Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

18th ICML LUGANO

17. – 21. Juni 2025

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Prof. Dr. med. Gerald Illerhaus
Klinikum Stuttgart

ZNS-Lymphome

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ICML 2025 LUGANO, Italien wird in Kooperation mit fünf unterstützenden Firmen durchgeführt.
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Honorare	Roche, Gilead, Incyte, BMS, Janssen
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Immaterielle Interessenkonflikte	

Kapitel 1

THIOTEPA-CONDITIONED AUTOLOGOUS TRANSPLANTATION IN CNS-LYMPHOMA

THIOTEPA-CONDITIONED AUTOLOGOUS TRANSPLANTATION

086 EFFICACY OF THIOTEPA-CONDITIONED AUTOLOGOUS TRANSPLANTATION IS INDEPENDENT OF RESPONSE TO HD-MTX-BASED INDUCTION IN PRIMARY CNS LYMPHOMA: EBMT SERIES OF 1,545 PATIENTS

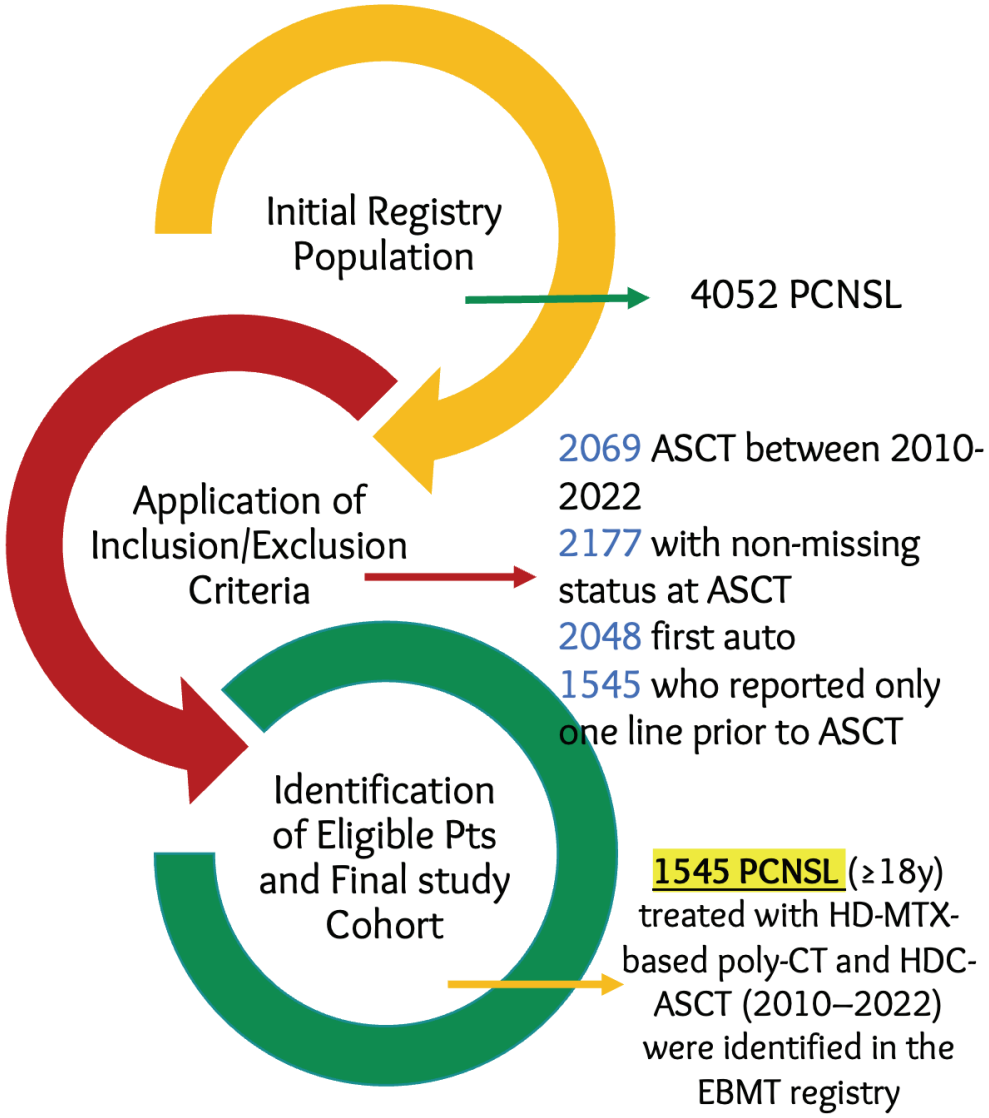
Teresa Calimeri, Mathilde Fekom, Paolo Fiore, Patricia Lopez Pereira, Christopher P. Fox, Gerald Illerhaus, Robert Zeiser, Kate Cwynarski, Hervé Ghesquieres, Wolfgang Bethge, Christof Scheid, Deborah Richardson, Urban Novak, Friedrich Stölzel, Marek Trneny, Giulio Cassanello, Alberto Mussetti, Bertram Glass, Catherine Thieblemont, Anna Sureda, Andrés J.M. Ferreri*, and Ali Bazarbachi*

THIOTEPA-CONDITIONED AUTOLOGOUS TRANSPLANTATION

MAIN OBJECTIVE

to evaluate the impact of response (CR vs. PR vs. PD) to an HD-MTX based induction on the final outcome after HDC-ASCT (PFS and OS) in a real-life setting (EBMT cohort) of newly diagnosed PCNSL.

PRIMARY ENDPOINT: progression-free survival, stratified by response to induction



THIOTEPA-CONDITIONED AUTOLOGOUS TRANSPLANTATION

Conditioning Details

	Overall, N = 1545
Conditioning regimen	
Thiotepa-BCNU based	1094 (71%)
TBC based	84 (5.5%)
Other thiotepa-based	279 (18%)
Not thiotepa-based	81 (5.3%)

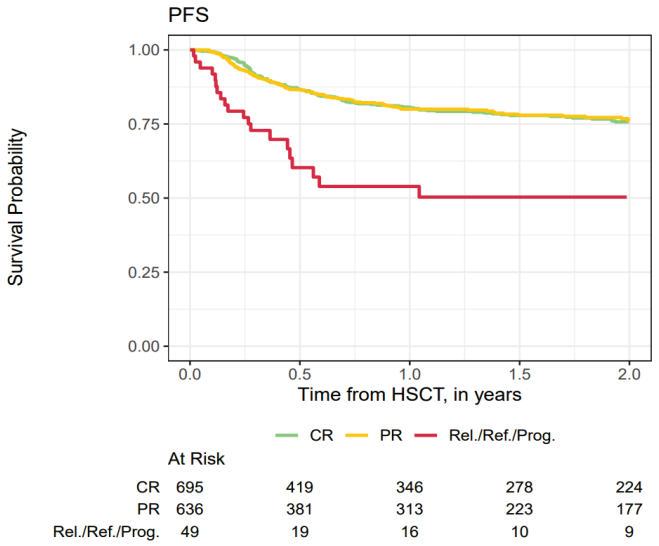
THIOTEPA-CONDITIONED AUTOLOGOUS TRANSPLANTATION

