Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

64th ASH Meeting 2022

New Orleans & virtuell

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Primäre ZNS-Lymphome (PZNSL)

Offenlegung potentieller Interessenskonflikte

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

Anstellungsverhältnis, Führungsposition	-
Beratungs-/ Gutachtertätigkeit	-
Besitz von Geschäftsanteilen, Aktien oder Fonds	-
Patent, Urheberrecht, Verkaufslizenz	-
Honorare	Riemser Pharma
Finanzierung wissenschaftlicher Untersuchungen	Riemser Pharma, Roche Pharma
Andere finanzielle Beziehungen	-
Immaterielle Interessenkonflikte	-

Kapitel 1

Ist die konsolidierende Hochdosistherapie und autologe Stammzelltransplantation der konventionellen Chemotherapie in der Erstlinienbehandlung jüngerer PZNSL Patient*innen überlegen?

LBA-3 - Effects on Survival of Non-Myeloablative Chemoimmunotherapy Compared to High-Dose Chemotherapy Followed By Autologous Stem Cell Transplantation (HDC-ASCT) As Consolidation Therapy in Patients with Primary CNS Lymphoma - Results of an International Randomized Phase III Trial (MATRix/IELSG43)

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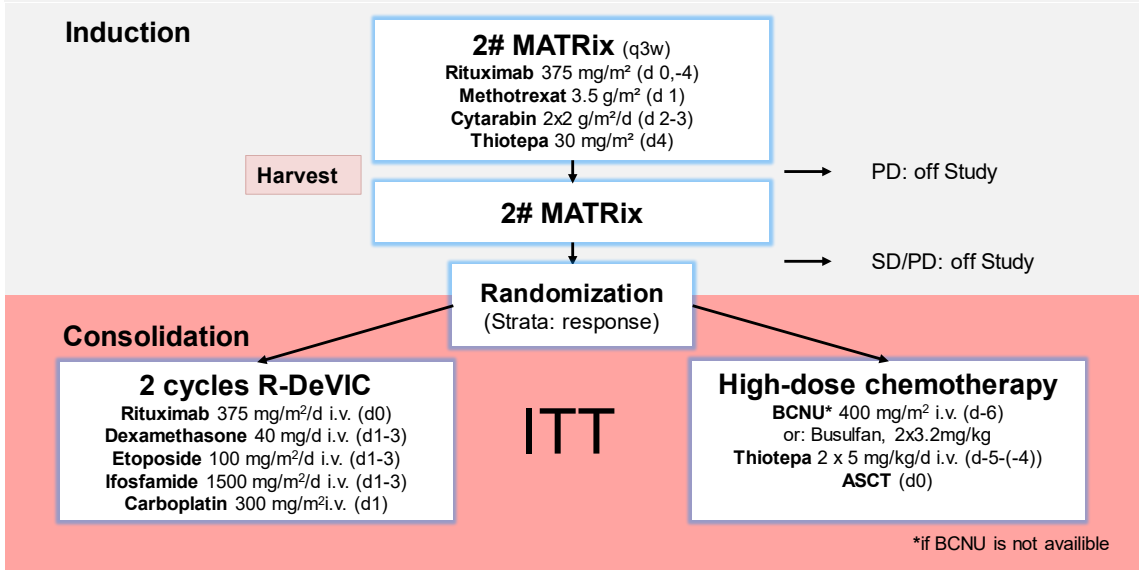
Study Design and Population

Study Design

- Randomized phase III
- 79 centers in 5 European countries (Germany, Italy, Denmark, Norway, Switzerland)
- Primary endpoint: PFS

