n = 1171)	HD-MTX (n = 284)
DLBCL [%, n] HGBCL mit MYC + BCL2/BCL6 [%, n]	93,5 (1768) 6,5 (122)	90,2 (370) 9,8 (40)	94,2 (1103) 5,8 (68)	90,5 (257) 9,5 (27)
CNS-IPI 4-6 [%, n]	89,2 (2052)		87,0 (1267)	
B-Symptome [%, n]	54,1 (1007)	53,9 (219)	48,4 (560)	48,4 (136)
Erhöhtes LDH [%, n]	87,9 (1648)	86,5 (351)	84,8 (989)	83,7 (236)
Behandlung [%, n] a) R-CHOP, G-CHOP, R-CEOP b) DA-EPOCH-R	 94,2 (1780) 5,8 (110)	 92,2 (378) 7,8 (32)	 93,9 (1100) 6,1 (71)	 91,2 (259) 8,8 (25)
Keine ZNS Prophylaxe [%, n] HD-MTX [%, n] IT-MTX [%, n] HD-MTX + IT-MTX [%, n]	77,0 (1455) - 23,0 (435) -	- 64,6 (265) - 35,4 (145)	74,6 (873) - 25,4 (298) -	- 59,9 (170) - 40,1 (114)

Ist die intravenöse HD-MTX Prophylaxe für Hochrisiko-DLCBL Patienten eigentlich wirksam und sicher?

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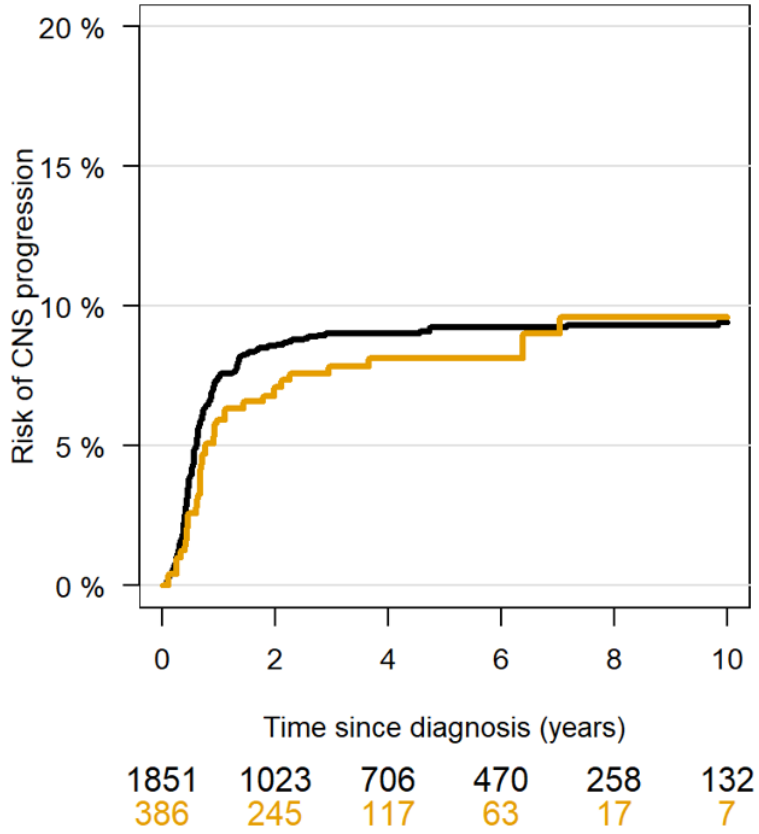
Cumulative incidence of CNS relapse: All-pts (n=2267)



Median time to CNS relapse from diagnosis:

- HD-MTX 8.5 months
- No HD-MTX 6.7 months

No HD MTX HD MTX

Cumulative incidence of CNS relapse All-pts: adjusted for LDH, age, extranodal

Ist die intravenöse HD-MTX Prophylaxe für Hochrisiko-DLCBL Patienten eigentlich wirksam und sicher?