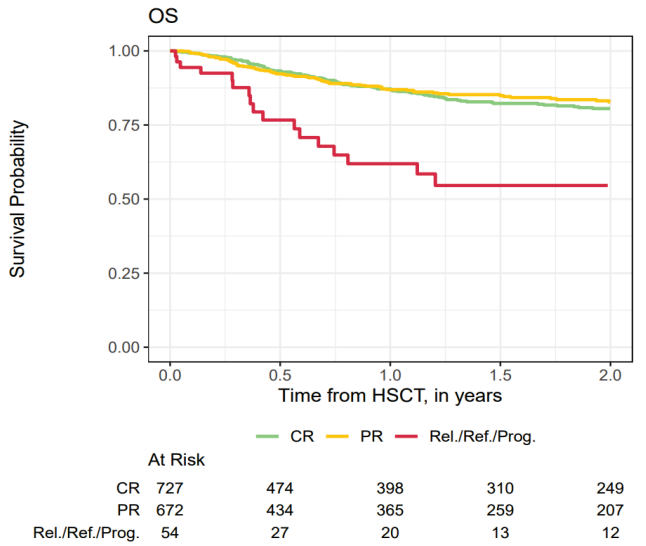
Outcomes by Disease Status

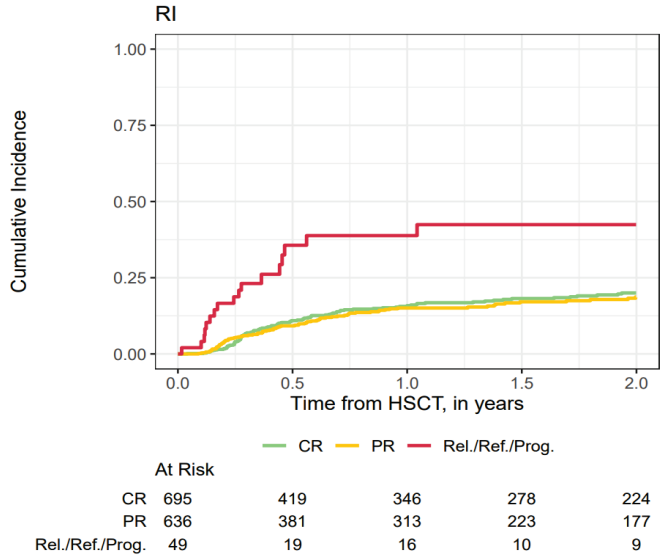
No difference in PFS and OS between **CR and PR @ASCT** time: **2-year PFS of 76%**

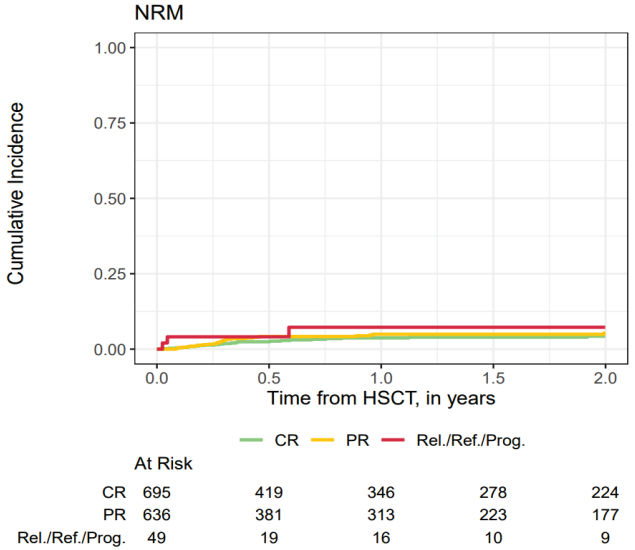
PD @ASCT outcomes: **2-year PFS of 50%**

CR PR Rel./Ref./Prog.









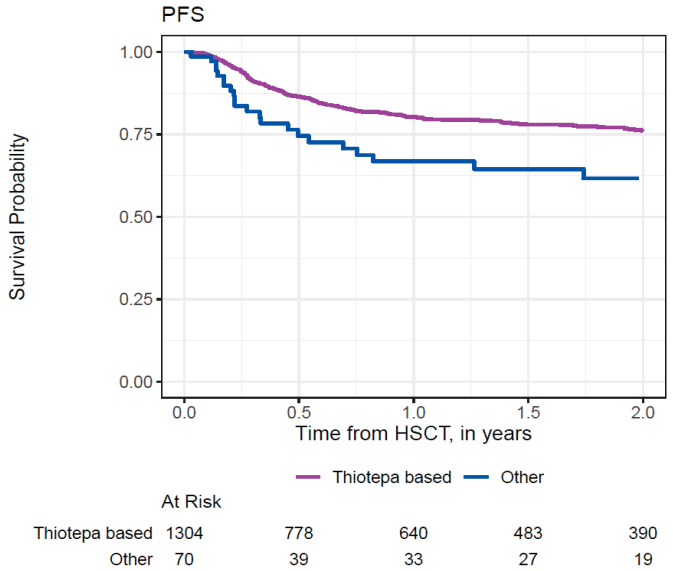
THIOTEPA-CONDITIONED AUTOLOGOUS TRANSPLANTATION

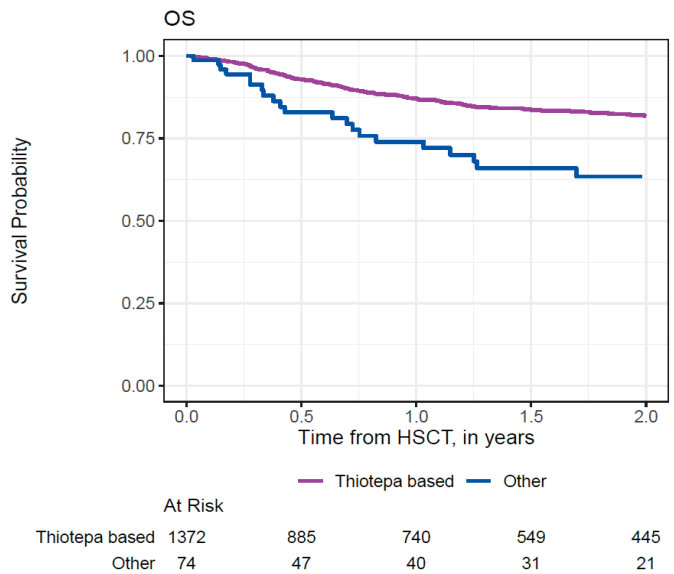
Outcomes by Conditioning Regimen

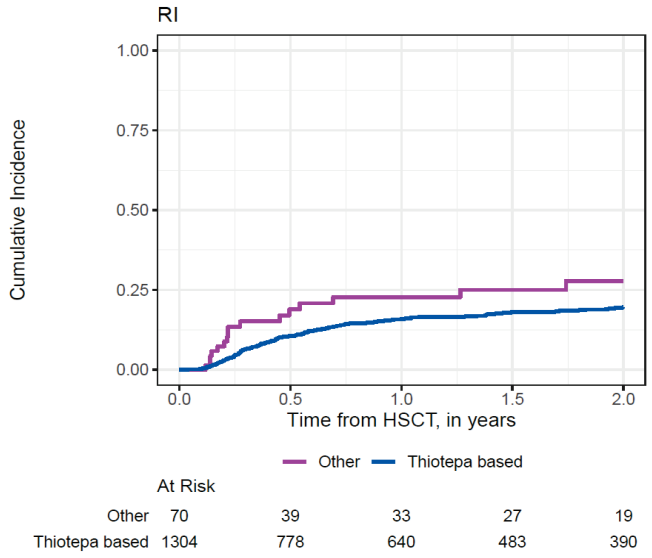
Thiotepa-based conditioning regimens improved outcomes *vs.* Others

