ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Aggressive Lymphoma Workshop

Bologna, Royal Hotel Carlton

May 8-9, 2023

Tafasitamab + Lenalidomide

Johannes Düll

Universitätsklinik Würzburg

Germany

President: **Pier Luigi Zinzani**

Disclosures

Disclosures of Johannes Düll

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Morphosys	x						
Incyte	x		x		x		
Stemline					x		

Five-year efficacy and safety of tafasitamab in patients with relapsed or refractory DLBCL:

Final results from the Phase II L-MIND study

Johannes Duell,[1*] Pau Abrisqueta,[2] Marc Andre,[3] Marinela Augustin,[4] Gianluca Gaidano,[5] Eva González Barca,[6] Wojciech Jurczak,[7] Nagesh Kalakonda,[8]
Anna Marina Liberati,[9] Kami J Maddocks,[10] Tobias Menne,[11] Zsolt Nagy,[12] Olivier Tournilhac,[13] Abhishek Bakuli,[14] Aasim Amin,[14] Konstantin Gurbanov,[14] Gilles Salles[15]

[1]Medizinische Klinik und Poliklinik II, Universitätsklinik Würzburg, Würzburg, Germany; [2]Department of Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; [3]Department of Hematology, CHU UCL Namur, Yvoir, Belgium; [4]Department of Hematology and Oncology, Klinikum Nuernberg, Paracelsus Medical University, Nuernberg, Germany; [5]Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy; [6]Institut Català d'Oncologia, Hospital Duran i Reynals, IDIBELL, Universitat de Barcelona, Barcelona, Spain; [7]Department of Clinical Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Kraków, Poland; [8]Department of Molecular and Clinical Cancer University of Liverpool, Liverpool, United Kingdom; [9]Università degli Studi di Perugia, Azienda Ospedaliera Santa Maria di Terni, Terni, Italy; [10]Department of Internal Medicine, Arthur G James Comprehensive Cancer Center, Ohio State University Wexner Medical Center, Columbus, OH, USA; [11]Freeman Hospital, The Newcastle upon Tyne Hospitals, Newcastle upon Tyne, UK; [12]Semmelweis University, Budapest, Hungary; [13]CHU de Clermont-Ferrand, Clermont Ferrand, France; [14]MorphoSys AG, Planegg, Germany; [15]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

Introduction and Objective

- 1L SoC in patients with newly diagnosed DLBCL is six cycles of R-CHOP,[1] but **30–40%** will **have R/R** disease[1,2]
- In R/R setting, many patients are **ineligible** for options such as HDC, ASCT, CAR-T therapy due to advanced age or comorbidities[2–4]
- **Effective treatment options in 2L and beyond** are much needed in patients with **R/R DLBCL**

Tafasitamab
Anti-CD19 monoclonal antibody immunotherapy

Tafasitamab + LEN* was effective and well tolerated in ASCT-ineligible patients with R/R DLBCL, in the **Phase II L-MIND study**[1]

	Primary 1-year analysis	3-year† analysis
ORR, %	60.0	57.5
CR, %	43.0	40.0
mDoR, months	21.7	43.9
mOS, months	NR	33.5

Objective: report final, **5-year efficacy and safety of tafasitamab + LEN** in the L-MIND study

*Tafasitamab + LEN was granted accelerated approval in the US (July 2020) and conditional marketing authorization in Europe (August 2021)[5,6]
†3-year analysis refers to ≥35 months

2L, second line; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ASCT, autologous stem cell transplantation; CAR-T, chimeric antigen receptor T-cell; CR, complete response; DLBCL, diffuse large B–cell lymphoma; mDoR, median duration of response; HDC, high-dose chemotherapy; LEN, lenalidomide; NR, not reached; ORR, objective response rate (ORR = CR + partial response [PR]); mOS, median overall survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed or refractory; SoC, standard of care.

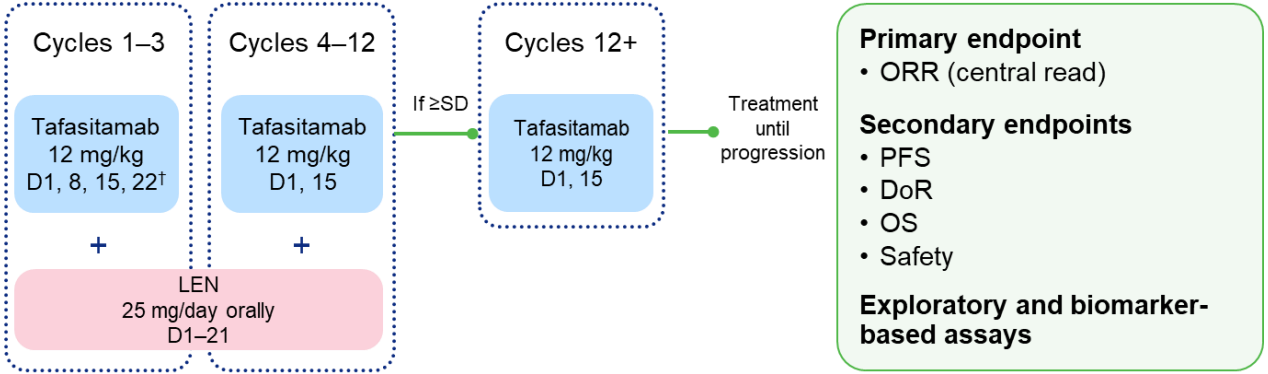
1. Sarkozy C, Sehn LH. Ann Lymphoma 2019;310; 2. Crump M, et al. Blood 2017;130(16):1800–8; 3. Duell J, et al. Haematologica 2021;106(9):2417–26; 4. Sarkozy C, Coiffier B. Clin Cancer Res 2013;19(7):1660–9; 5. MONJUVI. Prescribing information. Boston, MA: MorphoSys. 2020 [Accessed March 2023]; 6. European Medicines Agency. SmPC Minjuvi. 2021 [Accessed March 2023].