Treatment algorithm



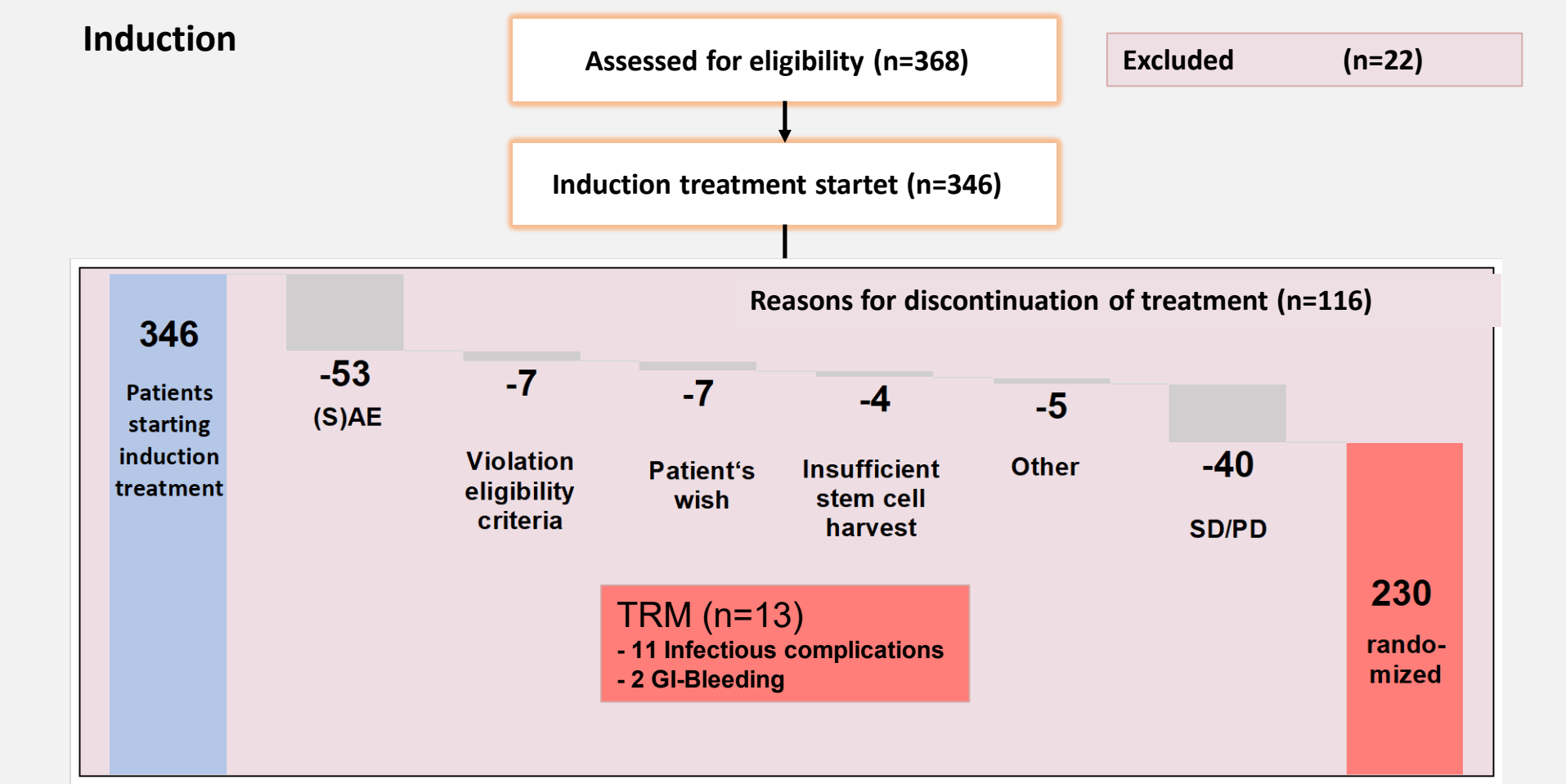
Main eligibility criteria

- Immunocompetent patients with newly-diagnosed PCNSL
- Age 18-65 years irrespective of ECOG or 66-70 years (with ECOG PS ≤2)
- At least one radiologically measurable lesion
- Adequate organ function (i.e. creatinine clearance > 60ml/min)