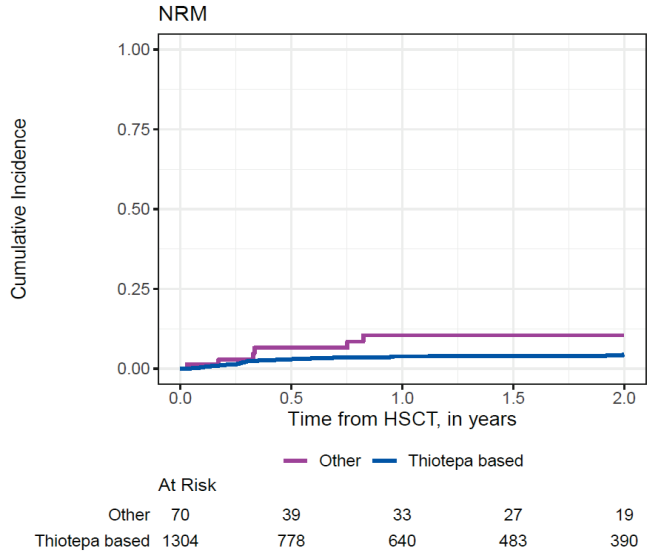
2-year PFS: 76% vs. 62% (p=.015)

2-year OS: 82% vs. 63% (p=.002)









Kapitel 2

Zanubrutinib Monotherapy in PCNSL

Zanubrutinib in PCNSL

The PRiZM+ Phase II Platform Study for Refractory & Relapsed Primary CNS Lymphoma: First Results from Cohort 1 Zanubrutinib Monotherapy

C.P Fox, J Wang, G McIlroy, J Khwaja, A Jackson, R Boucher, S Maycock, F Yates, E Homer, A Davies, G Collins, P McKay, S Kassam, D Lewis, H Marr, T Cummin, E Phillips, N Martinez-Calle, S Thust, J Smith, D.P Auer, J Okosun, K Cwynarski.

Zanubrutinib in PCNSL

Design

Inclusion:

✓ R/R PCNSL, ECOG PS 0-3

✓ PD after ≥1 line of HD-MTX-therapy

Exclusion:

✗ Prior BTKi exposure

✗ Systemic lymphoma

Design:

- Sequential, single arm, Bayesian, phase II *platform* Each cohort will recruit 20 patients
- **Cohort 1: Zanubrutinib monotherapy 160mg BD**

Zanubrutinib in PCNSL

Design

Primary endpoint:

- ORR (CR/CRu + PR) after 2 cycles (8 weeks) treatment

Secondary endpoint:

- CR/CRu rate by local and central review
- PFS/OS/DoR/DoCR
- Safety

Exploratory outcomes:

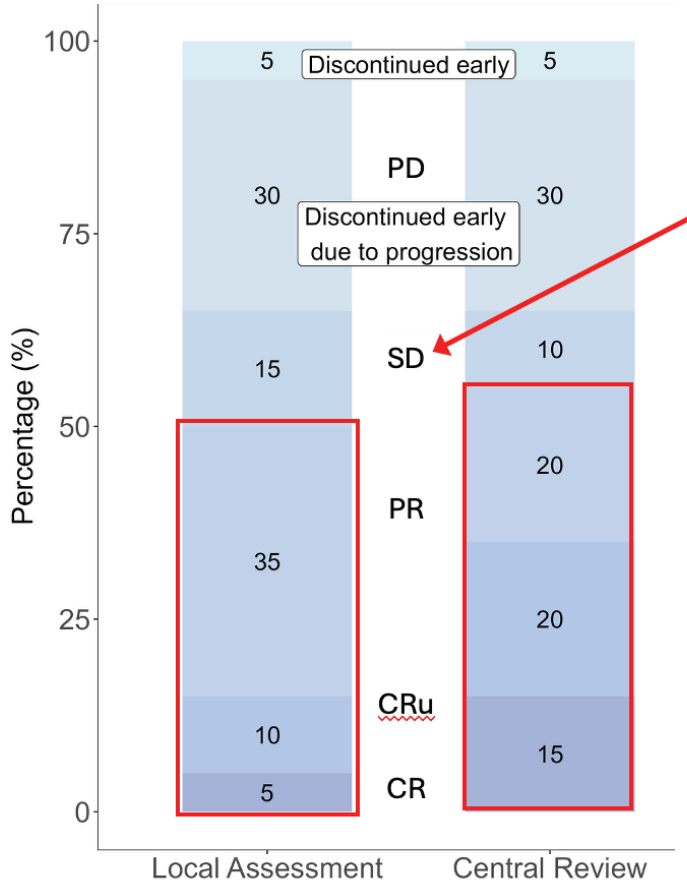
- Zanubrutinib pharmacokinetics (CSF and plasma)
- Tumour genomics & ctDNA (CSF and plasma)
- Novel MRI techniques

Zanubrutinib in PCNSL

Response

PRiZM+

Primary endpoint: ORR (local evaluation) at 8 weeks



NB 2 patients categorised as SD, had sustained clinical responses; not yet experienced PD

ORR= 50%
by local evaluation

ORR= 55%
by central Neuroradiology review

Data-cut 26th February 2025

Fox CP *et al* Abstract 087 ICML 2025

Zanubrutinib in PCNSL

Response

PRiZM+

Key secondary endpoint – CR/CRu at 8 weeks

CR= 15%
by local evaluation

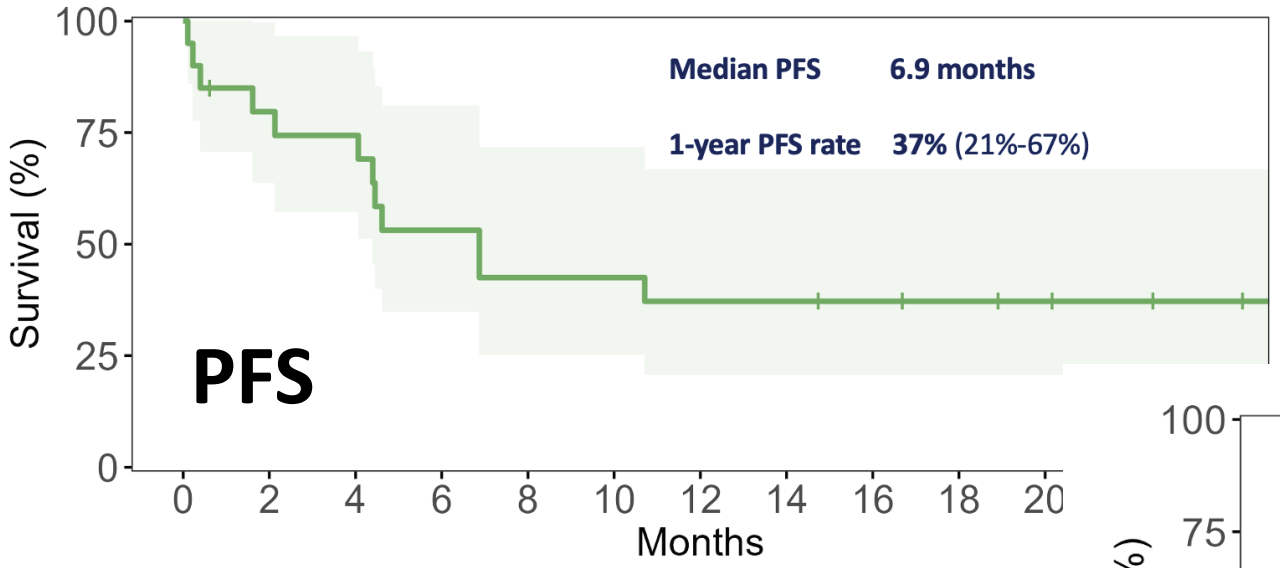
CR= 35%
by central Neuroradiology review

