Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML-Experten berichten

EHA2021 VIRTUAL

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

Prof. Dr. med. Georg Lenz
Medizinische Klinik A | Universitätsklinikum Münster

Aggressive Lymphome

Offenlegung potentieller Interessenskonflikte

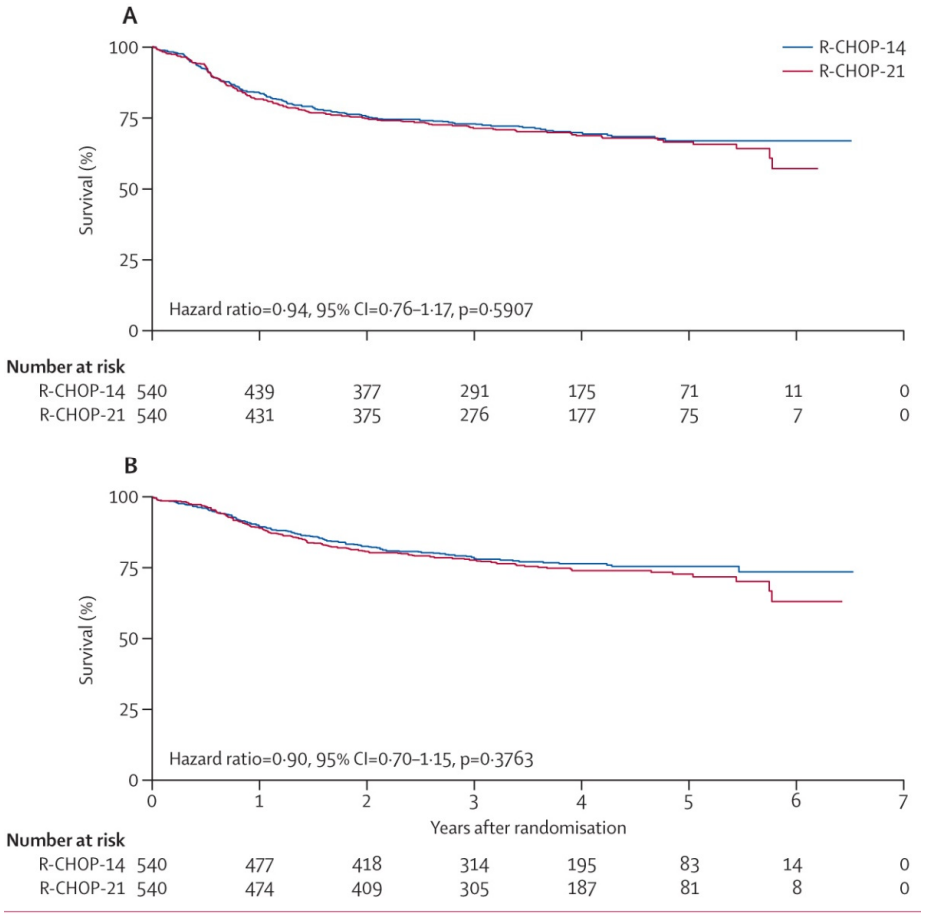
LymphomKompetenz KOMPAKT – EHA2021 wird in Kooperation mit sechs unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Anstellungsverhältnis, Führungsposition	Keine
Beratungs-/ Gutachtertätigkeit	Roche, Gilead, Janssen, Bayer, BMS/Celgene, Novartis, AstraZeneca, Takeda, NanoString, Abbvie, Incyte, MorphoSys, Genmab, Karyopharm, Oncopeptides
Besitz von Geschäftsanteilen, Aktien oder Fonds	Keine
Patent, Urheberrecht, Verkaufslizenz	Keine
Honorare	Roche, Gilead, Janssen, Bayer, BMS/Celgene, Novartis, AstraZeneca, Takeda, NanoString, Abbvie, Incyte, MorphoSys, Genmab, Karyopharm, Oncopeptides
Finanzierung wissenschaftlicher Untersuchungen	Roche, Gilead, Janssen, AstraZeneca, Bayer, AQUINOX, AGIOS, MorphoSys, Celgene
Andere finanzielle Beziehungen	Keine
Immaterielle Interessenkonflikte	Keine