Duell J, et al. AACR 2023. Abstract 9810.

L-MIND: Study Design

Open-label, single-arm, multicenter, global, Phase II study; **N=81**

- R/R DLBCL
- Not eligible for ASCT
- 1–3 prior regimens
- Patients with primary refractory disease were not eligible*
- ECOG PS 0–2



NCT02399085[1]

*Primary refractory is defined as no response to, or progression/relapse during/within 6 months of, front-line therapy; 15 patients with refractory disease were included under an early version of the protocol.

†A loading dose of tafasitamab was administered on Day 4 of Cycle 1.
ASCT, autologous stem cell transplantation; D, days; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HDC, high-dose chemotherapy; LEN, lenalidomide; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory; SD, stable disease.

1. ClinicalTrials.gov NCT02399085 (accessed Apr 2023).

Duell J, et al. AACR 2023. Abstract 9810.

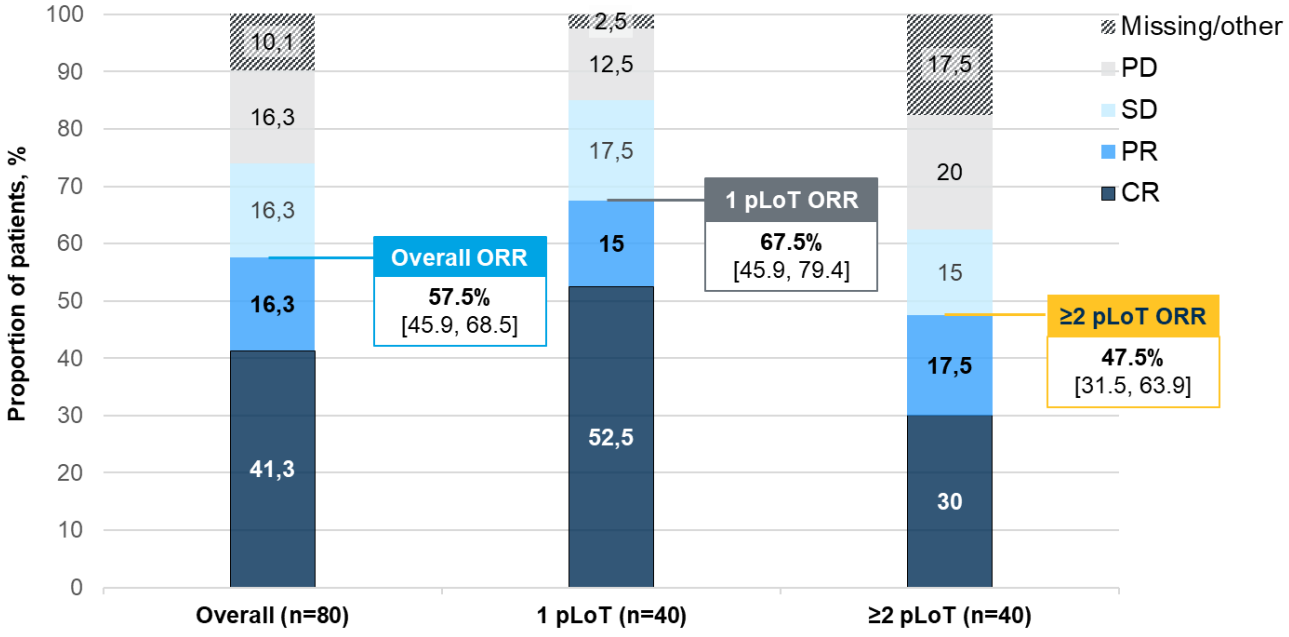
L-MIND: Baseline Characteristics

		All patients (FAS)	1 pLoT	≥2 pLoT
N		80	40	40
Median age, years (range)		72.0 (41.0–86.0)	72.0 (53.0–86.0)	70.5 (41.0–82.0)
Age >70 years, n (%)		45 (56.2)	25 (62.5)	20 (50.0)
Sex, n (%)	Female Male	37 (46.2) 43 (53.8)	19 (47.5) 21 (52.5)	18 (45.0) 22 (55.0)
Ann Arbor stage, n (%)	I–II III–IV	20 (25) 60 (75)	11 (27.5) 29 (72.5)	9 (22.5) 31 (77.5)
IPI score, n (%)	0–2 3–5	40 (50) 40 (50)	25 (62.5) 15 (37.5)	15 (37.5) 25 (62.5)
Elevated LDH, n (%)	Yes No	44 (55.0) 36 (45.0)	18 (45.0) 22 (55.0)	26 (65.0) 14 (35.0)
Primary refractory*, n (%)	Yes No	15 (18.8) 65 (81.2)	6 (15.0) 34 (85.0)	9 (22.5) 31 (77.5)
Refractory to previous therapy line, n (%)	Yes No	35 (43.8) 45 (56.2)	6 (15.0) 34 (85.0)	29 (72.5) 11 (27.5)
Prior ASCT, n (%)	Yes No	9 (11.2) 71 (88.8)	2 (5.0) 38 (95.0)	7 (17.5) 33 (82.5)
Cell of origin (by IHC), n (%)	GCB Non-GCB Unknown / NE	38 (47.5) 22 (27.5) 20 (25.0)	16 (40.0) 14 (35.0) 10 (25.0)	22 (55.0) 8 (20.0) 10 (25.0)

*Primary refractory is defined as no response to, or progression/relapse during or within 6 months of, front-line therapy.
ASCT, autologous stem cell transplantation; FAS, full analysis set; GCB, germinal-center B-cell; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NE, not evaluable; pLoT, prior line of therapy.