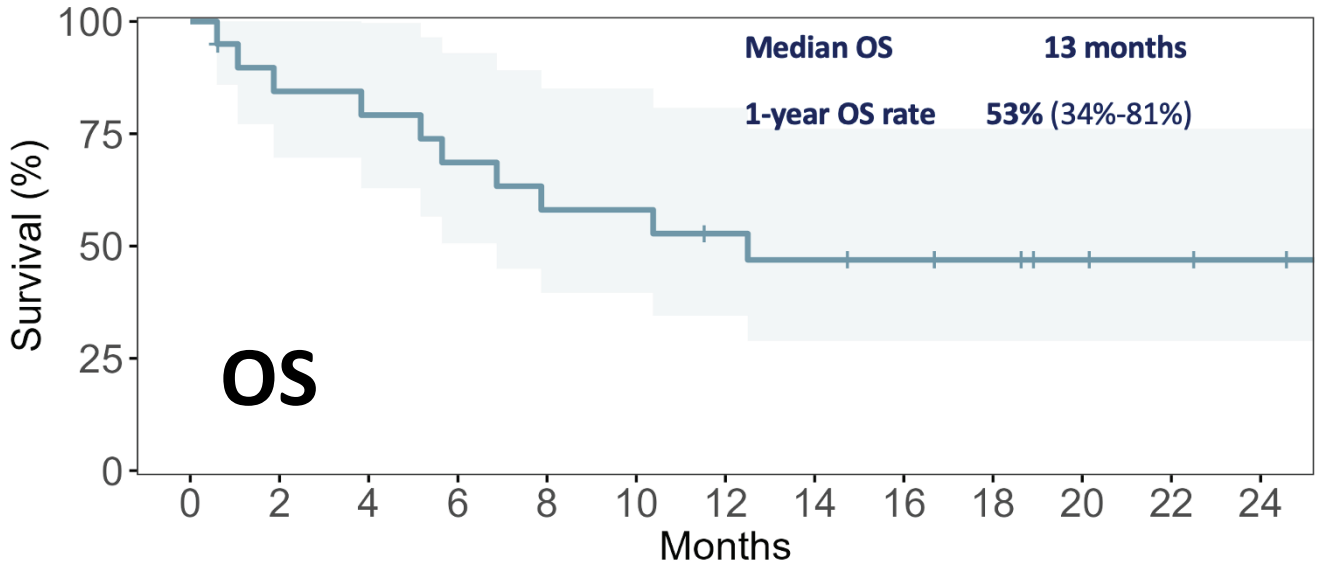
Data-cut 26th February 2025

Fox CP *et al* Abstract 087 ICML 2025

Zanubrutinib in PCNSL

Outcome (Median fu 19 months)





Zanubrutinib in PCNSL

Safety

Summary of Serious Adverse Events by Category and Event

Event type	Patients (n=20)	SAE (n=10)
Number of SAEs	7 (35%)	10
Infections & infestations	3 (15%)	5 (50%)
Lung infection	1 (5%)	1 (10%)
COVID	2 (10%)	2 (20%)
Sepsis	1 (5%)	1 (10%)
Other (NOS)	1 (5%)	1 (10%)
Nervous System Disorders	3 (15%)	3 (30%)
Seizure	2 (10%)	2 (20%)
Hydrocephalus	1 (5%)	1 (10%)
Gastrointestinal disorders	2 (10%)	2 (20%)
Diarrhoea	1 (5%)	1 (10%)
Vomiting	1 (5%)	1 (10%)

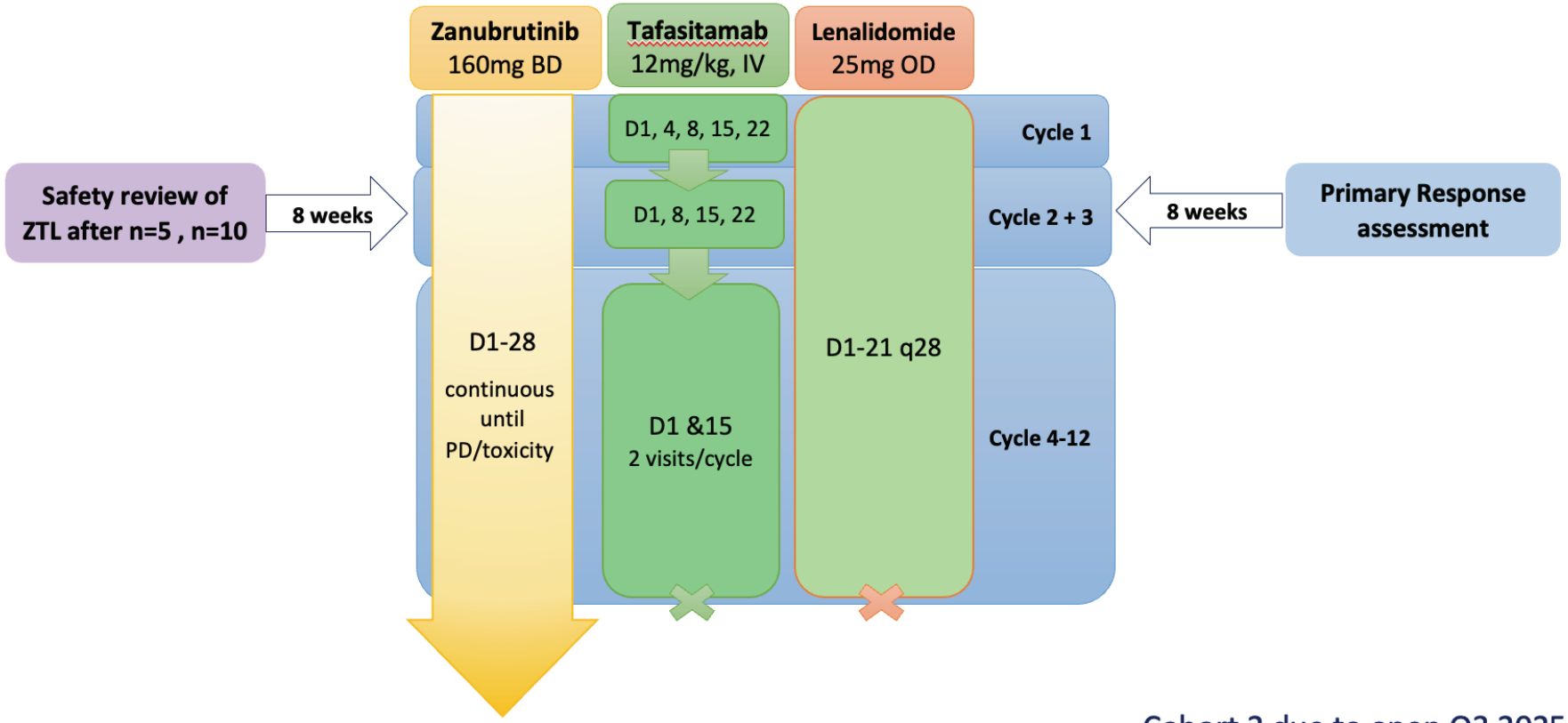
- No patients discontinued treatment due to AEs
- 20% of all AEs were grade 3 or 4
  - 9 SAEs: grade 3
  - 1 SAEs: grade 4
    - resolved without sequalae
- No SAEs resulted in deaths
- All 10 deaths were PCNSL-related