Kapitel 1

Erstlinientherapie

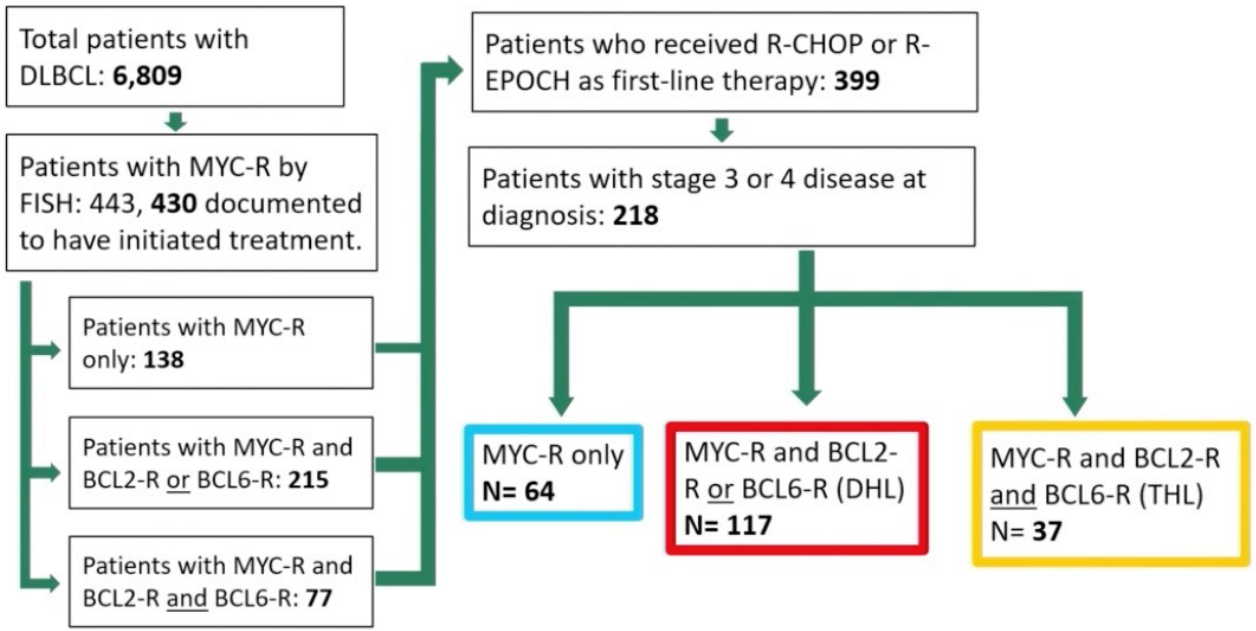
Erstlinientherapie DLBCL Patienten



Cunningham et al., Lancet, 2013

Erstlinientherapie DLBCL Patienten – Stellenwert der Intensivierung

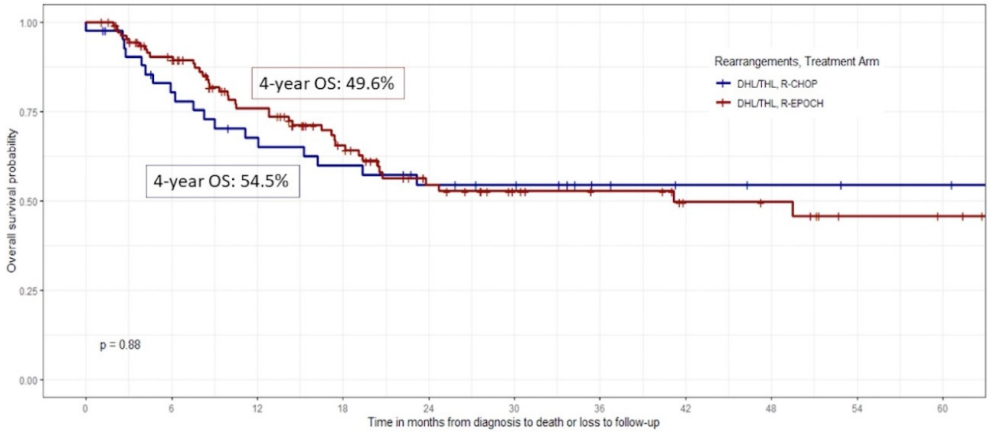
Methods



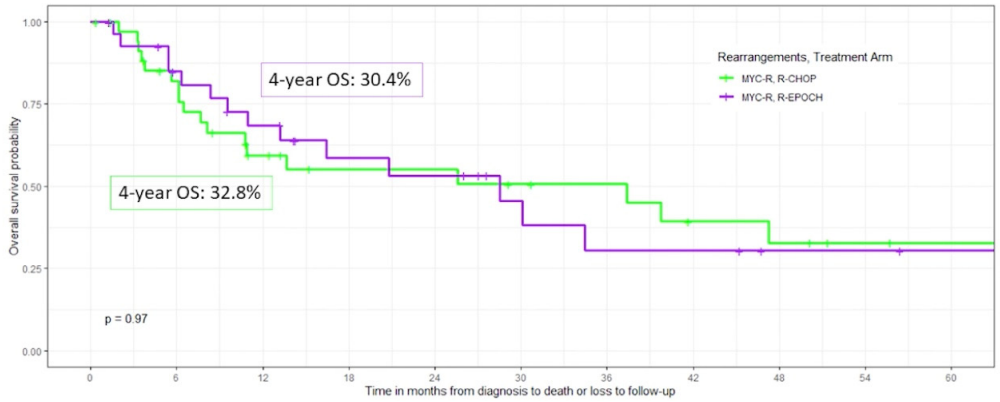
Magnusson et al., EHA, S224

Erstlinientherapie DLBCL Patienten – Stellenwert der Intensivierung

Results: OS for advanced stage DHL/THL by treatment



Results: OS for advanced stage MYC-R alone by treatment



Magnusson et al., EHA, S224

Erstlinientherapie älterer DLBCL Patienten

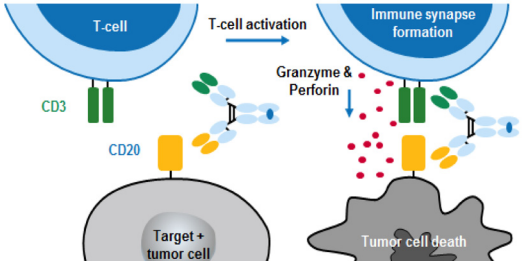
EP503

Mosunetuzumab monotherapy for elderly/unfit patients with first-line diffuse large B-cell lymphoma (DLBCL) continues to show promising safety and efficacy with durable complete responses

Adam Olszewski,[1] Abraham Avigdor,[2,3] Sunil Babu,[4] Itai Levi,[5] Herbert Eradat,[6] Uri Abadi,[3,7] Houston Holmes,[8] Matthew McKinney,[9] Dariusz Woszczyk,[10] Krzysztof