Baseline Characteristics

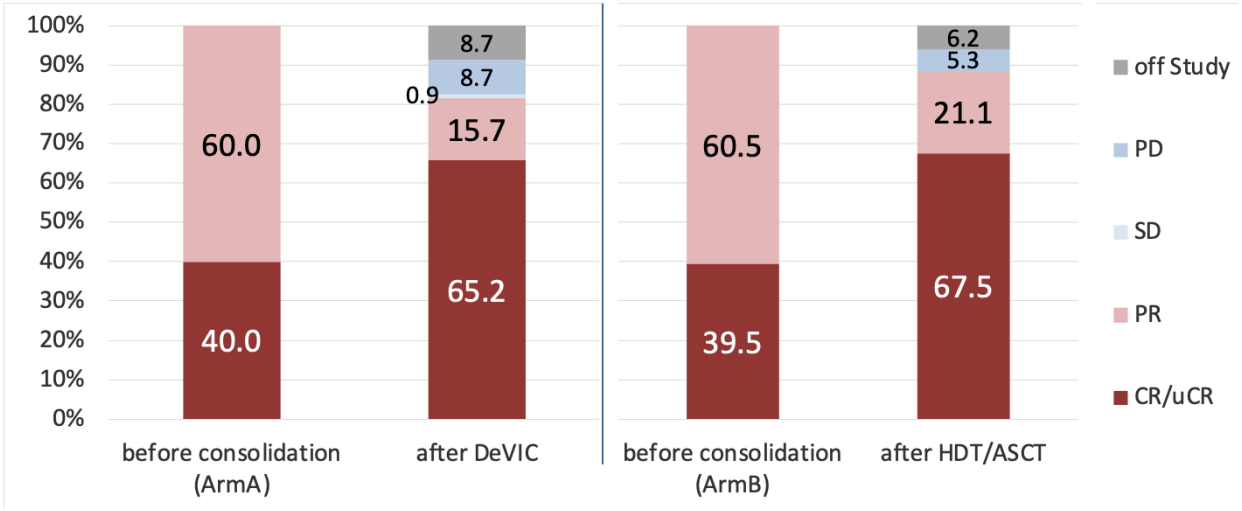
	Arm A (R-DeVIC, n= 115)	Arm B (HDT-ASCT, n= 114)
Median age (range)	59.9 (21-70)	58.5 (24-69)
Age ≥ 65	28 (24.3%)	23 (20.2%)
Histology: DLBCL	111 (98.2%)	111 (97.4%)
Females	53 (46.1%)	49 (43.0%)
ECOG PS >1	26 (22.7%)	32 (28.4%)
Increased LDH	43 (37.4%)	35 (30.7%)
Increased CSF protein	41 (40.6%)	44 (41.1%)
Meningeal involvement (MRI)†	5 (4.4%)	5 (4.4%)
Multiple lesions (MRI)	72 (63.7%)	65 (57.0%)