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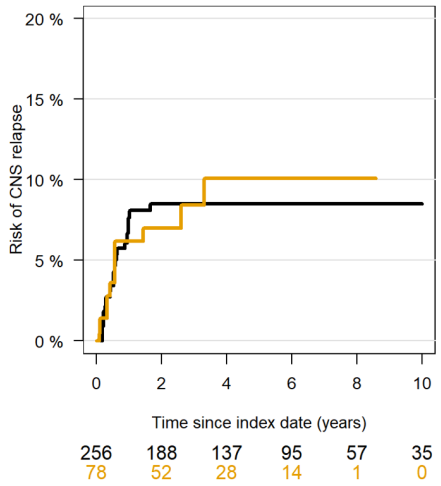
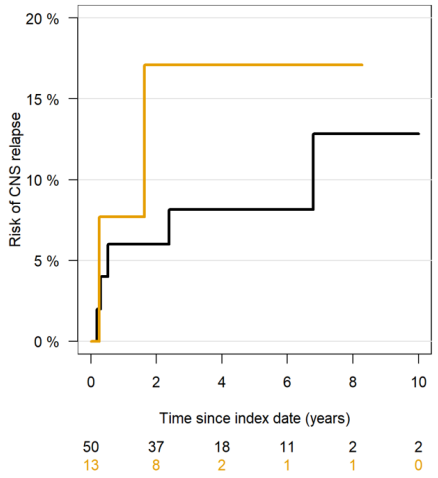
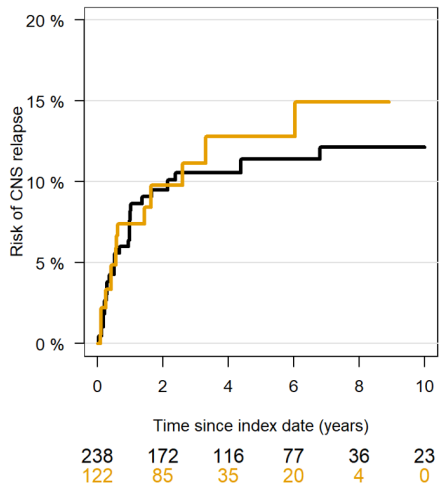
CNS-IPI = 5



CNS-IPI = 6



CNS-IPI = 6 + extras*



No HD MTX HD MTX

*extras = patients with specific high risk extranodal sites (testis, breast, renal, adrenal)

Cumulative incidence of CNS relapse All pts: adjusted for LDH, age, extranodal

SUMMARY AND CONCLUSIONS

Diese größte und sehr ordentliche retrospektive Analyse für die Wirksamkeit der iv HD-MTX Prophlyaxe zeigt

- Bestätigte (!) Gesamtinzidenz ZNS-Rezidive im HR Kollektiv = 9%

➢ Keine Verminderung von gesamten SCNS-Rezidiv Raten oder CR-Patienten nach kurativer Therapie

➢ Wahrscheinlich kein Zusammenhang mit klinisch relevanter Reduktion der SCSN-Rezidiv-Raten

Kapitel 3

Erstes frühes Rezidiv oder Progress unter der Erstlinientherapie eines aggressiven großzelligen B-Zell Lymphoms (LBLC) bei Hochdosistherapie-fähigen Patienten:

Ist die gegen CD19 gerichtete CAR T-Zelltherapie der Hochdosistherapie überlegen?

Ist die gegen CD19 gerichtete CAR T-Zelltherapie der Hochdosistherapie überlegen?

LBA 6 – Tisagenlecleucel Vs Standard of Care As Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III Belinda Study