Giannopoulos,[11] Wojciech Jurczak,[12] Ron McCord,[13] Yuying Xie,[14] Mingzhu Zhou,[15] Naseer Qayum,[16] Carol O'Hear,[13] Gila Sellam,[17] Netanel Horowitz[18]

Background

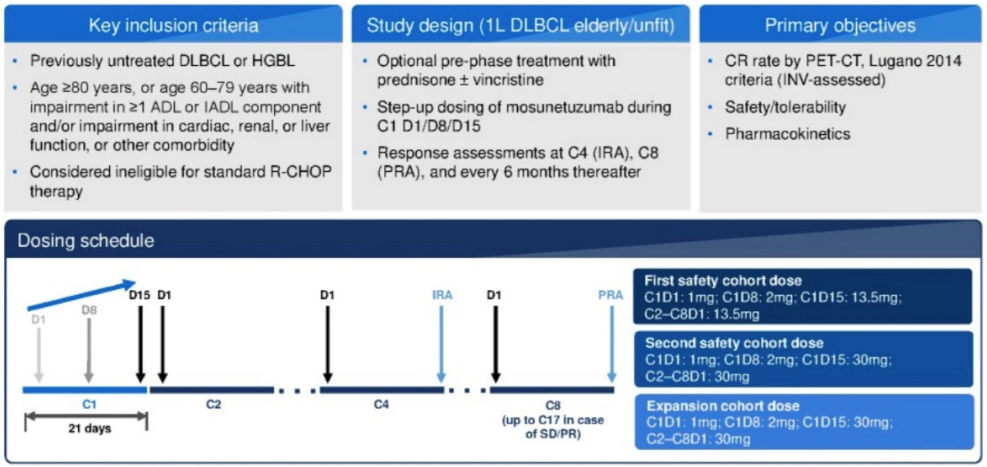
- Mosunetuzumab (RG7828; BTCT4465A)
  - Full-length, fully humanized IgG1 bispecific antibody[1]
  - Redirects T cells to engage and eliminate B cells; T-cell activation, cytokine elevation and increase in TILs observed (**Hernandez et al. ASH 2019 P-1585**)
  - No ex-vivo T cell manipulation required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



Olszewski et al., EHA, EP503

Erstlinientherapie älterer DLBCL Patienten

Figure 1: Study design



1L, first line; ADL, activity of daily living; CR, complete response; D, day; HGBL, high-grade B-cell lymphoma; IADL, instrumental ADL; INV, investigator; IRA, interim response assessment; PET-CT, positron emission tomography-computed tomography; PR, partial response; PRA, primary response assessment; SD, stable disease.

