Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

KML-Expert:innen berichten

17th ICML 2023 LUGANO

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Expert:innen berichten zu Lymphomen & Leukämien

Prof. Dr. med. Kai Hübel
Uniklinik Köln

Follikuläre Lymphome (FL)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ICML2023 wird in Kooperation mit fünf unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Anstellungsverhältnis, Führungsposition	Oberarzt, Uniklinik Köln
Beratungs-/ Gutachtertätigkeit	Roche, BMS, Incyte, EUSA, AbbVie, Novartis, Gilead, Miltenyi Biotec, BeiGene
Besitz von Geschäftsanteilen, Aktien oder Fonds	entfällt
Patent, Urheberrecht, Verkaufslizenz	entfällt
Honorare	Roche, Incyte, EUSA, Sandoz, Novartis, BeiGene, AbbVie
Finanzierung wissenschaftlicher Untersuchungen	Roche, Gilead, Incyte, Sandoz
Andere finanzielle Beziehungen	entfällt
Immaterielle Interessenkonflikte	entfällt

Kapitel 1

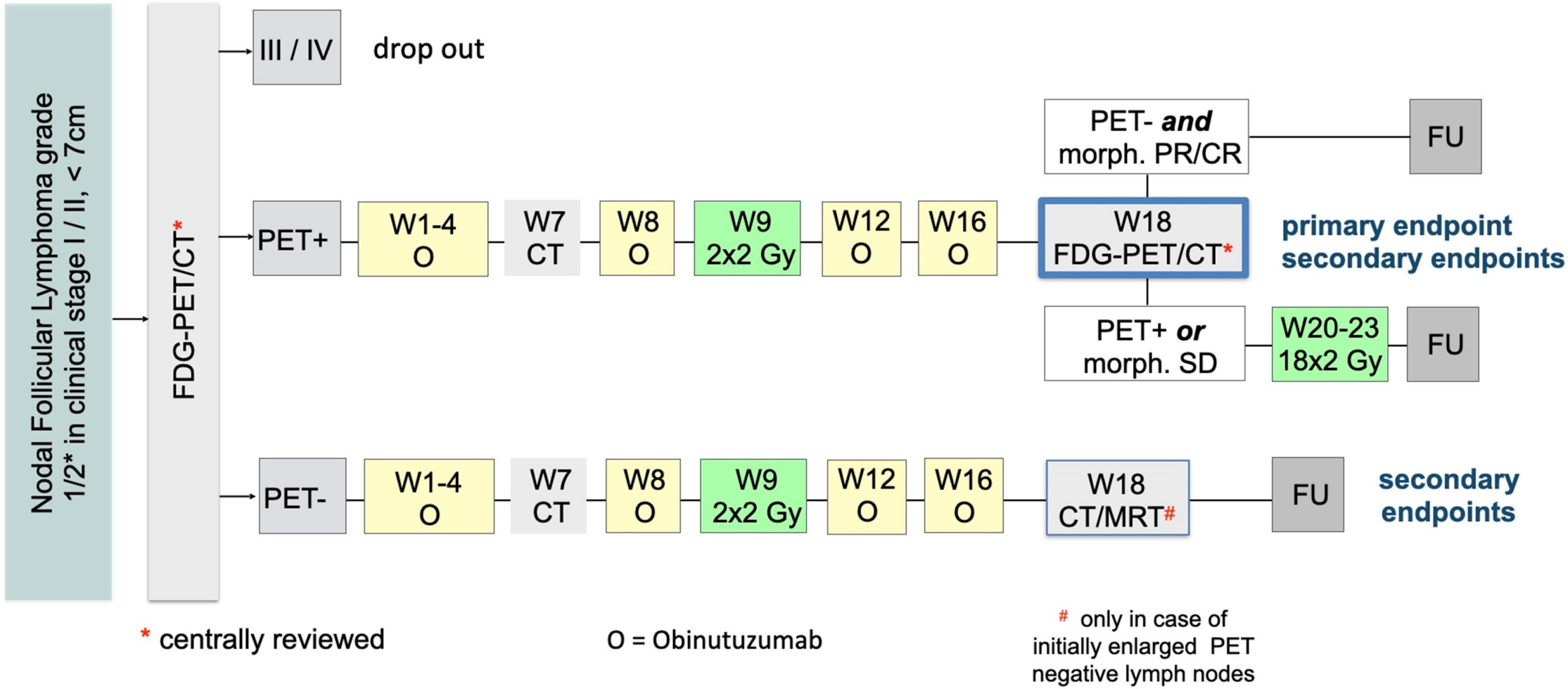
Follikuläres Lymphom im frühen Stadium: Brauchen wir noch die Strahlentherapie?

High rate of metabolic complete response after low dose radiotherapy and Obinutuzumab in early stage follicular lymphoma: Initial results of the GAZAI study (GLA 2018-3)

Abstract Nr. 142

Klaus Herfarth et al.