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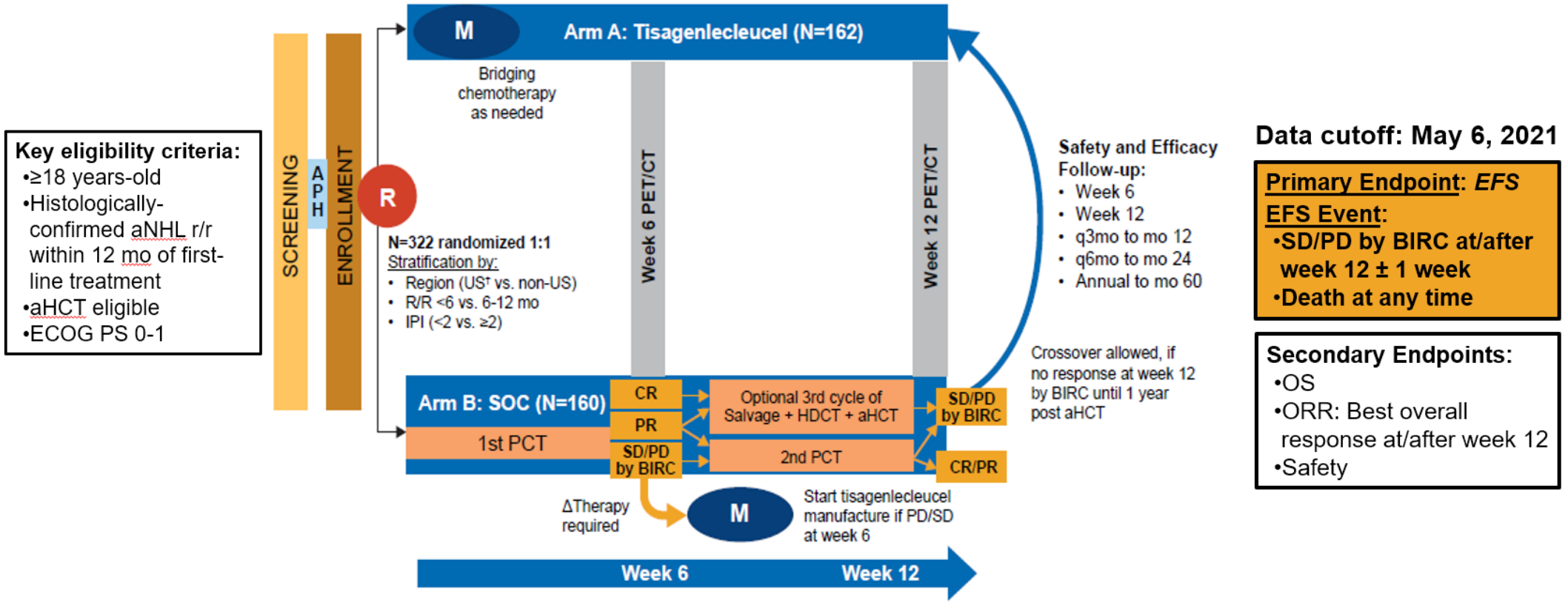
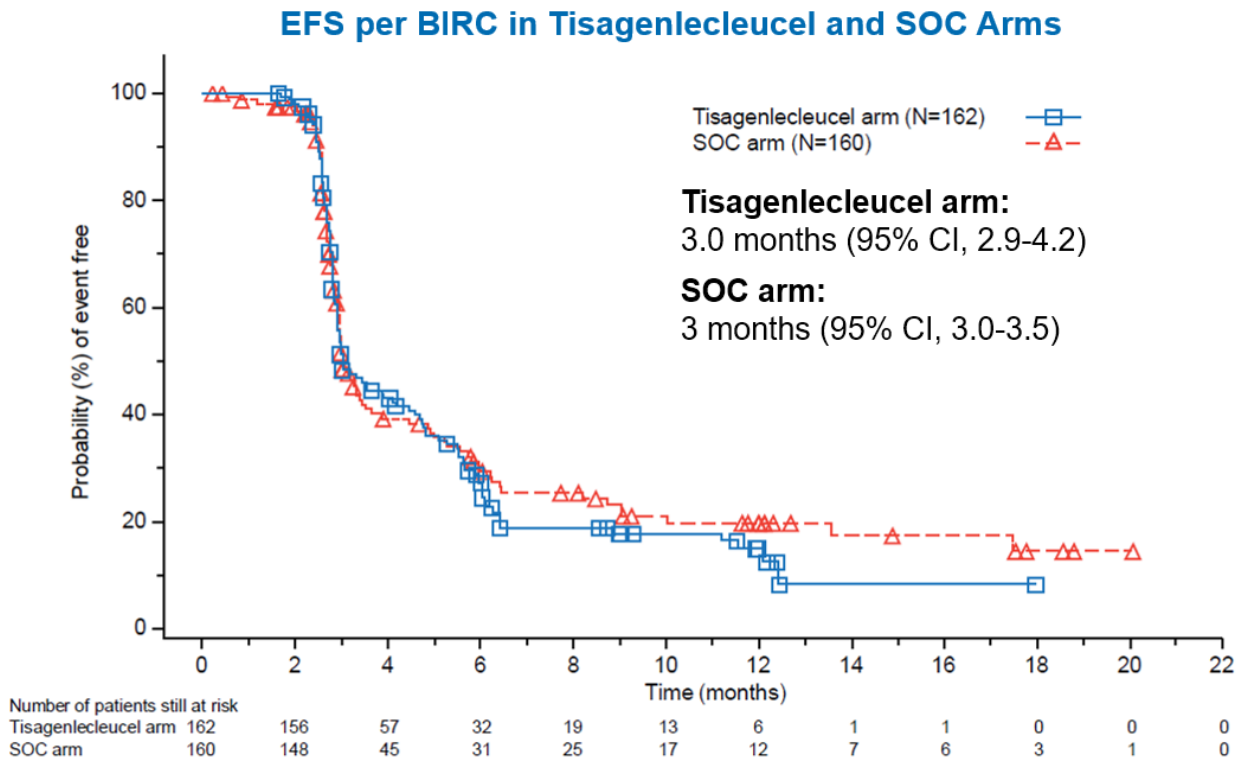
Ist die gegen CD19 gerichtete CAR T-Zelltherapie der Hochdosistherapie überlegen?