Table 1: Baseline patient and disease characteristics

n (%) unless stated	1L DLBCL (N=48)
Median age, years (range)	83 (65–100)
Aged ≥80 years	36 (75.0)
Aged <80 years	12 (25.0)
Female	31 (64.6)
IPI score ≥2	37 (77.1)
ECOG Performance Status	
0	9 (18.8)
1	23 (47.9)
2	16 (33.3)
Ann Arbor Stage	
I	7 (14.6)
II	15 (31.3)
III	6 (12.5)
IV	20 (41.7)
Elevated LDH	23 (47.9)
Cell of origin	
GCB	20 (41.7)
Non-GCB*	23 (47.9)
WHO subtype	
DLBCL	39 (81.3)
DHL/THL	9 (18.8)

Olszewski et al., EHA, EP503

Erstlinientherapie älterer DLBCL Patienten

Mosunetuzumab monotherapy was efficacious in older and/or unfit pts

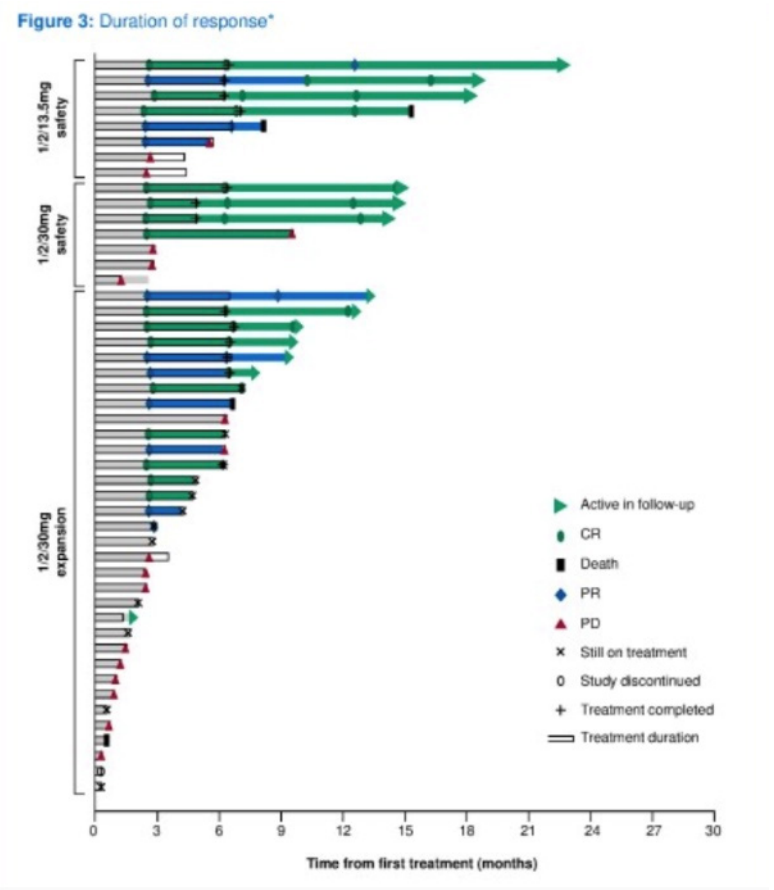
- Median duration of follow-up was 9.4 months (range: 0.2–22.7), although follow-up for some pts in the expansion cohort was very limited.
- ORRs and CR rates in efficacy-evaluable pts were 61.5% (24/39) and 43.6% (17/39), respectively (**Table 3**).
- Eight of 17 complete responders had a follow-up of ≥12 months and maintained a complete remission (**Figure 3**).

Table 3: Best overall response by investigator in efficacy-evaluable pts*

n (%)	ORR	CR	PR	SD	PD
All patients (n=39)	24 (61.5)	17 (43.6)	7 (17.9)	1 (2.6)	9 (23.1)
13.5mg cohort (n=8)	6 (75.0)	4 (50.0)	2 (25.0)	0	2 (25.0)
30mg cohort (n=31)	18 (58.1)	13 (41.9)	5 (16.1)	1 (3.2)	7 (22.6)

*Assessed by PET-CT after 4 or 8 cycles using Lugano 2014 criteria.
PD, progressive disease.