Feasibility

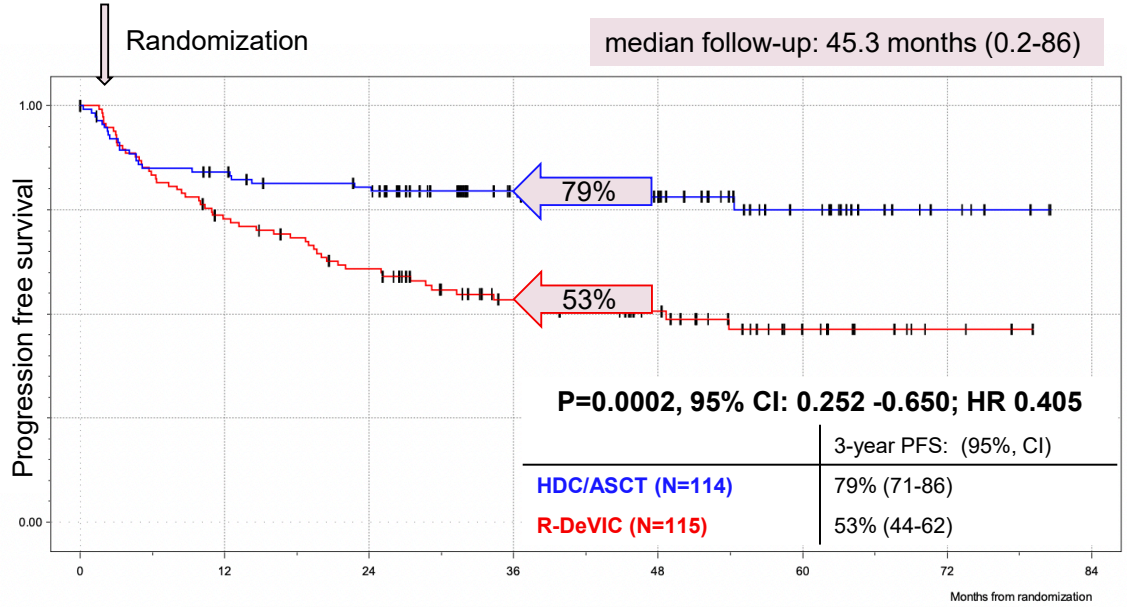


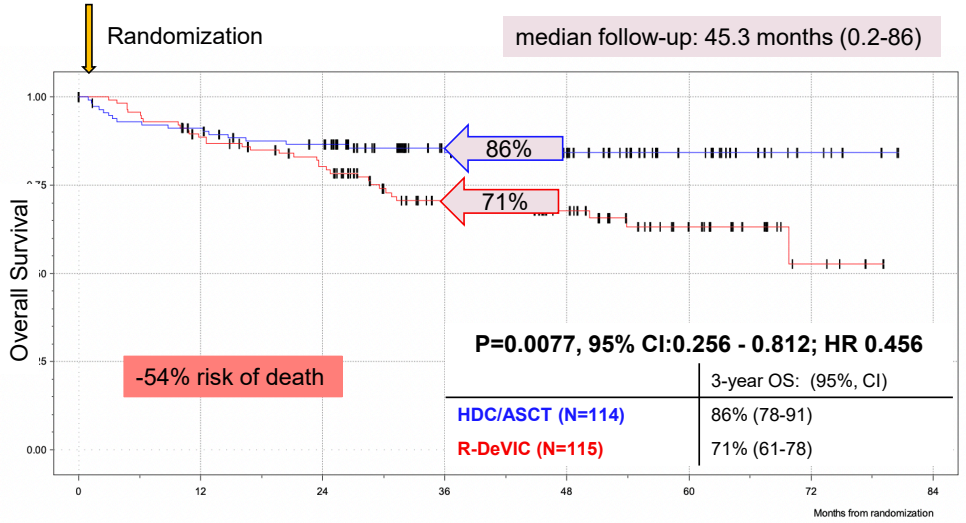
Study Outcome

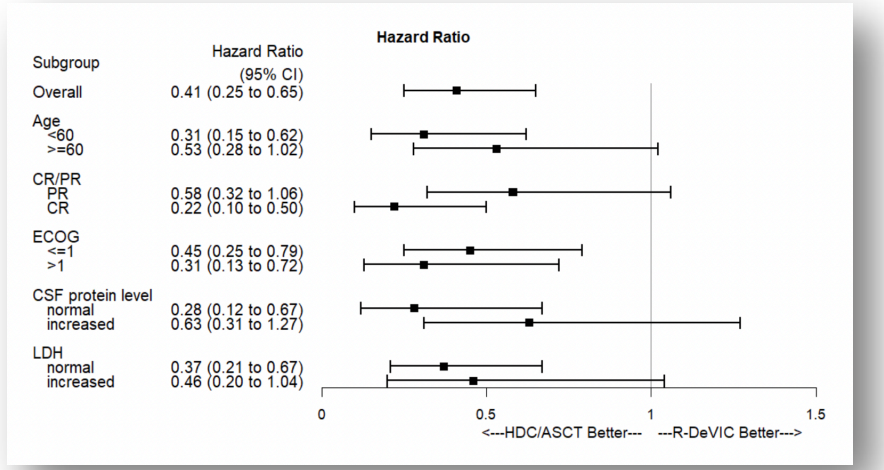
Response to treatment



Survival (randomized patients)