Duell J, et al. AACR 2023. Abstract 9810.

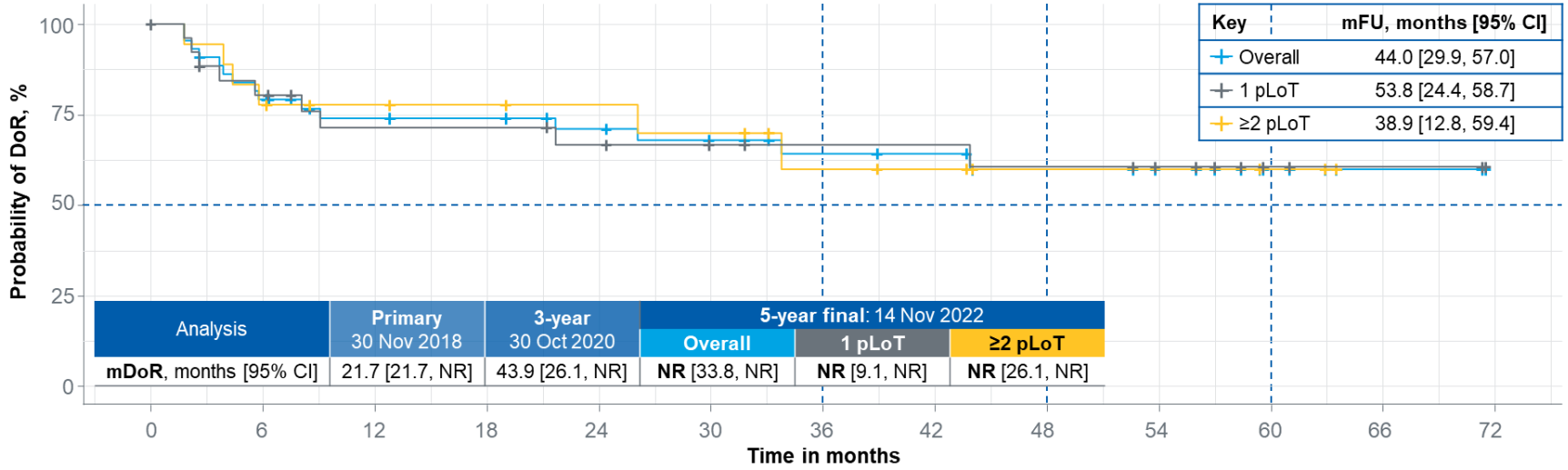
Efficacy Results: Best Response at 5-year Follow-up



CR, complete response; ORR, objective response rate; PD, progressive disease; pLoT, prior line of therapy; PR, partial response; SD, stable disease.

Duell J, et al. AACR 2023. Abstract 9810.

Efficacy Results: DoR at 5-year Follow-up



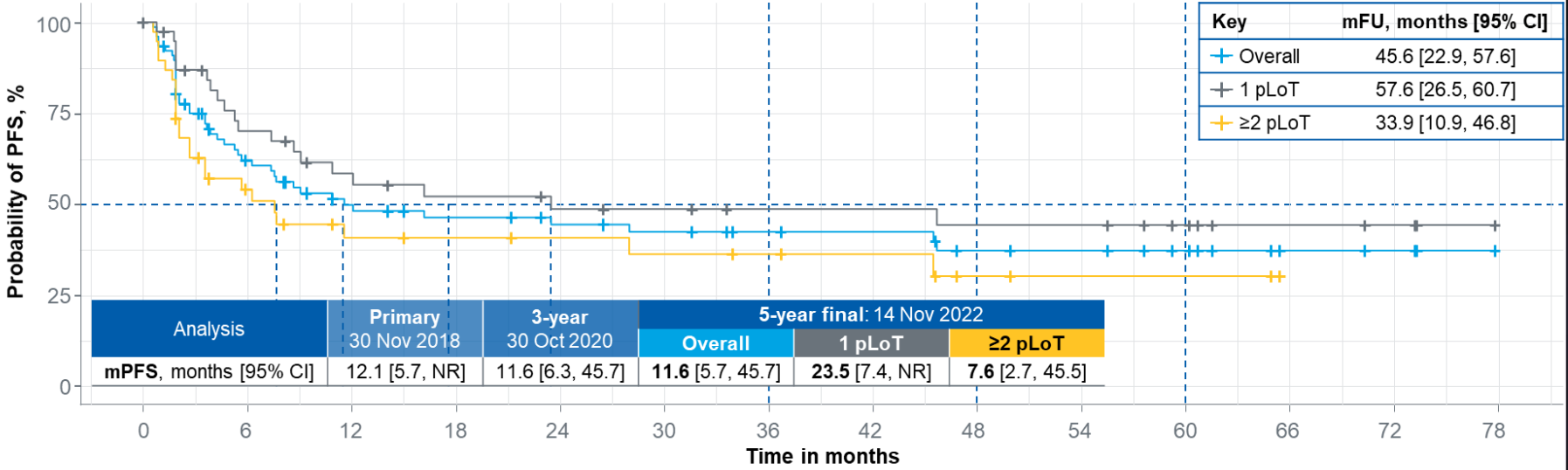
Number at risk:

Overall	46	34	28	27	24	21	17	16	13	11	5	2	0
1 pLoT	27	20	16	16	14	12	11	11	10	8	3	2	0
≥2 pLoT	19	14	12	11	10	9	6	5	3	3	2	0	0

DoR, duration of response; mDoR, median DoR; mFU, median follow-up; NR, not reached; pLoT, prior line of therapy.