– BELINDA: bridging allowed, cross-over allowed, primary endpoint EFS



Study outcomes

Wirksamkeit	Arm A (n=162) Tisa-Cel	Arm B (n=160) SOC
Progression nach 6 Wo [%]	26	14
Medianes EFS [Mo]	3	3
Gesamt Ansprechrate (ORR) Wo 12 [%]	46	43
Vollständige Ansprechrate (CRR) [%]	28	28



- ASH 2021: Locke F.L. *et al.,* 2: Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel (Axi-Cel) Versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

SUMMARY AND CONCLUSIONS

BELINDA als erste negative randomisierte, globale, multizentrische Phase-3-Studie zu Tisa-cel vs. 2L SOC bei R/R LBCL

- Tisa-cel in der Zweitlinientherapie bei R/R aNHL Patienten führte nicht zu längerem ereignisfreiem Überleben als unter SOC

- Mögliche Einflussfaktoren sind:
  - das Studiendesign und die EFS Definition
  - das optionale PCT Bringing bei Arm A
  - der optionale PCT-Wechsel in Arm B

Ist die gegen CD19 gerichtete CAR T-Zelltherapie der Hochdosistherapie überlegen?

2 – Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel (Axi-Cel)

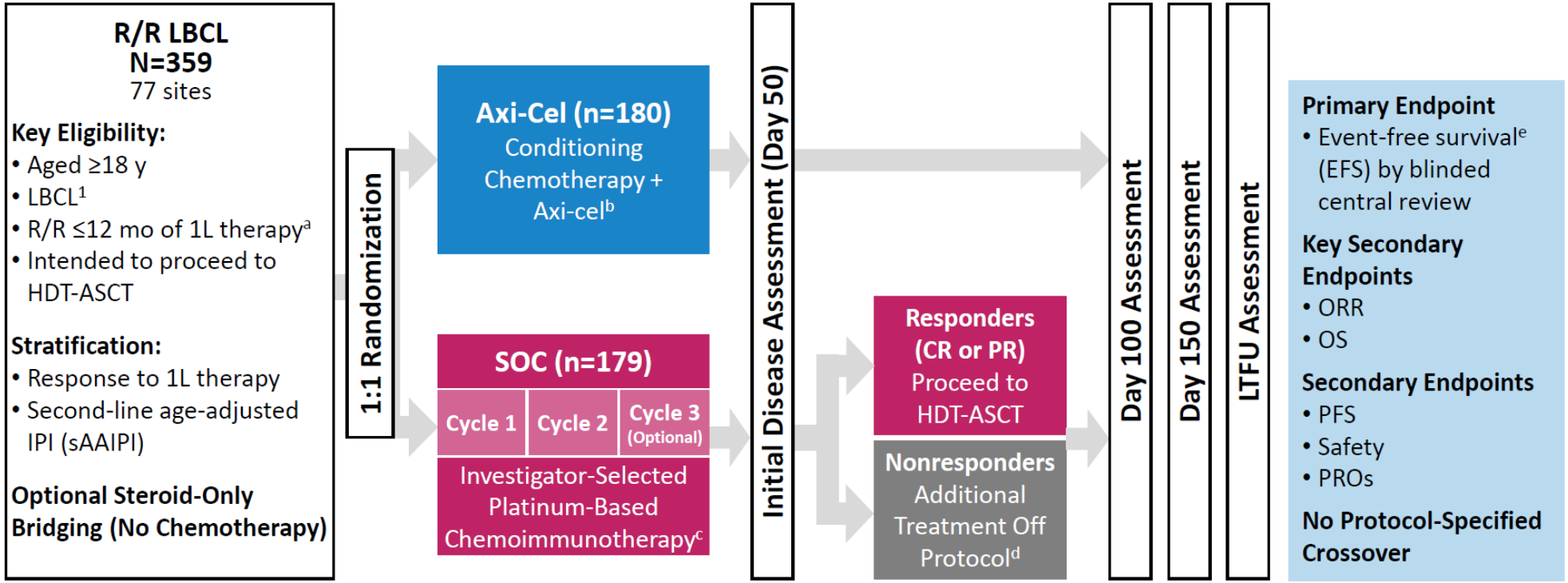
Versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