Summary and Conclusions

- HDT-ASZT ist der konventionellen Chemoimmuntherapie mit R-DeVIC als Konsolidierung von Patient*innen mit Erstdiagnose eines PZNSL signifikant überlegen
- Exzellentes Nutzen-Risiko Verhältnis für die Patient*innen, die die Konsolidierung erreichen
- Nahezu identische Gesamtansprechraten und ähnliche Effektivität beider Arme innerhalb der ersten 6 Monate
- Upfront HDT-ASCT = Standard in der Konsolidierungstherapie von fitten Patient*innen mit PZNSL

Kapitel 2

Ist die HDT-ASZT auch in der Erstlinienbehandlung älterer PZNSL Patient*innen (> 65 Jahre) sicher und effektiv?

736 - High-Dose Chemotherapy and Autologous Stem Cell Transplant in Elderly and Fit Primary CNS Lymphoma Patients – a Multicenter Study By the Cooperative PCNSL Study Group (MARTA study)

Elisabeth Schorb, MD1*, Lisa Isbell, MD1*, Andrea Kerkhoff, MD2*, Stephan Mathas, MD3*, Friederike Braulke, MD4,5*, Gerlinde Egerer, MD6*, Alexander Roeth, MD7, Simon Christian Schliffke, MD8*, Peter Borchmann9, Uta Brunnberg, MD10*, Frank P. Kroschinsky, MD, MBA11, Robert Möhle, MD12, Andreas Rank, MD13*, Dominique Wellnitz, MD14*, Benjamin Kasenda, MD PhD15*, Lisa Pospiech16*, Julia Wendler, MD16*, Gabriele Ihorst1,17*, Florian Scherer, MD1*, Martina Deckert, MD18*, Elina Henkes, MD19*, Justus Duyster1*, Jürgen Finke, MD, PhD1 and Gerald Illerhaus, MD16

Study Design and Population

Study Design

- Open label, single arm phase II
- 15 German centers
- Primary endpoint: 1-year PFS

Treatment algorithm

Induction

Rituximab 375 mg/m² (d 0, 4)
Methotrexat 3.5 g/m² (d 1)
Cytarabin 2x2 g/m²/d (d 2-3) (q3w)

SC harvest

Rituximab 375 mg/m² (d 0, 4)
Methotrexat 3.5 g/m² (d 1)
Cytarabin 2x2 g/m²/d (d 2-3)

PD: off study ← Response Assessment (MRI)

Consolidation

Rituximab 375 mg/m2 (d -8)
Busulfan 3.2 mg/kg/d (d -7-(-6))
Thiotepa 5 mg/kg/d (d -5-(-4))
ASCT (d 0)

Main eligibility criteria

- Immunocompetent patients with newly-diagnosed PCNSL
- Age > 65 years with ECOG-Performance Status ≤ 2 (or higher, if PCNSL-related)
- Creatinine clearance > 60 ml/min
- Eligibility for intensive treatment according to investigator's choice

Baseline Characteristics

Patient characteristics	number (n=51)
Age (median; range)	72 (65-80) 66-69: 15 (30%) 70-74: 18 (35%) 75-80: 18 (35%)
Female (%)	27/51 (53%)
ECOG PS ≥ 2 (%)	27/51 (53%)
Multiple lesions (%)	33/51 (65%)
Elevated serum LDH level (%)	22/51 (43%)
CSF involvement (%)	9/46 (19.5%)
Intraocular involvement (%)	4/45 (9%)
Histotype (diffuse large B-cell lymphoma)	51 (100%)
Charlson Comorbidity Index ≥ 1 (%)	26/51 (51%)

Study Outcome

57 registered patients

→ 6 patients with violation of eligibility criteria (3 patients excluded after start of treatment)

51 patients (ITT; 100%)

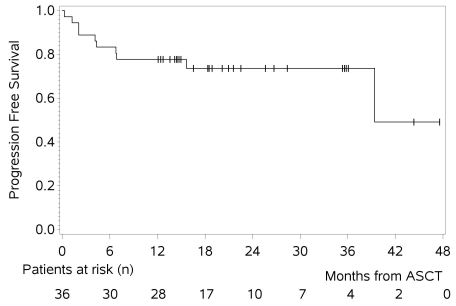
→ 7 patients (14%) with treatment discontinuation