Duell J, et al. AACR 2023. Abstract 9810.

Efficacy Results: PFS at 5-year Follow-up



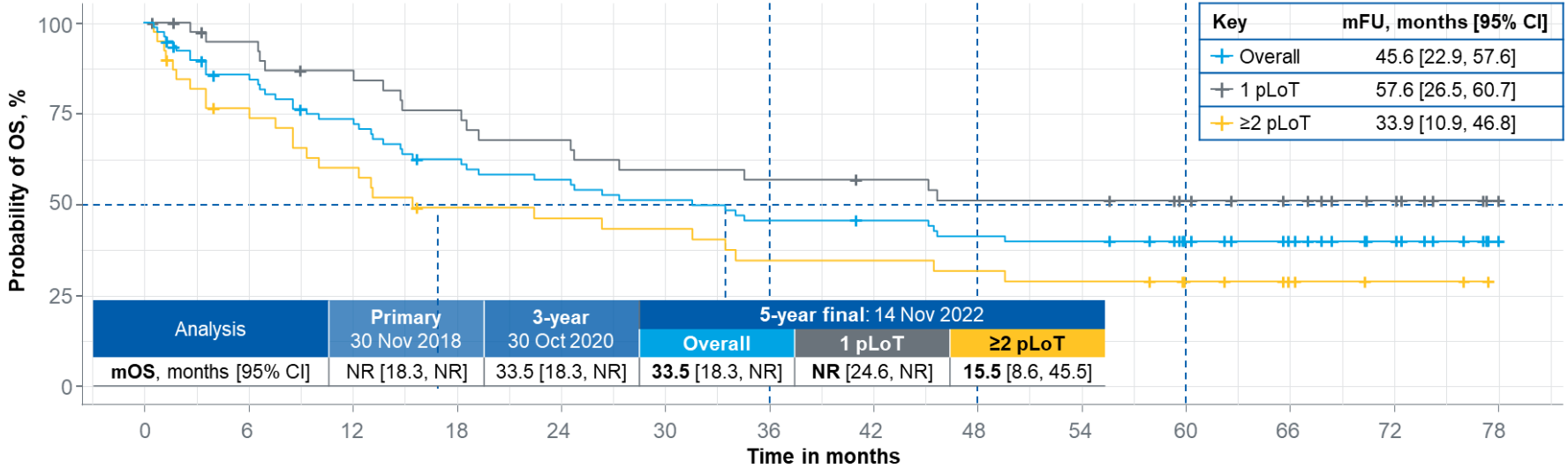
Number at risk:

Overall	80	42	30	26	23	21	18	17	13	12	9	4	3	0
1 pLoT	40	25	19	16	14	13	11	11	10	10	7	4	3	0
≥2 pLoT	40	17	11	10	9	8	7	6	3	2	2	0	0	0

mFU, median follow-up; mPFS, median PFS; NR, not reached; PFS, progression-free survival; pLoT, prior line of therapy.

Duell J, et al. AACR 2023. Abstract 9810.

Efficacy Results: OS at 5-year Follow-up



Analysis	Primary 30 Nov 2018	3-year 30 Oct 2020	5-year final: 14 Nov 2022		
			Overall	1 pLoT	≥2 pLoT
mOS, months [95% CI]	NR [18.3, NR]	33.5 [18.3, NR]	**33.5** [18.3, NR]	**NR** [24.6, NR]	**15.5** [8.6, 45.5]