Frederick L. Locke, MD1, David B. Miklos, MD, PhD2, Caron Jacobson, MD3, Miguel-Angel Perales, MD4, Marie Jose Kersten, MD, PhD5, Olalekan O. Oluwole, MBBS, MPH6, Armin Ghobadi, MD7*, Aaron P. Rapoport, MD8, Joseph P. McGuirk, DO9, John M. Pagel, MD, PhD10, Javier Munoz, MD, MS, MBA, FACP11*, Umar Farooq, MD12, Tom Van Meerten, MD, PhD13*, Patrick M. Reagan, MD14, Anna Sureda15, Ian W. Flinn, MD, PhD16, Peter Vandenberghe, MD, PhD17, Kevin Song, MD, FRCPC18, Michael Dickinson, MBBS19, Monique C. Minnema, MD20, Peter A. Riedell, MD21, Lori A. Leslie, MD22*, Sridhar Chaganti, MD23*, Yin Yang, MS, MD24*, Simone Filosto, PhD24*, Marco Schupp, MD24*, Christina To, MD24*, Paul Cheng, MD, PhD24, Leo I. Gordon, MD25 and Jason R. Westin, MD26

Study Design

ZUMA-7, no bridging, no cross-over (out of protocol 56% CARs in SOC), primary endpoint EFS, HDCT in SOC 36%

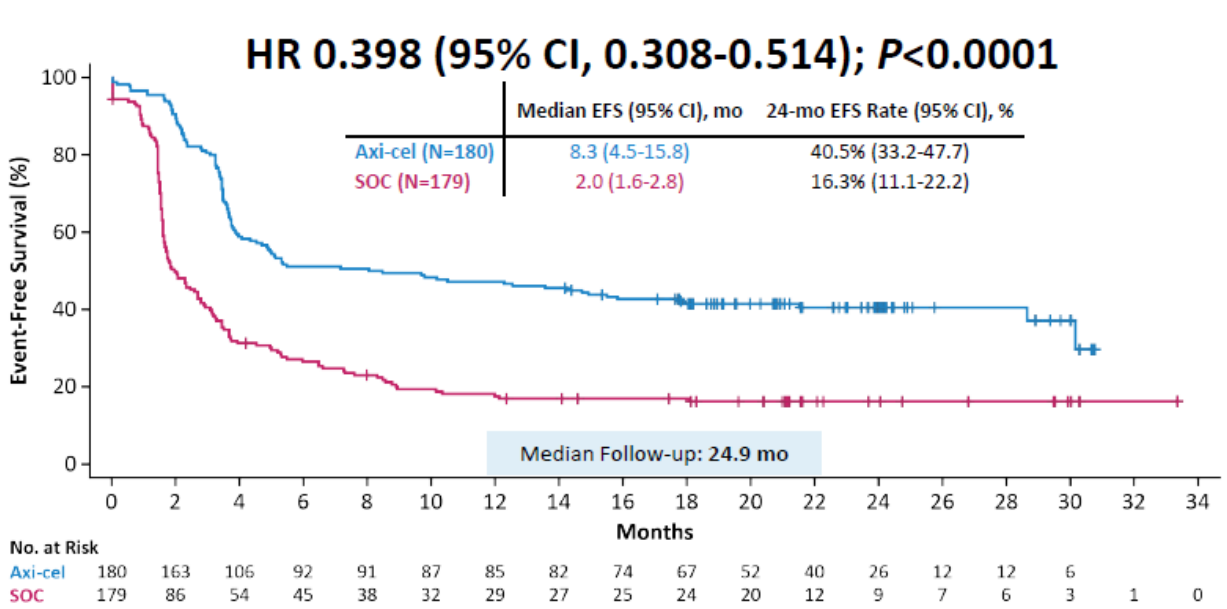
Median FU 24.9 m, median age around 60 y, LDH Y UNL around 50%, refractory disease around 74%