Zanubrutinib in PCNSL

Next step

PRiZM+

Cohort 2 plans: novel triplet for rrPCNSL



Cohort 2 due to open Q3 2025

Kapitel 3

Tirabrutinib in PCNSL – PROSPECT-Trial

Tirabrutinib in PCNSL – PROSPECT-Trial

Tirabrutinib for the treatment of relapsed or refractory primary central nervous system lymphoma: efficacy and safety from the phase II PROSPECT study

Lakshmi Nayak[1]*, Christian Grommes[2]*, Avyakta Kallam[3], David Peereboom[4], Prakash Ambady[5], Joe Mendez[6], Dawit Aregawi[7], Ashley Sumrall[8], Antonio Omuro[9†], Fabio Iwamoto[10], Jorg Dietrich[11], Yoshie Umemura[12‡], Reinhold Munker[13], Ugonma Chukwueke[1], Lauren Schaff[2], Sergio Prados[14], Akira Takazawa[14], Arata Aoi[14], Tracy Batchelor[15]

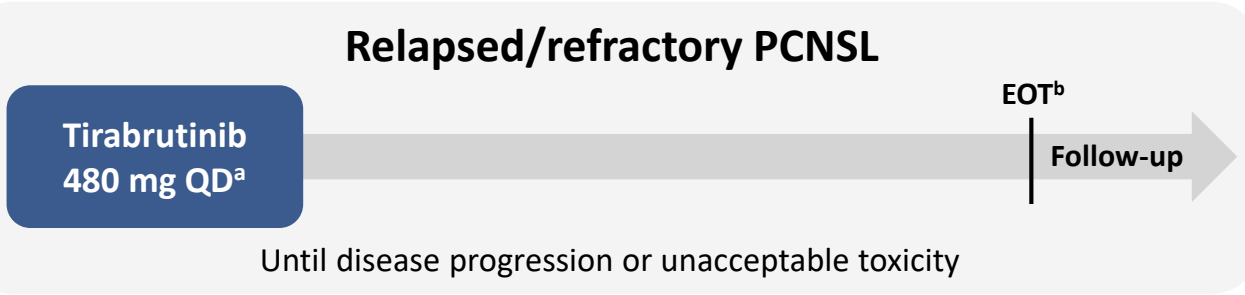
PROSPECT – Trial: Tirabrutinib in PCNSL

Design

Phase II, open-label, multicenter, US-based study of tirabrutinib in pts with r/r PCNSL

Eligibility

- Age ≥18 years
- ECOG PS 0-2
- Measurable brain lesion with a minimum diameter >1.0 cm
- Disease r/r status
- At least 1 prior HD-MTX based therapy
- Life expectancy of ≥3 months



Endpoints

Primary

- ORR per IPCG criteria, assessed by IRC

Secondary

- DOR, TTR, BOR, safety

Exploratory

- OS, PFS

PROSPECT – Trial: Tirabrutinib in PCNSL

Characteristics

PROSPECT – Trial: Tirabrutinib in PCNSL

Efficacy / Outcome

Primary Endpoint: ORR by IRC[a]

		ORR by IRC	
		n (%)	95% CI
ORR (CR+CRu+PR)		32 (67)	52, 80
CRR (CR+CRu)		21 (44)	29, 59
BOR	CR	13 (27)	15, 42
	CRu	8 (17)	8, 30
	PR	11 (23)	12, 37
	SD	9 (19)	9, 33
	PD	6 (13)	5, 25
	NE	1 (2)	0, 11

- Median time to response by IRC = 1.0 months (range, 0.9-3.7)

PROSPECT – Trial: Tirabrutinib in PCNSL

Efficacy / Outcome

Primary Endpoint: ORR by IRC[a]

		ORR by IRC	
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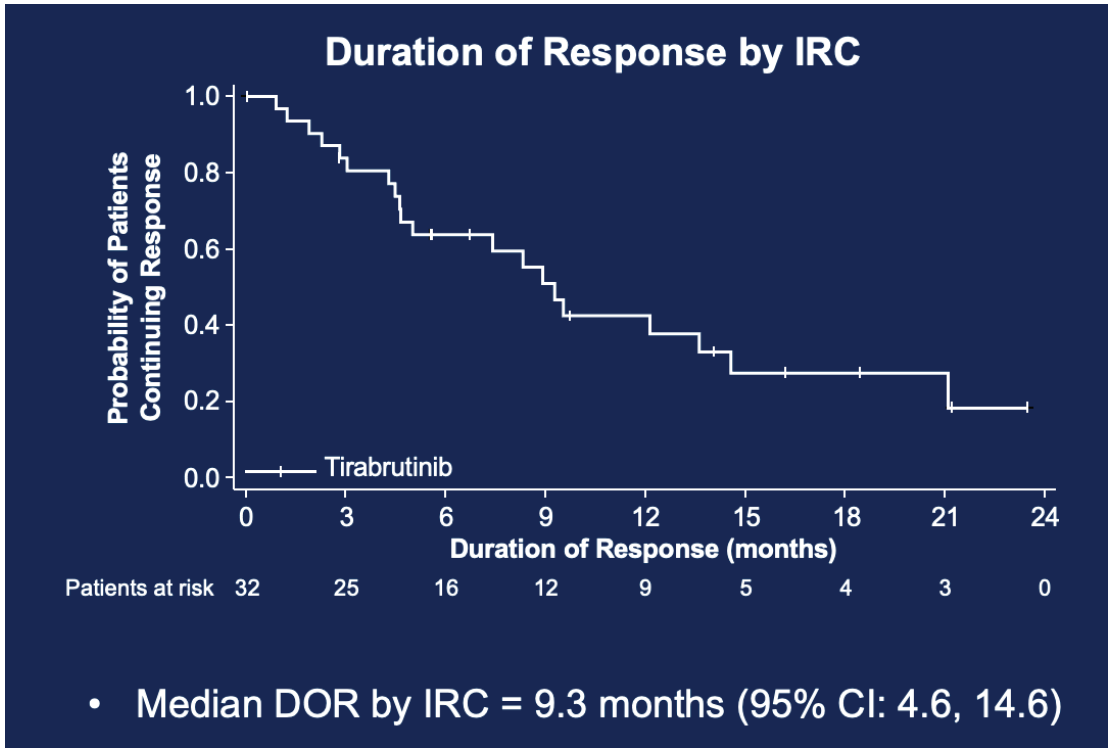
	PD	6 (13)	5, 25
	NE	1 (2)	0, 11