44 patients (86%)

→ 8 patients (16%) with treatment discontinuation

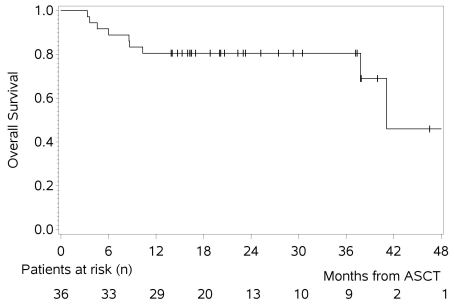
36 patients undergoing HCT-ASCT (71%)

Progression-free Survival



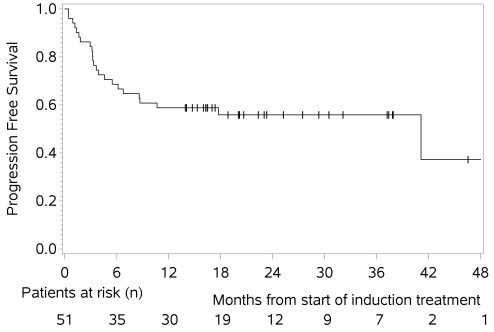
1-year PFS: 77.8% (95% CI 60.4%-88.2%)
Median PFS: 39.4 months

Overall Survival



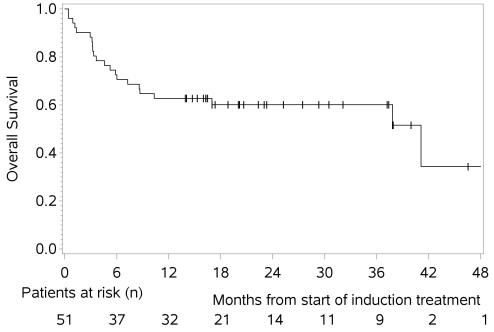
1-year OS: 80.6% (95% CI 63.5%-90.2%)
Median OS: 39.4 months

Progression-free Survival



1-year PFS: 58.8% (95% CI 44.1%-70.9%)
Median PFS: 41 months

Overall Survival



1-year OS: 62.7% (95% CI 48.0%-74.4%)
Median OS: 41 months

median FU: 23 months

Summary and Conclusions

- Nach den vielversprechenden Pilotdaten der MARiTA Studie bestätigt die Phase II MARTA Studie die Machbarkeit und hohe Effektivität der altersadaptierten HDT-ASZT bei fitten älteren Patient*innen
- Keine andere prospektive Studie konnte bislang vergleichbare Ergebnisse in diesem vulnerablen Patientenkollektiv zeigen
- Exzellentes Outcome der Patient*innen, die die Hochdosistherapie erreichen
- Für die Einschätzung der Hochdosisfähigkeit fehlt es noch an standardisierten Tools

Kapitel 3

Bahnt sich die CD19-gerichtete CAR-T Zelltherapie auch bei zerebralen Lymphomen den Weg in die vorderen Therapielinien?

440 - A Pilot Study of Axicabtagene Ciloleucel (axi-cel) for the Treatment of Relapsed/Refractory Primary and Secondary Central Nervous System Lymphoma (CNSL)