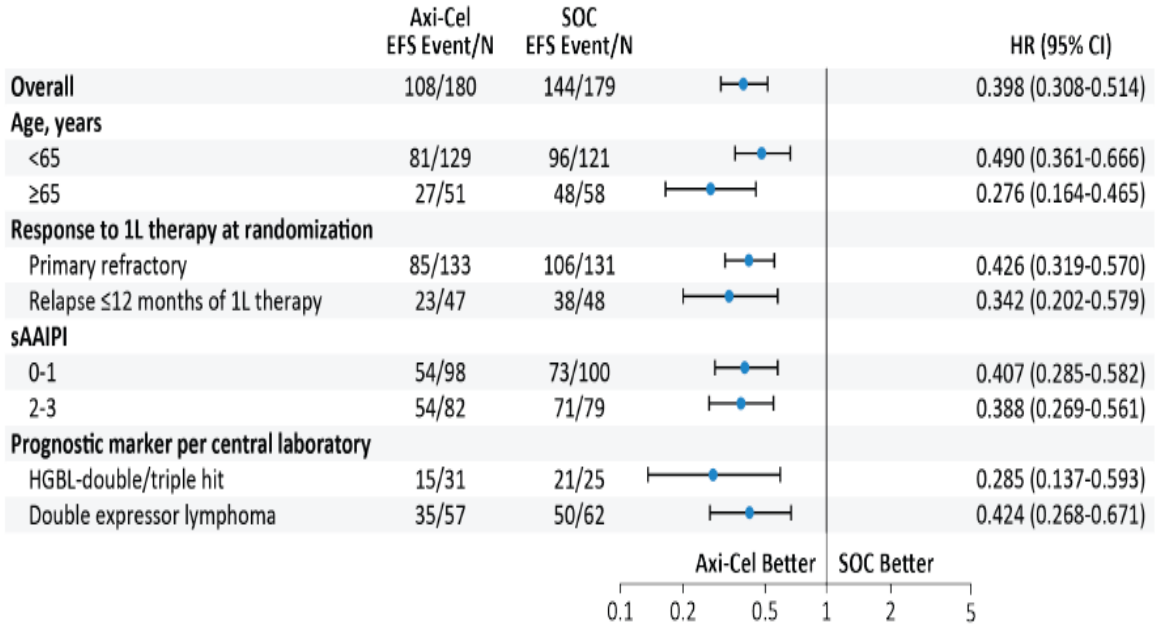


[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] 56% of patients received subsequent cellular immunotherapy. [e] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

1. Swerdlow SH, et al. *Blood.* 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

Study outcomes





Kaplan-Meier-Schätzungen 24 Monate EFS [%]	41	16		
Median OS [Mo]	NR	35,1	HR 0,730	P=0,027

- ASH 2021: Locke F.L. *et al.,* 2: Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel (Axi-Cel) Versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

SUMMARY AND CONCLUSIONS

ZUMA-7 als erste randomisierte, globale, multizentrische Phase-3-Studie zu axi-cel vs. 2L SOC bei R/R LBCL

Axi-cel zeigt Überlegenheit gegenüber dem SOC

- Signifikante und klinisch relevante Verbesserung des EFS
- Dauerhafter Unterschied im EFS: 41% versus 16% nach 2 Jahren
- Doppelt so hohen CR-Rate

Authors´ conclusions: new standard of care for relapsed DLBCL patients

Ist die gegen CD19 gerichtete CAR T-Zelltherapie der Hochdosistherapie überlegen?