Figure 3: Duration of response*



Olszewski et al., EHA, EP503

Kapitel 2

Neue therapeutische Ansätze

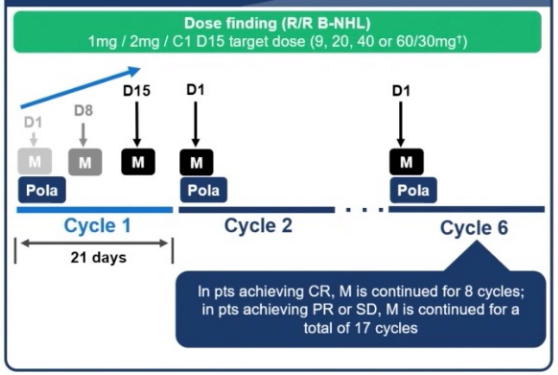
Neue therapeutische Ansätze – Kombination von Polatuzumab und Mosunetuzumab

GO40516: Phase Ib/II, open label, multicentre study of M-Pola in pts with R/R B-NHL

GO40516 (NCT03671018): Study characteristics

- Pts with R/R follicular lymphoma (FL, grade [Gr] 1–3a) or aggressive NHL (aNHL), including *de novo* diffuse large B-cell lymphoma (DLBCL), transformed FL (trFL) and FL Gr 3b (FL3b), received M-Pola
- Step-up doses of M were given in Cycle (C)1 day (D) 1, 8 and 15 to mitigate cytokine release syndrome (CRS)[1]
- C1D15 dose of M given on D1 from Cycle 2 onwards
- Pola (1.8mg/kg) given on D1 of each 21-day cycle for six cycles
- Response assessments are based on the Lugano criteria[2]
- Primary endpoint: to determine the RP2D
- Biomarker analyses included whole blood flow cytometry and plasma cytokine ELISA, and ex-vivo single-cell cytokine assay of PBMC

M-Pola dosing schedule*



*Premedication with steroids (20mg IV dexamethasone or 80mg IV methylprednisolone) required C1–2 and optional C3+.

†The C1D15 and C2D1 dose was 60mg; D1 dose was 30mg from C3 onwards.

CR, complete response; ELISA, enzyme-linked immunosorbent assay; IV, intravenous; PBMC, human peripheral mononuclear cell; PR, partial response; RP2D, recommended Phase 2 dose; SD, stable disease.

1. Schuster SJ, et al. ASH 2019;
2. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

Pt characteristics were typical of a heavily pre-treated R/R B-NHL population

Data cut-off date of March 15, 2021

Characteristic	R/R B-NHL 1mg / 2mg / C1 D15 target dose (N=22)
Median age, years (range)	70 (38–81)
Male, n (%)	11 (50)
NHL subtype, n (%)	
DLBCL	12 (55)
FL 3b	3 (14)
trFL	4 (18)
FL 1–3a	3 (14)
ECOG PS 0–1 at baseline, n (%)	22 (100)
Ann Arbor Stage, n (%)	
II	3 (14)
III	9 (41)
IV	9 (41)
IPI score, n (%)	
2	4 (18)
3–5	8 (36)
Median prior therapies, n (range)	3 (1–10)
Prior CAR-T, n (%)	7 (32)
Refractory to last prior therapy,* n (%)	18 (82)
Refractory to last prior anti-CD20 therapy,* n (%)	20 (91)

*Defined as not achieving a response (partial response or CR) or progressing within ≤6 months of applicable treatment.

CAR-T, chimeric antigen receptor T-cell; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index.

Ghosh et al., EHA, S222

Neue therapeutische Ansätze – Kombination von Polatuzumab und Mosunetuzumab

M-Pola achieved CRs in patients with R/R aNHL (including post-CAR-T) and FL

- Responses were observed after M-Pola in patients with aNHL (including post-CAR-T) and FL
- M-Pola confers good response rates in pts with R/R B-NHL with predominantly aggressive histologies