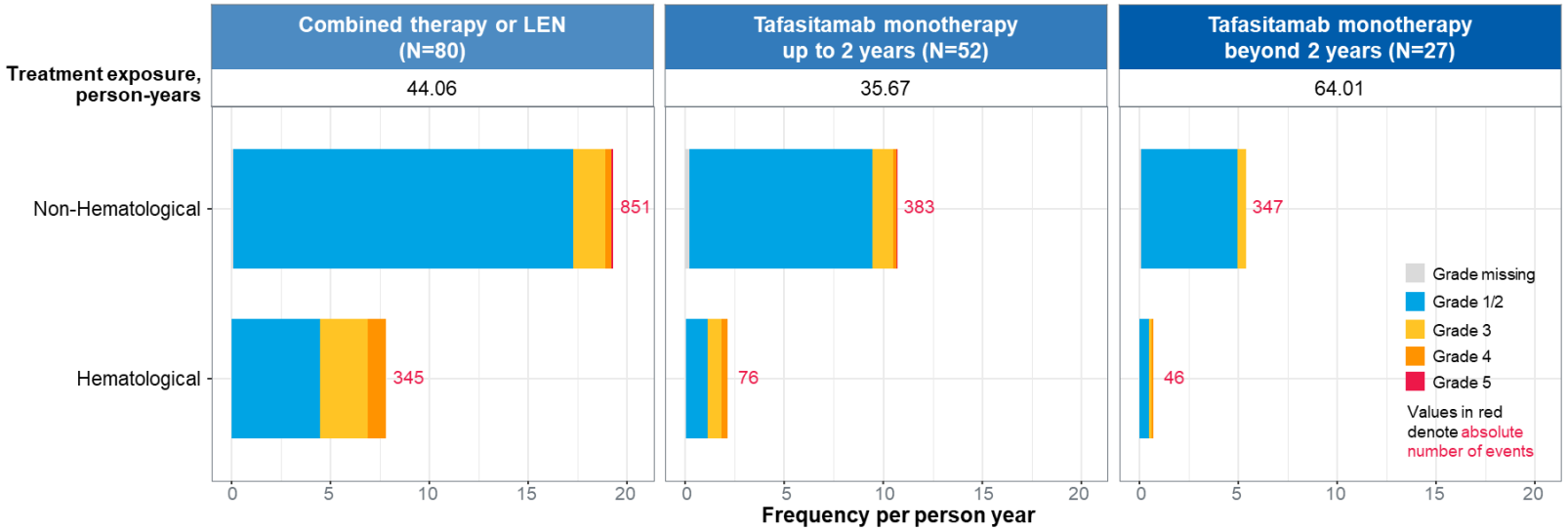
Number at risk:

Overall	80	64	54	45	41	37	33	32	29	28	21	15	9	1
1 pLoT	40	36	32	28	25	22	21	20	18	18	14	11	7	1
≥2 pLoT	40	28	22	17	16	15	12	12	11	10	7	4	2	0

mFU, median follow-up; mOS, median OS; NR, not reached; OS, overall survival; pLoT, prior line of therapy.

Safety Results: Exposure-Adjusted Comparison of TEAE Frequency across Treatment Periods

TEAE Summary

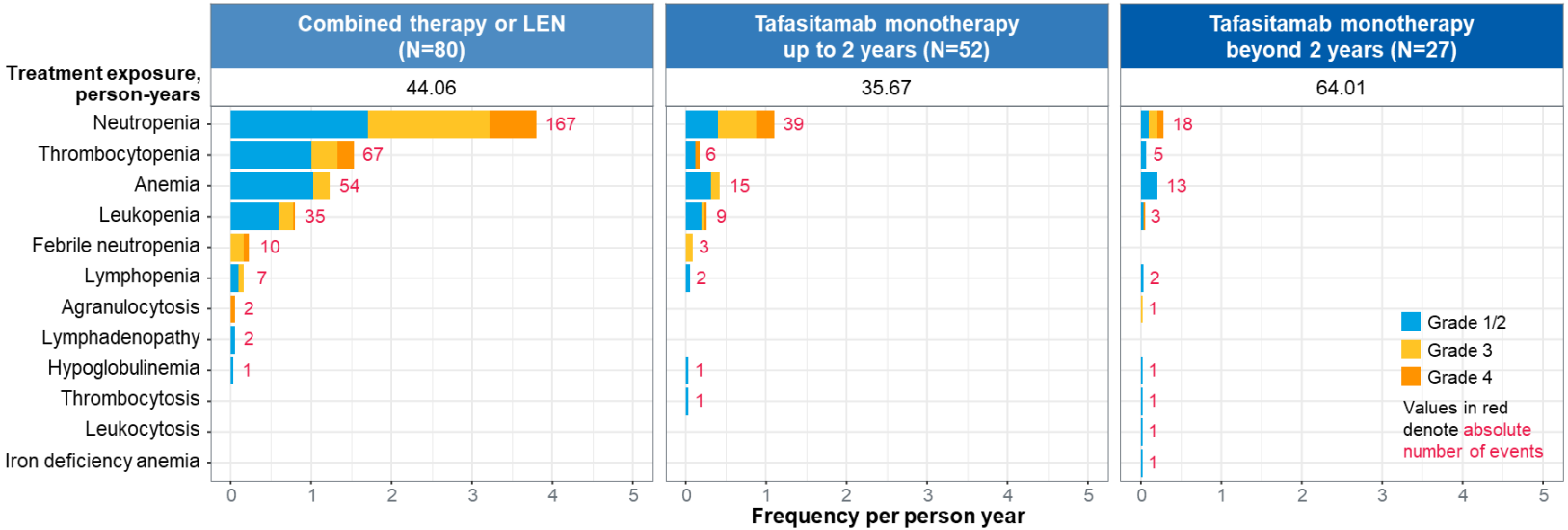


CTCAE grading system.
LEN, lenalidomide; TEAE, treatment-emergent adverse event.

Duell J, et al. AACR 2023. Abstract 9810.