Duration of Response by IRC



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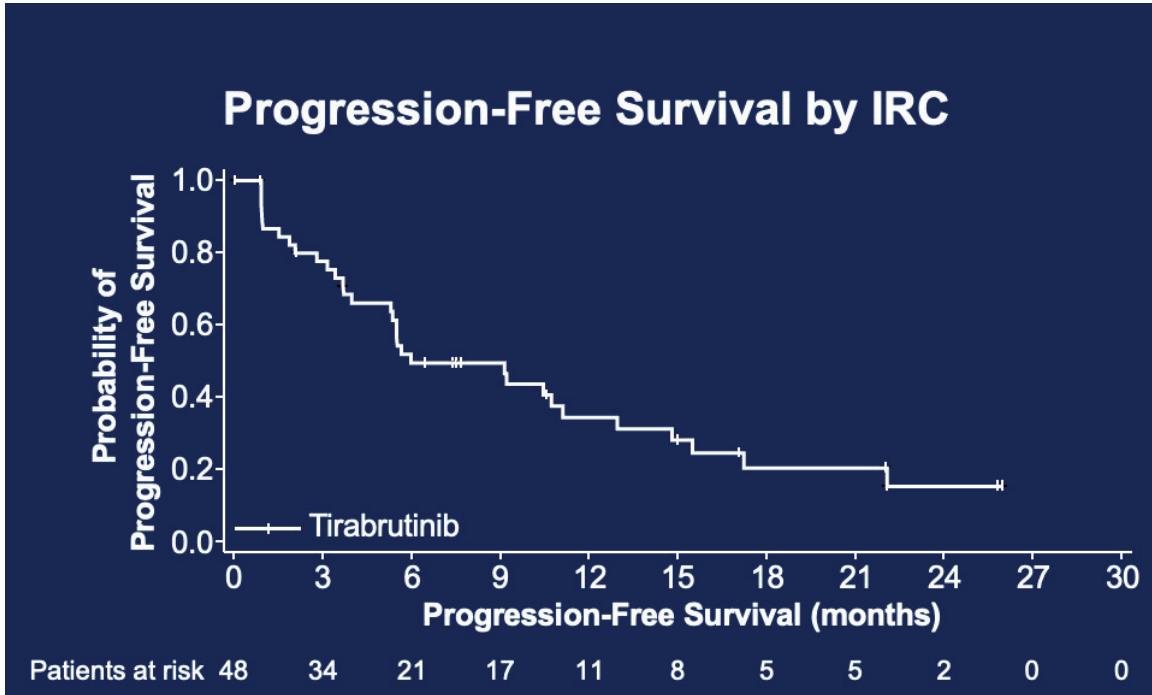
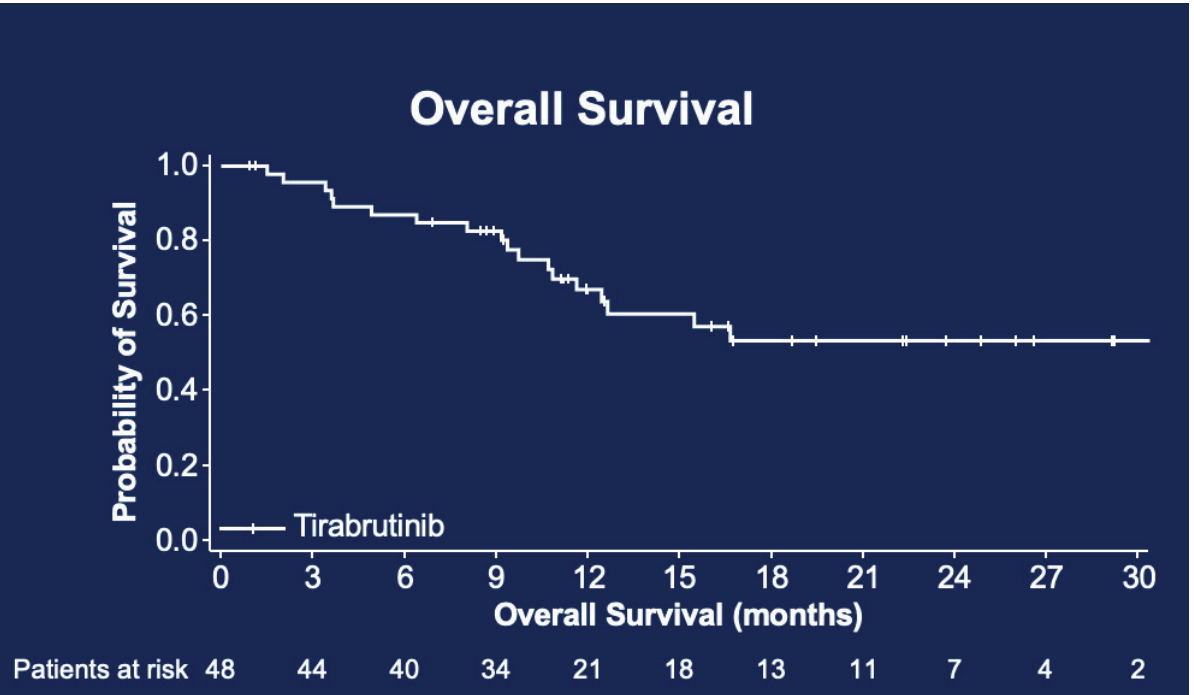
PROSPECT – Trial: Tirabrutinib in PCNSL