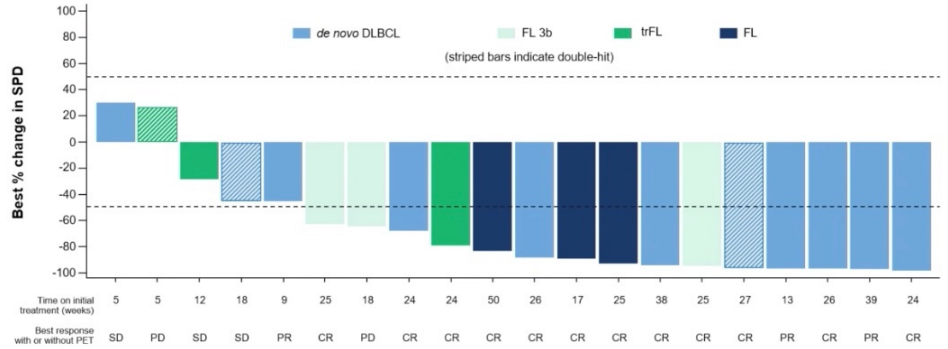
Best response rates[1] in all efficacy evaluable pts (N=22)

Responses, n (%)	All pts (N=22)	aNHL pts (n=19)	Post-CAR-T aNHL pts (n=7)	FL Gr 1–3a pts (n=3)
BOR	15 (68.2)	12 (63.2)	4 (57.1)	3 (100)
CR	12 (54.5)	9 (47.4)	2 (28.6)	3 (100)

BOR, best overall response; CAR-T, chimeric antigen receptor T-cell; CR, complete response.

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

M-Pola showed anti-tumour activity across various dose levels and histologies*



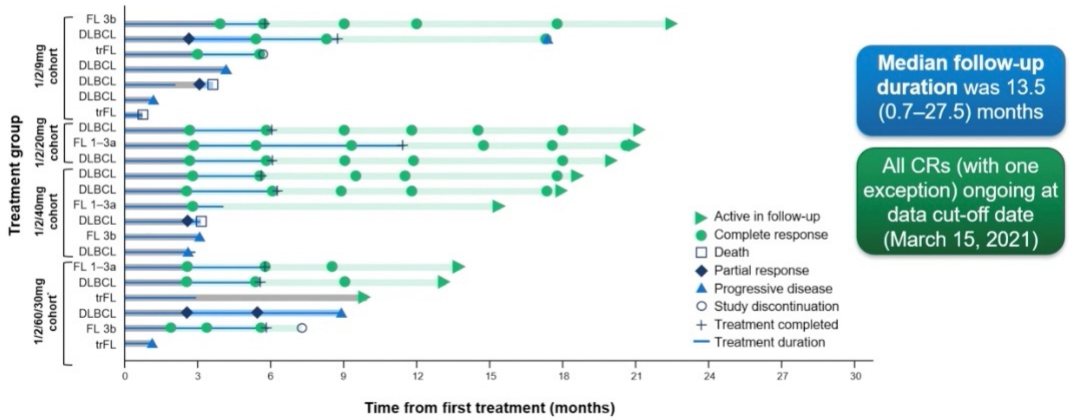
*Lesion measurements were missing for 2 patients.

CR, complete response; PD, progressive disease; PET, positron-emission tomography; PR, partial response; SD, stable disease; SPD, sum of the product of greatest diameter.

Ghosh et al., EHA, S222

Neue therapeutische Ansätze – Kombination von Polatuzumab und Mosunetuzumab

Responses appear durable



Median follow-up duration was 13.5 (0.7–27.5) months

All CRs (with one exception) ongoing at data cut-off date (March 15, 2021)

*The C1D15 and C2D1 dose was 60mg; D1 dose was 30mg from C3 onwards.

No grade ≥2 CRS observed

- CRS events were all Gr 1 and occurred during Cycle 1 step-up dosing, all after M initial dose; median time to first CRS onset was 2 days (range: 1–3)
- All CRS events resolved without tocilizumab, intensive care unit admission, or vasopressors
- No immune effector cell-associated neurotoxicity syndrome-like events were observed

AEs of special interest, n (%)	R/R B-NHL All cohorts (N=22)
CRS*	2 (9.1)
Gr 1	2 (9.1)
Gr ≥2	0
CRS signs and symptoms	
Pyrexia	2 (9.1)
Chills	1 (4.5)
Infections	7 (31.8)
Gr 1–2	5 (22.7)
Gr ≥3	2 (9.1)
Peripheral neuropathy	9 (40.9)
Gr 1–2	6 (27.3)
Gr ≥3	3 (13.6)
Neutropenia	12 (54.5)
Gr 1–2	3 (13.6)
Gr ≥3	9 (40.9)
Febrile neutropenia	0

*Defined by ASTCT 2019 criteria[1].
AE, adverse events; ASTCT, American Society for Transplantation and Cellular Therapy.