Safety Results: Exposure-Adjusted Comparison of TEAE Frequency across Treatment Periods

Hematological TEAEs



- Hematological TEAEs were less frequent during tafasitamab monotherapy compared with tafasitamab + LEN combination therapy
- The low incidence of TEAEs with tafasitamab monotherapy up to 2 years was maintained or further reduced from 2 years onwards

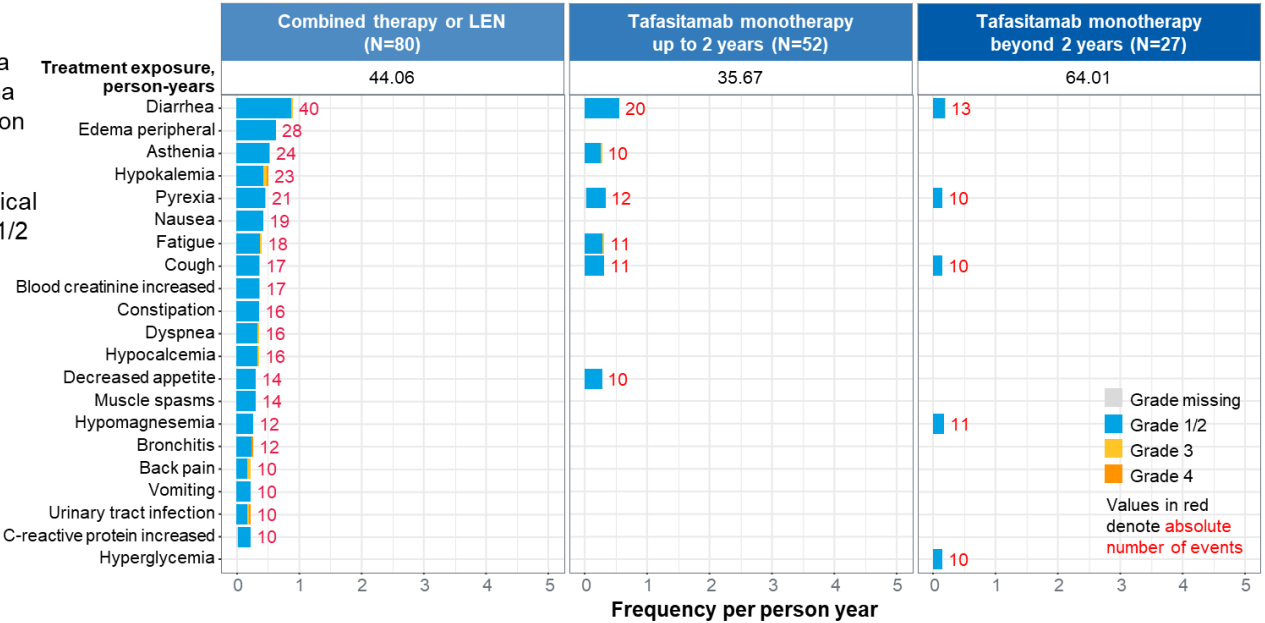
CTCAE grading system.
LEN, lenalidomide; TEAE, treatment-emergent adverse event.

Duell J, et al. AACR 2023. Abstract 9810.

Safety Results: Exposure-Adjusted Comparison of TEAE Frequency across Treatment Periods

Non-hematological TEAEs (cut-off: ≥10 events in any treatment period)

- The most common TEAEs were diarrhea and peripheral edema during the combination therapy phase
- Most non-hematological TEAEs were Grade 1/2

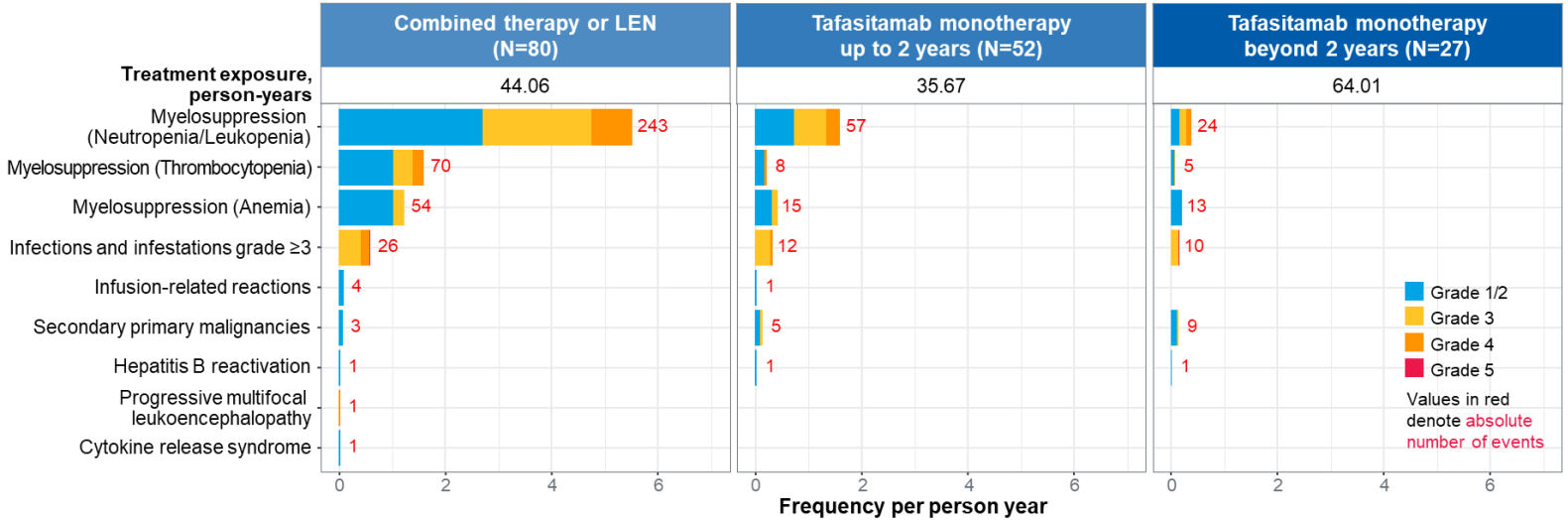


CTCAE grading system.
LEN, lenalidomide; TEAE, treatment-emergent adverse event.