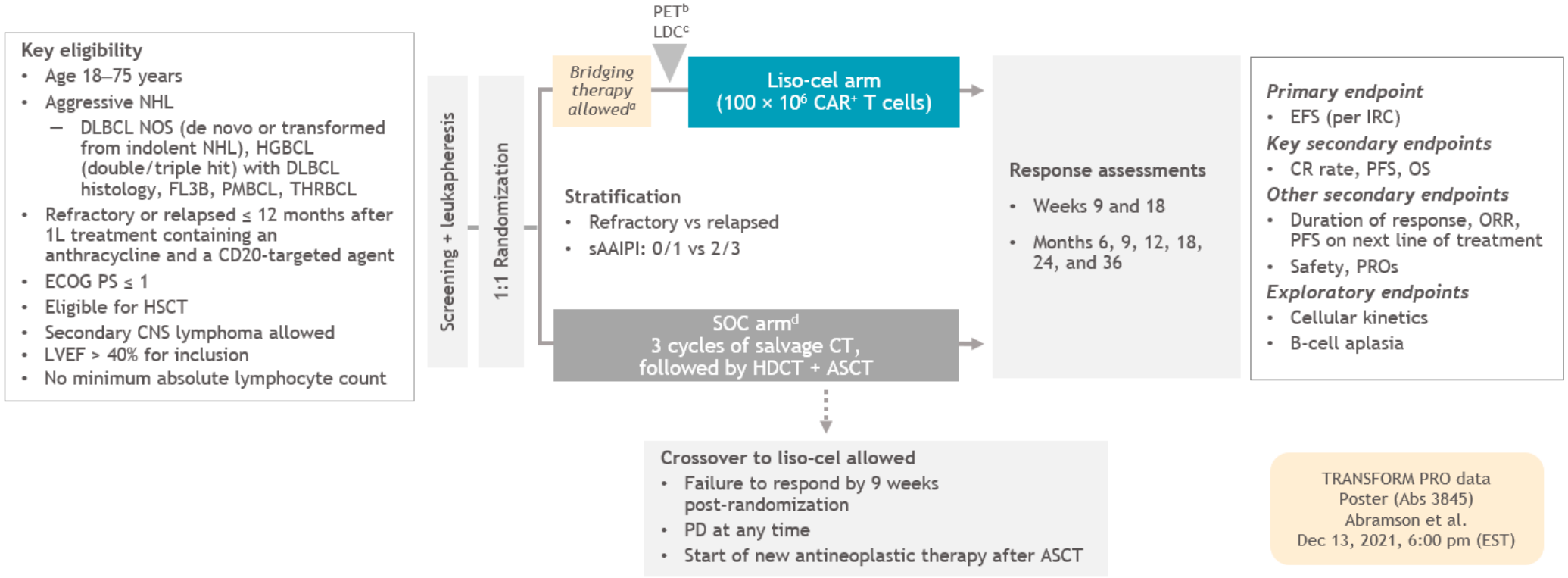
91 – Lisocabtagene Maraleucel (liso-cel), a CD19-Directed Chimeric Antigen Receptor (CAR) T Cell Therapy, Versus Standard of Care (SOC) with Salvage Chemotherapy (CT) Followed By Autologous Stem Cell Transplantation (ASCT) As Second-Line (2L) Treatment in Patients (Pts) with Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL): Results from the Randomized Phase 3 Transform Study

Manali Kamdar, MD1, Scott R. Solomon, MD2, Jon E. Arnason, MD3, Patrick B. Johnston, M.D., Ph.D.4, Bertram Glass, MD5*, Veronika Bachanova, MD, PhD6, Sami Ibrahimi, MD7, Stephan Mielke, MD8, Pim G.N.J. Mutsaers, MD, PhD9*, Francisco J. Hernandez-Ilizaliturri, MD10, Koji Izutsu, MD, PhD11*, Franck Morschhauser, MD, PhD12,13*, Matthew A. Lunning, DO, FACP14, David G. Maloney, MD, PhD15, Alessandro Crotta, MD16*, Sandrine Montheard, MS17*, Alessandro Previtali, MSc16*, Lara Stepan, BS18*, Ken Ogasawara, PhD, MPH19*, Timothy Mack, PhD18* and Jeremy S. Abramson, MD20