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

Ghosh et al., EHA, S222

Neue therapeutische Ansätze – Naratuximab Emtansine

SAFETY AND EFFICACY OF CD37-TARGETING NARATUXIMAB EMTANSINE PLUS RITUXIMAB IN DLBCL AND OTHER B-NHL – A PHASE 2 STUDY

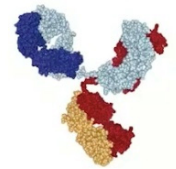
Moshe Yair Levy[1], Zhanet Grudeva-Popova[2], Marek Trneny[3], Wojciech Jurczak[4], Halyna Pylypenko[5], Deepa Jagadeesh[6], Marc Andre[7], Sunita Nasta[8], Dalit Rechavi-Robinson[9], Sara Toffanin[9], Sandrine Micallef[9], Antoine Attinger[9], Elisabeth Rouits[9], Mariola Dymkowska[9], Heidi Nauwelaerts[9], Feng Jung Sherida Harriette Woei-A-Jin[10]

[1]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [2]Department of Clinical Oncology, Medical University of Plovdiv, Plovdiv, Bulgaria; [3]Charles University, General Hospital, Prague, Czech Republic; [4]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [5]Department of Hematology, Cherkassy Regional Oncological Center, Cherkassy, Ukraine; [6]Cleveland Clinic, Cleveland, Ohio, USA; [7]CHU Dinant-Godinne, UCL Namur, Yvoir, Belgium; [8]Division of Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [9]Debiopharm International SA, Lausanne, Switzerland; [10]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium.

12 June 2021
Late-Breaking Oral Session

Background

- Patients with R/R NHL, and particularly R/R DLBCL, who are not candidates for stem cell transplant (SCT) or CAR-T cell therapy have a poor prognosis
  - There is a medical need for new treatment options
- CD37, a surface marker of B-lymphocytes, is highly expressed in NHL, including DLBCL[1]
- **Naratuximab emtansine (nara, Debio 1562, formerly IMGN529)** is an antibody-drug conjugate (ADC) consisting of a humanized anti-CD37 antibody, K7153A, conjugated via a thioether-based linker to a cytotoxic maytansinoid, DM1
  - Nara is the most advanced CD37-targeting ADC in clinical development in DLBCL
- A Phase 1 monotherapy study demonstrated a good safety profile with a 22% overall response rate (ORR) in patients with DLBCL (NCT0153471)[2]



1. Deckert J et al., Blood 2013;122:3500-10. 2. Stathis A et al., Invest New Drugs 2018;36(5):869-76.
DLBCL: Diffuse Large B-Cell Lymphoma; R/R: Relapsed/Refractory; NHL; Non-Hodgkin's Lymphoma

Levy et al., EHA, p205-3

Neue therapeutische Ansätze – Naratuximab Emtansine

Open label, Multicenter, Adaptive Phase 2 Study (NCT02564744)

Part 1		Part 2
Safety run-in	**Run-in expansion**	
R/R NHL: • DLBCL: N=9 • Other NHL: N=8 • Q3W	Cohort 1: • R/R DLBCL: N=8 • Q3W Cohort 2: • Other R/R NHL: N=12 • Q3W	Cohort A: • DLBCL: N=33 • Q3W Cohort B: • DLBCL: N=30 • QW

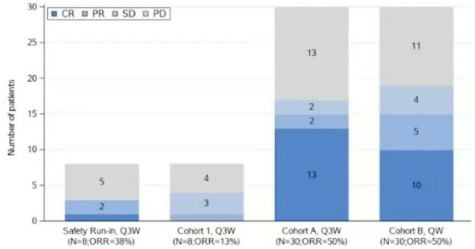
QW: 21-day cycles, nara on day 1, 0.4 mg/kg, and on days 8 and 15, 0.2 mg/kg, followed by rituximab 375 mg/m² on day 1
Q3W: 21-day cycles, nara on day 1, 0.7 mg/kg, followed by rituximab 375 mg/m²

Primary endpoints:
- Number of patients with clinical responses (ORR) as assessed by the Lugano Classification of response assessments
- Treatment emergent adverse events (TEAEs), clinically significant changes in laboratory tests, ECG and vital signs

DLBCL: Diffuse Large B-Cell Lymphoma; R/R: Relapsed/Refractory; NHL: Non-Hodgkin's Lymphoma; ORR: Overall Response Rate; N: Number of patients