Efficacy / Outcome



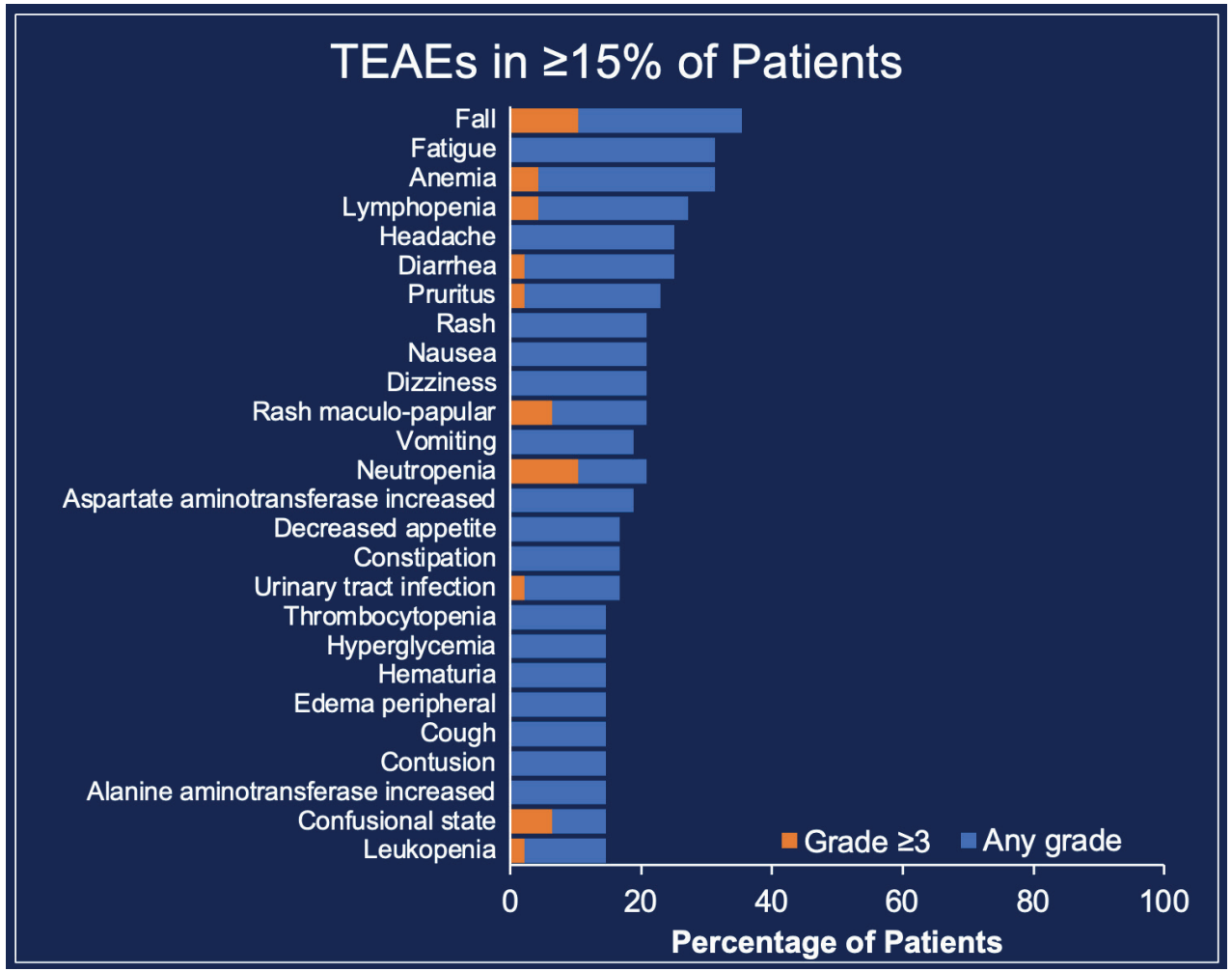


- Median PFS by IRC = 6.0 months (95% CI: 5.3, 11.1)
- Median OS = NR (95% CI: 12.5, NA)

PROSPECT – Trial: Tirabrutinib in PCNSL

Safety

TEAEs	Tirabrutinib (N=48)	
	Any grade, n (%)	Grade ≥3, n (%)
Pts with ≥1 TEAE	47 (98)	27 (56)
Pts with ≥1 treatment-related TEAE	36 (75)	13 (27)
Pts with TEAEs leading to dose interruption Treatment-related	24 (50) 16 (33)	15 (31) 8 (17)
Pts with TEAEs leading to dose reduction Treatment-related	5 (10) 3 (6)	0 0
Pts with TEAEs leading to study withdrawal Treatment-related	5 (10) 1 (2)	4 (8) 1 (2)
Pts with serious TEAEs Treatment-related	21 (44) 5 (10)	17 (35) 5 (10)
	Any grade, n (%)	
Pts with fatal TEAEs Treatment-related	2 (4) 0	



- Tirabrutinib was well tolerated in this population, with a low incidence of cardiac events (<10%, all grade 1-2)

Kapitel 4

CAR-T Zellen in Central Nervous System Lymphoma (PCNSL/SCNSL)

CAR-T Zellen in Central Nervous System Lymphoma (PCNSL/SCNSL)

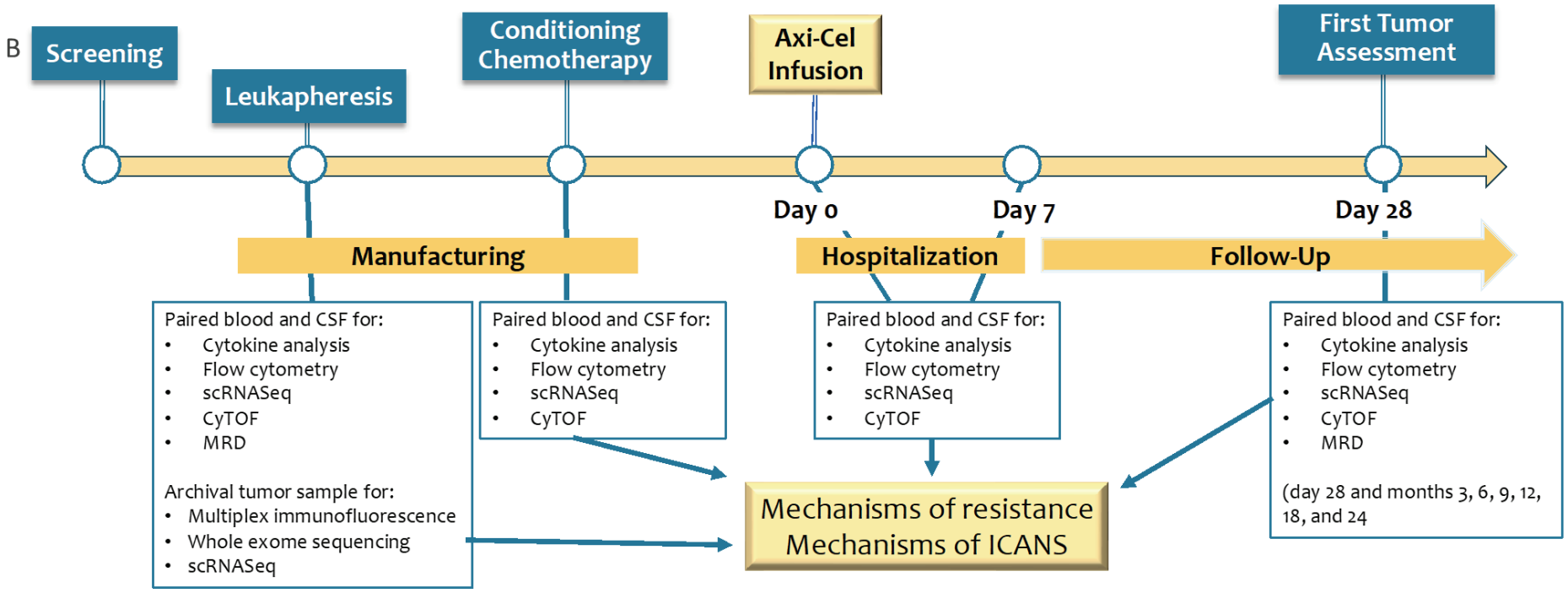
A Pilot Study of Axicabtagene Ciloleucel (axi-cel) for the Treatment of Relapsed /Refractory Primary and Secondary Central Nervous System Lymphoma (CNSL)

Jacobson CA, Falvey C, Bouvier R, Durlacher E, Wei H, Dela Cruz J, Redd R, Lee E, Gonzalez Castro LN, Chukwueke UN, Kim A, Lee EQ, McFaline Figueroa JR, Aquilanti E, Youssef G, Murakami M, Torres A, Kean LS, Gerdemann U, Albanese A, Keskula P, Mattie M, Filosto S, Poddar S, Armand P, Nayak L

Axi-Cel in CNS-Lymphoma

Background & Design

- CAR T-cells (axi-cel) are effective in LBCL and enter CSF.
- CNSL (PCNSL & SCNSL) has poor prognosis and limited options.
- Study goal: assess safety and efficacy of axi-cel in r/r CNSL.