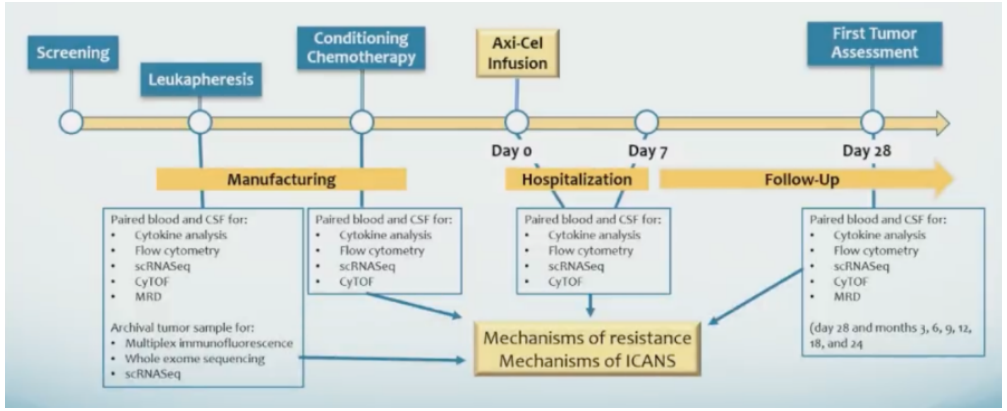
Caron A. Jacobson, MD1, Caroline Falvey1*, Riemke Bouvier1*, Sarah Hogan1*, Elizabeth Kendricken, BSN, RN1*, Julia Jones1*, Elizabeth Grimm1*, Robert A. Redd, MS2*, Eudocia Q Lee1*, Luis Gonzalez Castro1*, Ugonma Chukwueke1*, Jose McFaline Figueroa1*, Austin I. Kim, MD3, Alexandra Torres1*, Linda Ramsdell1*, Leslie S. Kean, MD, PhD4, Ulrike Gerdemann, MD5, Alexandre Albanese6*, Paula Keskula5*, David Meredith7*, Lynette Sholl7*, Soumya Poddar, PhD8*, Madison Davis9*, Daquin Mao9*, Simone Filosto, PhD8*, Mike Mattie, PhD8*, Philippe Armand, MD PhD10 and Lakshmi Nayak, MD11

Study Design and Population

Study Design

- Phase I Studie, 3+3 Design
- 2 cohorts: cohort 1 CNS only disease; cohort 2 CNS and systemic disease
- Primary endpoint: Safety (rate of TLTs and grade ≥ 3 AEs)
- Secondary endpoints: Efficacy (ORR, CR, DOR, PFS, OS)

Treatment scheme



- Standard lymphodepletion with fludarabine and cyclophosphamide followed by axi-cel infusion at a dose of 2x106 cells/kg

Main eligibility criteria

- Adult patients with primary or secondary CNSL
- Refractory to or relapsing after prior CNS directed therapy
- No bridging therapy other than stable steroid dosing

Patient characteristics

Characteristic		N=9 (%)
Gender	Male Female	4 (44) 5 (56)
Age (years)	Median (range)	60 (33-74)
PCNSL v SCNSL	PCNSL SCNSL	6 (67) 3 (33)
Cell of Origin (Hans)	GCB Non-GCB Unknown	1 (11) 5 (56) 3 (33)
DHL or THL	Yes No Unknown	0 (0) 6 (67) 3 (33)
Double expressor	Yes No Unknown	3 (33) 4 (44) 2 (22)
Tumor Location	Parenchymal CSF cytology positive	9 (100) 2 (22)
Number of prior systemic tx	Median (range)	2 (1-6)
Disease status to last tx	Relapsed Refractory	4 (44) 5 (56)
Time from CNSL diagnosis to enrollment	Days (range)	281 (121-8666)
Time from last systemic tx to enrollment	Days (range)	57 (16-392)

Study Outcome

Feasibility

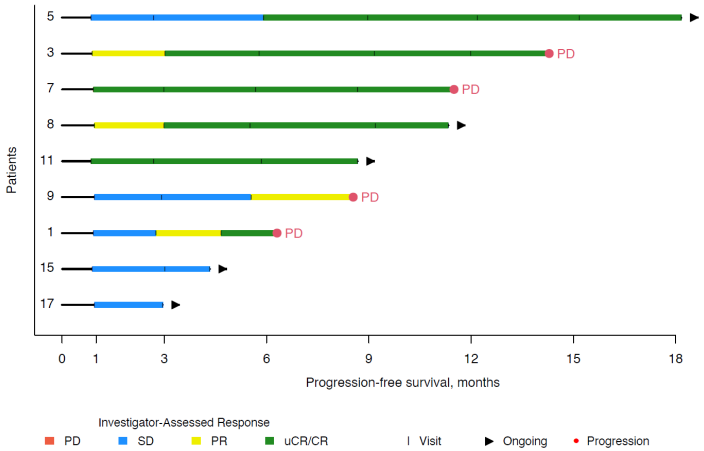
- Axi-cel was successfully manufactured in 9/9 patients
- Steroids were tapered to dexamethasone 2 mg qd or equivalent by axi-cel infusion
- 3 patients continued steroids from screening to treatment, 2 patients were on steroids at the time of infusion
- 5/9 patients received palliative targeted radiation immediately prior to screening for the trial