Response in the Efficacy Evaluable DLBCL Population

- 80 patients with DLBCL were dosed
- 76 were efficacy evaluable*
- The ORR was 50% in both Cohort A and Cohort B
  - CR rate in Cohort A: 43.3%
  - CR rate in Cohort B: 33.3%
- The ORR in all 76 patients was 44.7%, with 31.6% CR. In addition:
  - In patients with non-bulky DLBCL (longest diameter ≤7.5 cm; N=61), ORR was 50.8% (ICML2021 abstract #244)
  - 3rd line+, non-primary refractory patients (N=28) had an ORR of 46.4% and a CR rate of 32.1%



*Efficacy Evaluable: having both a baseline tumor assessment AND a post-baseline tumor assessment or an assessment of clinical PD

DLBCL: Diffuse Large B-Cell Lymphoma; N: Number of patients; QW: weekly regimen; Q3W: 3-weekly regimen; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; ORR: overall response rate

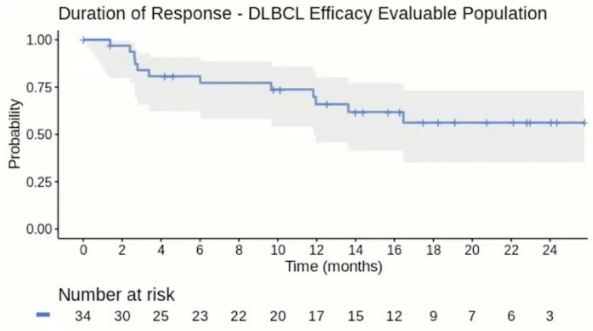
Levy et al., EHA, p205-3

Neue therapeutische Ansätze – Naratuximab Emtansine

Duration of Response (DoR)

Efficacy Evaluable DLBCL Population

- Median DoR was not reached
  - 95% CI: 12 months – NA
- Median duration of follow-up for responders was 15 months
  - 95% CI 9-18 months
- 66% of responders had a DoR >12 months



Safety

- The most frequently observed Grade 3–4 TEAEs were hematological and manageable
- Only 8 patients discontinued nara + RTX due to TEAE
- Of the 10 patients with Grade 5 TEAE, 2 were considered as related to treatment

	All (N=100)
Grade 3–4 TEAE, ≥10% of all patients, n (%)	
Neutropenia*	54 (54.0)
Leukopenia*	19 (19.0)
Lymphopenia*	17 (17.0)
Thrombocytopenia*	12 (12.0)
Grade 5 TEAE	10 (10.0)
SAE occurring in ≥3 pts	
Pneumonia and/or Lung Infection	5 (5.0)
Febrile neutropenia	4 (4.0)
General physical health deterioration	3 (3.0)
TEAE leading to nara + RTX discontinuation, n (%)**	8 (8.0)
TEAE leading to nara dose reduction, n (%)	6 (6.0)

*All cytopenias refer to the cytopenia term and/or the corresponding term of cell count decreased
** Per protocol, when nara was discontinued, patients had to discontinue rituximab as well

Note:
- G-CSF prophylaxis was not offered to all patients
- Only 3 liver TEAEs grade ≥3, and 2 cases of non-serious neuropathy grade ≥3 were observed

TEAE, treatment emergent adverse event: from 1st dose till 30 days after last dose; SAE, Serious adverse event; QW: weekly regimen; Q3W: 3-weekly regimen; DLBCL: Diffuse Large B-Cell Lymphoma; RTX: rituximab

Levy et al., EHA, p205-3

Zusammenfassung

- R-CHOP bzw. R-CHOP-ähnliche Regime bleiben der Standard in der Erstlinientherapie bei Patienten mit DLBCL
- Vielversprechende erste Ergebnisse durch Mosunetuzumab bei unbehandelten älteren Patienten
- Vielsprechende Ergebnisse von Naratuximab Emtansine bzw. von Polatuzumab in Kombination mit Mosunetuzumab bei Patienten mit rezidivertem/refraktärem DLBCL

Haben Sie Fragen zu diesem Thema?
Schreiben Sie uns!

eha2021@lymphome.de

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

Die Kurzpräsentationen sind online unter

www.lymphome.de/eha2021

Für den Inhalt verantwortlich:

Prof. Dr. med. Georg Lenz

Medizinische Klinik A | Universitätsklinikum Münster

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

Das Informationsprojekt wird unterstützt von den Firmen

abbvie

Bristol Myers Squibb™

Celgene | A Bristol Myers Squibb Company

HEXAL

AMGEN

gsk

janssen

PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Diese hatten keinen Einfluss auf die Inhalte.