Study Design

TRANSFORM, bridging allowed (63%), cross-over allowed (47 patients (51%) CARs in SOC), primary endpoint EFS, HDCT in SOC 42%

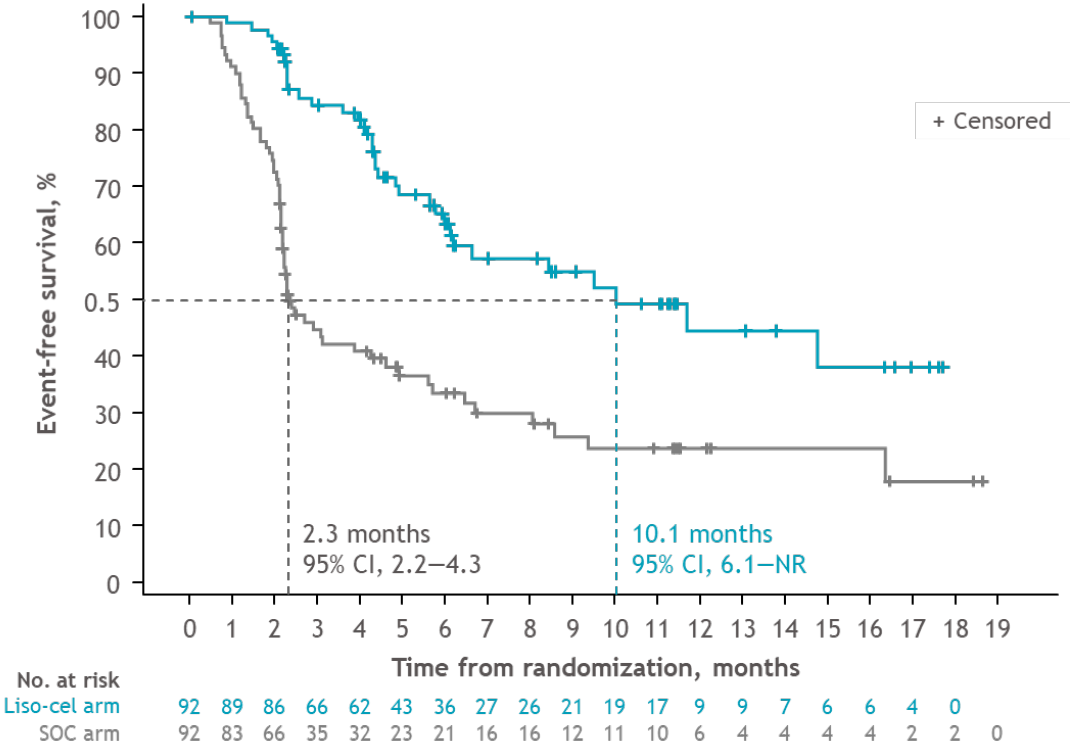
Median FU 6.2 m, median age around 60 y, LDH > 500 around 12.5%, refractory disease around 74%



TRANSFORM PRO data
Poster (Abs 3845)
Abramson et al.
Dec 13, 2021, 6:00 pm (EST)

- EFS is defined as time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first

Study outcomes



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	**0.349** (0.229—0.530)	
	***P* < 0.0001**	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0—74.7	23.0—43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4—59.6	13.4—34.1

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

Median OS [Mo]	NR	16,4	0.509 (0.258—1.004)	P = 0.0257

- ASH 2021: Locke F.L. *et al.,* 2: Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel (Axi-Cel) Versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

SUMMARY AND CONCLUSIONS

TRANSFORM als zweite positive randomisierte, globale, multizentrische Phase-3-Studie zu Liso-cel vs. 2L SOC bei R/R LBCL

Statistisch signifikante und klinisch bedeutsame Verbesserung von EFS, CR-Rate, PFS

Bei Patienten mit R/R LBCL und ≤ 12 Monate nach 1L

Authors´ conclusions:

“In this phase 3, randomized, controlled trial, liso-cel improved outcomes versus salvage CT followed by HDCT and ASCT and exhibited a favorable safety profile, providing support for liso-cel as a potential new standard of care for 2L treatment in patients with R/R LBCL”

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2021

Für den Inhalt verantwortlich:

Prof. Dr. med. Peter Borchmann

Uniklinik Köln

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

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