Duell J, et al. AACR 2023. Abstract 9810.

Safety Results: Exposure-Adjusted Comparison of TEAE Frequency across Treatment Periods

Important TEAEs of interest



- Most TEAEs of interest were hematological events during the tafasitamab + LEN combination period
- **Low incidence of infusion-related reactions and grade ≥3 infections and infestations**

CTCAE grading system.
LEN, lenalidomide; TEAE, treatment-emergent adverse event.

Duell J, et al. AACR 2023. Abstract 9810.

Conclusions

- The **5-year analysis of Phase II L-MIND** study showed **durable responses** in patients with R/R DLBCL who are not eligible for ASCT
  - **Median DoR was not reached** after 44 months of median follow-up
  - As expected, patients with **1 pLoT** had better outcomes than those with **≥2 pLoT**
  - **mDoR was not reached in either subgroup** indicating durability of response irrespective of treatment line
- The frequency of **TEAEs decreased** after **patients transitioned** from combination therapy to tafasitamab monotherapy, up to 2 years (previous analysis) and further beyond 2 years
- **No new safety signals** were identified, confirming the tolerable safety profile seen with earlier data cuts
- These long-term data suggest that **this immunotherapy may have curative potential**, which is being explored in further studies

ASCT, autologous stem cell transplantation; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; pLoT, prior line of therapy; R/R, relapsed or refractory; TEAE, treatment-emergent adverse event.

Duell J, et al. AACR 2023. Abstract 9810.

Open questions

Sequencing of CD19 therapies?

Sequencing of CD19 therapies

CD19 therapy (Tafa/Lonca) post CD19 CAR T cells:

- Scenario:
  - R-CHOP → CAR T → ?

CD19 expression after CAR T therapy?

CD19-negative relapse occurred in around 30% of patients following axi-cel therapy

LETTER TO BLOOD| SEPTEMBER 23, 2021 – Plaks et al

→ Biopsy!!!

Sequencing of CD19 therapies

CD19 therapy prior CD19 CAR T cells:

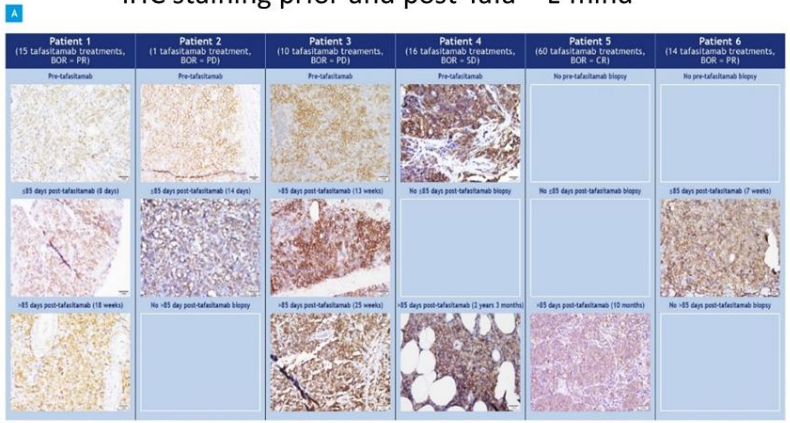
- Scenarios:
  - R-CHOP → Tafa/Len → CAR T
    - CD19 loss variants?
    - CD19 occupation?

Sequencing of CD19 therapies

CD19 expression is maintained in DLBCL patients after treatment with tafasitamab plus lenalidomide in the L-MIND study

→ DNA whole exome and RNA exome sequencing
→ CD19 IHC staining

IHC staining prior and post Tafa – L-mind



(A) IHC data CD19 from serial core needle lymph node FFPE biopsies of six L-MIND patients

Duell et al: Leuk Lymphoma. 2021 Nov 15;1-5

IHC, immune histochemistry; FFPE, formaline-fixed paraffin embedded

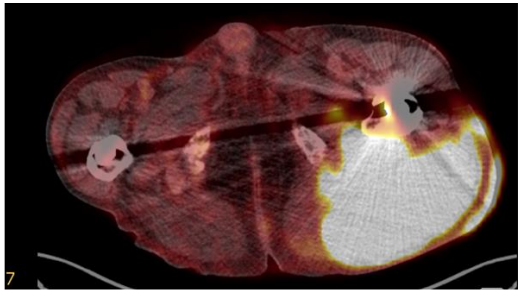
Sequencing of CD19 therapies

- Scenario:
  - R-CHOP → Tafa/Len → CAR T
    - CD19 occupation?