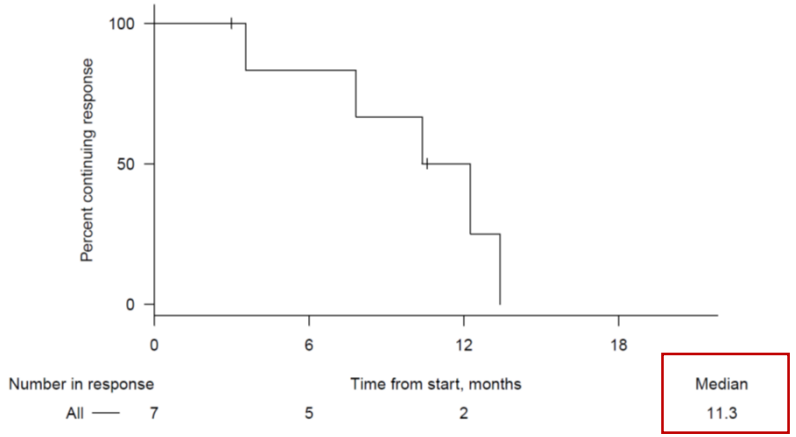
Toxicity (Primary endpoint)

	CRS	ICANS
Any grade, n (%)	8 (89)	4 (44)
Grade 3+, n (%)	0 (0)	3 (33)
Median time to onset (range)	2 days (1-6)	3.5 days (1-6)
Median duration (range)	4 days (1-8)	5.5 days (4-22)
Toci administered, n (%)	7 (78%)	0 (0)
Median number of doses (range)	1 (1-3)	n/a
Dex administered, n (%)	6 (67%)	3 (33%)
Median number of doses (range)	2 (1-10)	10 (9-26)

	1m	3m
Prolonged grade 3+ cytopenias	3/9 (33%)	0/9 (0%)
Neutropenia	3/9 (33%)	0/9 (0%)
Thrombocytopenia	1/9 (11%)	0/9 (0%)
Anemia	0/0 (0%)	0/9 (0%)

Efficacy





- No TLTs
- 1 SAE: staphylococcus meningitis related to Ommaya reservoir
- No patients experienced grade 4 ICANS
- Two deaths due to PD

Summary and Conclusions

- Ordentliche Verträglichkeit, insbesondere keine Häufung schwerer neurologischer Komplikationen
- Hohe Remissionsraten (CR Rate 67%), Dauer des Ansprechens aber limitiert (mDOR 11,3 Monate)
- CAVE: kleine Fallzahl, heterogenes Kollektiv bei multiplen Vor-/Begleittherapien (Radiatio, Steroide)
- Die Rolle und das optimale Setting der CAR-T Zelltherapie ist noch nicht gut definiert

Zusammenfassung | Take-Home-Messages

- Upfront HDT-ASCT = bestätigter Standard in der Konsolidierungstherapie von fitten PZNSL Patient*innen < 70 Jahre
- HDT-ASZT ist nach altersadaptierter, kurzer Induktionstherapie auch für fitte ältere Patient*innen eine hoch effektive Therapieoption
- Wachsende Evidenz für den Einsatz CD19-gerichteter CART-T Zelltherapie ohne ZNS-spezifische Toxizitätssignale, die Effektivität muss in größeren Kohorten weiter untersucht werden

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2022

Für den Inhalt verantwortlich:

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