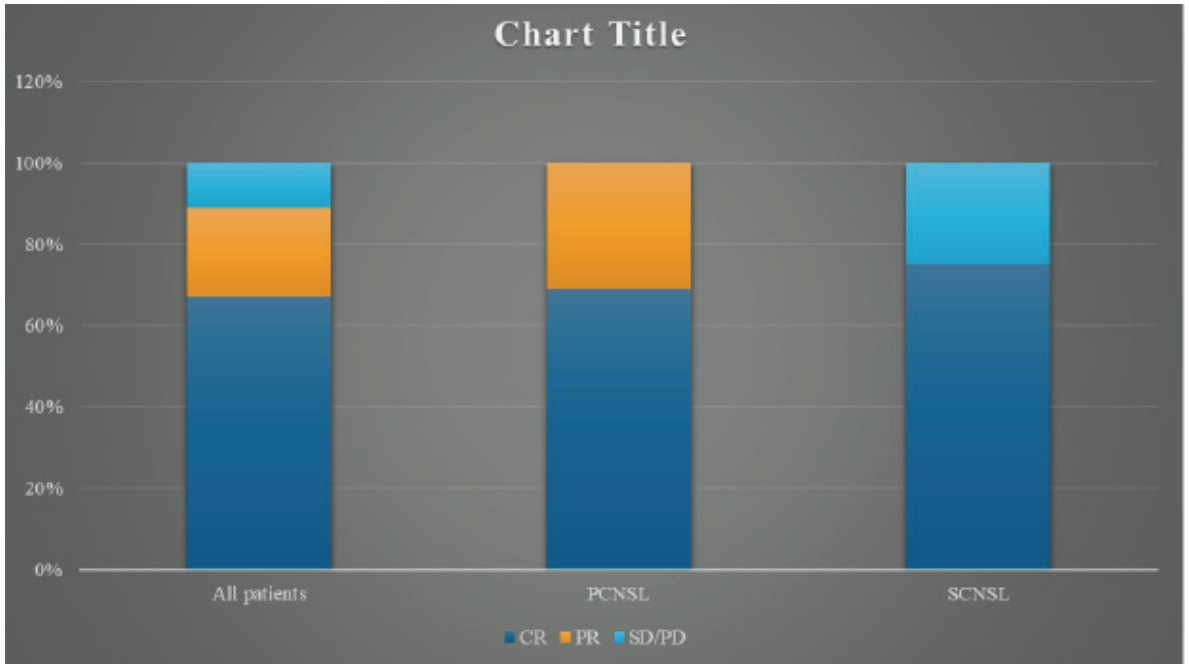
Axi-Cel in CNS-Lymphoma

Methods & Patient Characteristics

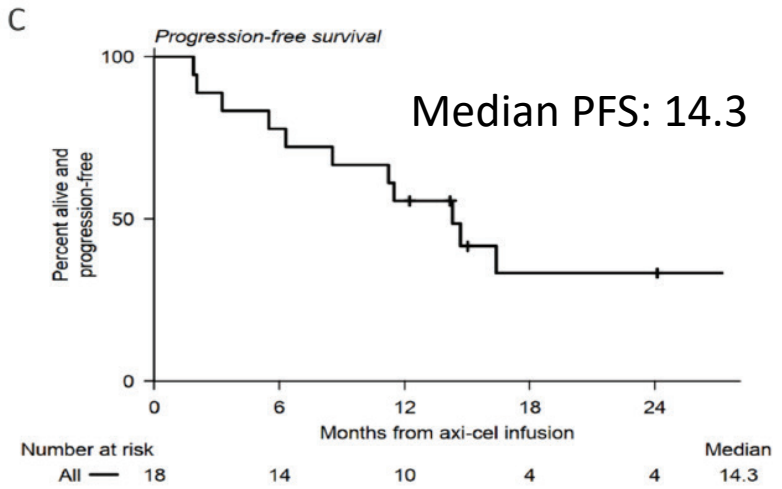
- 18 patients: 14 PCNSL, 4 SCNSL; median age: 63 (range 33–80).
- Median prior therapies: 2 (1–6); 83% refractory to last therapy.
- No bridging therapy; all received standard axi-cel regimen.
- Primary endpoint: safety.
- Secondary: ORR, CR, PFS, OS, correlative studies.

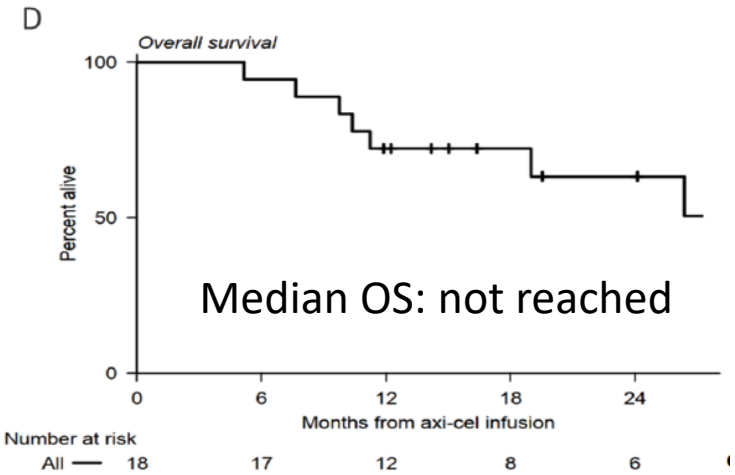
Axi-cel in r/r Primary & Secondary CNS Lymphoma

Efficacy / Outcome (median follow-up 24.1 m)



- ORR: 89%; CR rate: 67%.
- CR rates similar between PCNSL (69%) and SCNSL (75%).
- OS significantly longer in PCNSL group ($p < 0.001$).





Axi-cel in r/r Primary & Secondary CNS Lymphoma

Safety

Table 2. Safety Data	CRS	ICANS
Any grade, n (%)	16 (89%)	8 (44%)
Grade 3, n (%)	0 (0)	5 (28%)
Toci use, n (%)	14 (78%)	n/a
Median # doses (range)	1 (1-2)	n/a
Dex use, n (%)	13 (72%)	5 (29%)
Median # doses (range)	1 (1-7)	2 (1-9)
	1m	3m
Prolonged grade 3+ cytopenias	10 (56%)	0 (0%)
Neutropenia	7 (39%)	0 (0%)
Thrombocytopenia	1 (6%)	0 (0%)
Anemia	5 (28%)	0 (0%)

Axi-cel in r/r Primary & Secondary CNS Lymphoma

Conclusions

- CSF CAR T-cells show unique IFN and dysfunction signatures.
- Patienten mit dauerhafter kompletter Remission zeigen eine vermehrte Expression aktivierender T-Zell-Gene wie CD226.
- Differential gene expression identified potential markers for response.

Zusammenfassung – Take Home, Message

- Die Hochdosistherapie mit Thiotepa ist unabhängig von der Remission (CR/PR) vor Transplantation sehr effektiv.
  → Auch bei PD nach HDT liegt das OS / PFS über 50%

Zusammenfassung – Take Home, Message

- Die Hochdosistherapie mit Thiotepa ist unabhängig von der Remission (CR/PR) vor Transplantation sehr effektiv.
  → Auch im Falle PD liegt das OS / PFS über 50%

- Die neuen BTK-Inhibitoren Zanubrutinib und Tirabrutinib sind sehr effektiv und sicher bei ZNS-Lymphomen

Zusammenfassung – Take Home, Message

- Die Hochdosistherapie mit Thiotepa ist unabhängig von der Remission (CR/PR) vor Transplantation sehr effektiv.
  → Auch im Falle PD liegt das OS / PFS über 50%

- Die neuen BTK-Inhibitoren Zanubrutinib und Tirabrutinib sind sehr effektiv und sicher bei ZNS-Lymphomen

- Axi-cel zeigt bei 18 Patienten mit rr/PCNSL/SCNSL hohe Ansprechraten bei gutem Sicherheitsprofil.

Alle Kurzpräsentationen sind online unter

www.lymphome.de/icml2025

Für den Inhalt verantwortlich:

Prof. Dr. med. Gerald Illerhaus

Klinikum Stuttgart

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