Sequencing of CD19 therapies

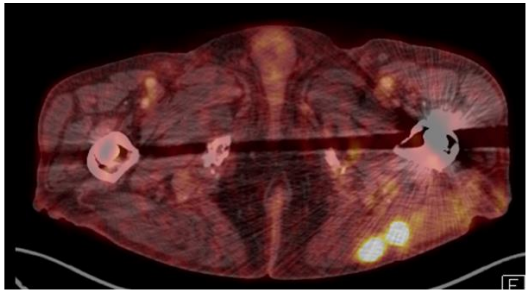
Case study

Prior Tafa/Len



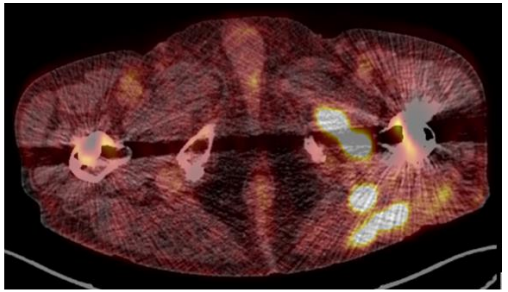
After 3 cycles

PR



After 6 cycles

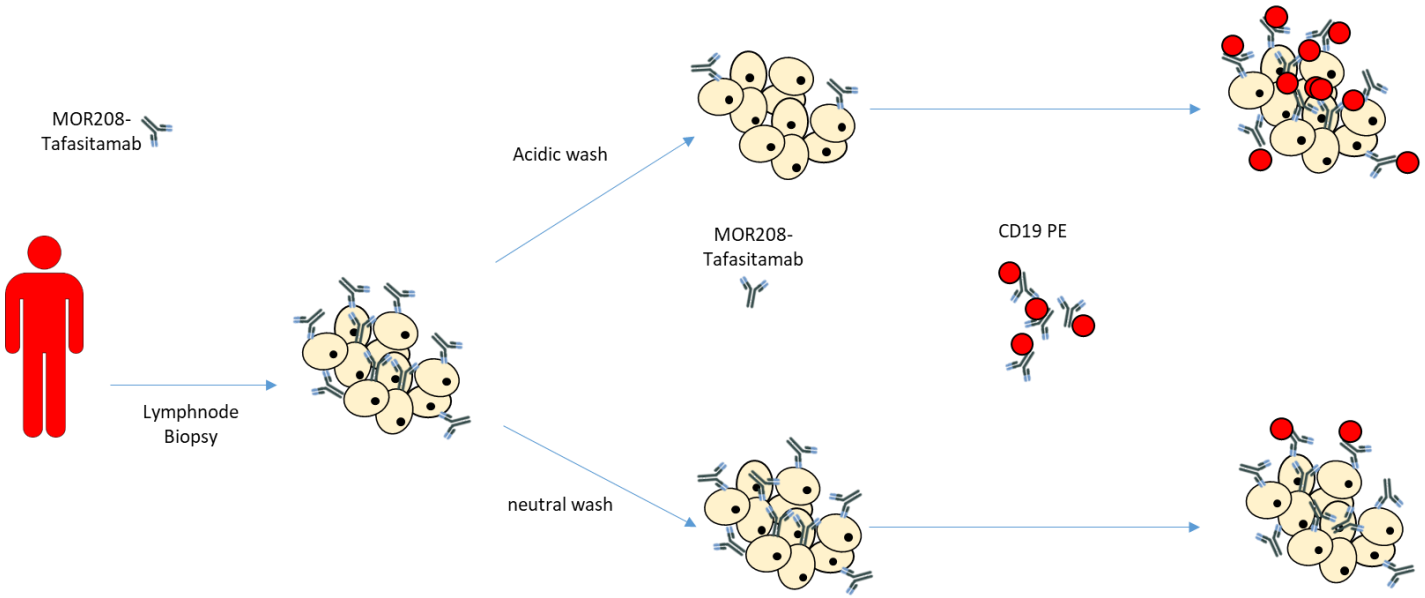
PD



Pictures: Nuclear Medicine Universitätsklinik Würzburg

PD, progressive disease; PR, partial response

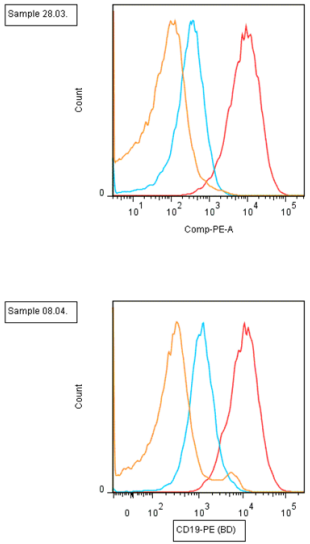
Sequencing of CD19 therapies



PE, phycoerythrin

Sequencing of CD19 therapies

CD19 expression levels and target occupancy



- Negative ctrl. (CD3+)
- Neutral wash
- Acidic wash

- After treatment with tafasitamab only few CD19 epitopes on cell surface available
- However there is no downregulation of CD19 expression during treatment
- **Acidic wash demasks epitopes and allows quantification of CD19 surface expression**

Free CD19 epitopes: after 1 week: 5%
after 2 weeks 10%
after 3 weeks 60%

unpublished data: Dülls Lab

Summary: sequencing of CD19 therapies

→ Biopsy and check for CD19 expression

→ no CD19 loss variants for Tafa/Len described

→ CD19 occupancy with Tafasitamab with CD19 recovery after 3 weeks

Open questions

Real world data

Qualls et al ASH 2022 #323

all about patient selection?

90% did not meet L-mind eligiblity criteria

ORR: 27%
CR: 17%
PFS: 2.8 month
OS: 6.8 month

patient related outcome

↓

more lines of therapy, prior CAR T, ECOG>3, GFR

disease related outcome

↓

higher IPI, >Stage III/IV, primary refractory, HGBCL

Summary: real world data

- → worse outcome than in the L-mind trial
- → Different patient population is maybe one reason
- → Further work needed to predict the Tafa/Len responders
- → Combination therapy should be evaluated (Tafa/Len+Bispec)

The patients and their families!

Max Topp, Würzburg
Andreas Rosenwald, Würzburg
Hermann Einsele, Würzburg
Florian Eisele, Würzburg
Leo Rasche, Würzburg

Study team Würzburg

Thank you!

IZKF Würzburg