GAZAI: Studiendesign

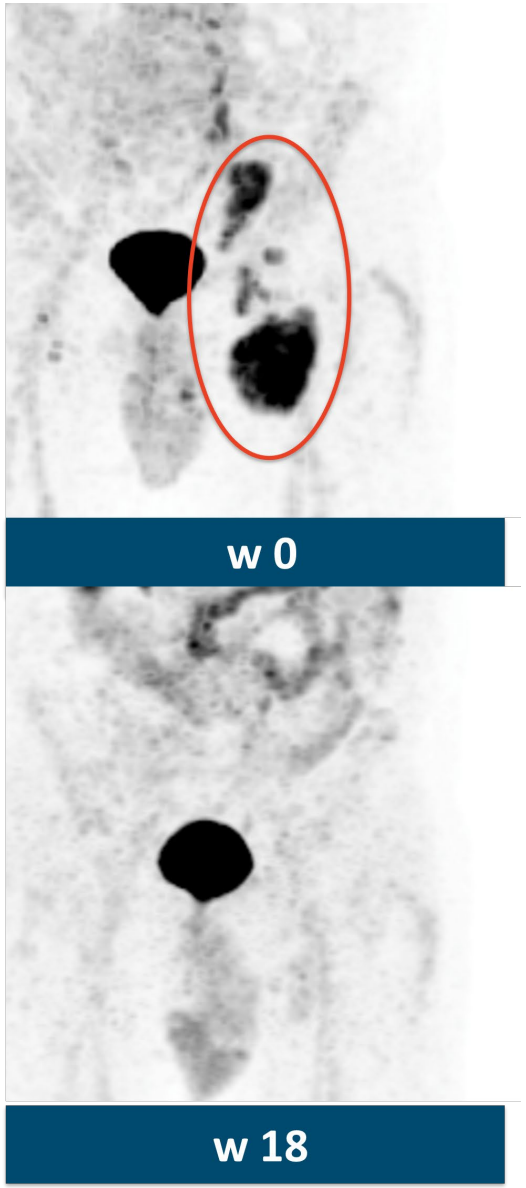


GAZAI: Therapieansprechen im PET

(n=53)

	w 18	DS
CR	**46 (87 %)**	1/2
PR	3 (6%)	3
PR	3 (6%)	4
PD	1* (2%)	

* f/u: metastases of urothelial carcinoma



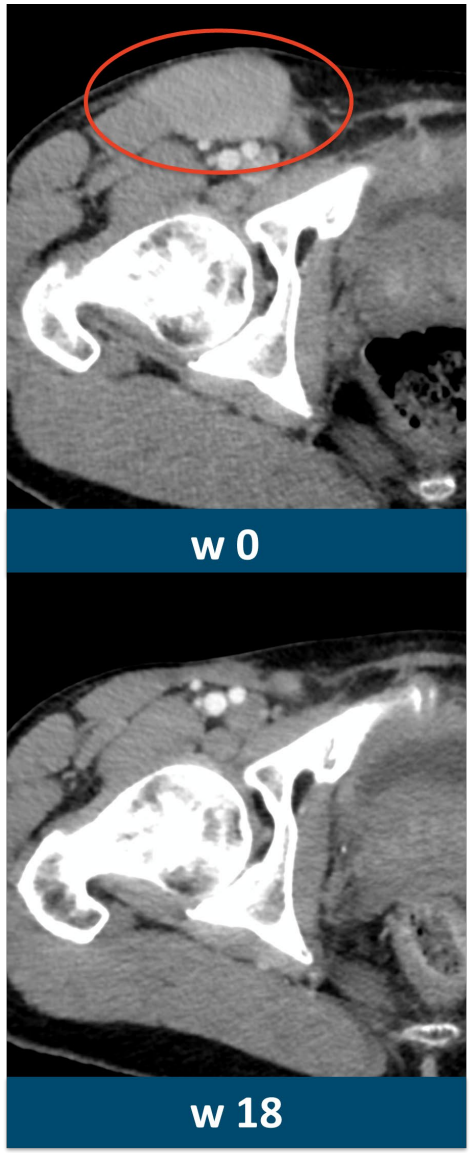
GAZAI: Therapieansprechen im CT

(n=54)

according Cheson 1999

	w 7	w 18
CR/CRu	**21 (39%)**	**49 (91 %)**
PR	18 (33%)	4 (7 %)
SD	15 (28%)	0 (0 %)
PD	0 (0%)	1* (2%)

* f/u: metastases of urothelial carcinoma



GAZAI: Minimal residual disease

Patients with positive markers in peripheral blood

allel-specific RQ PCR targeting t(14;18) translocations & clonal immunoglobulin heavy chain (IGH) rearrangements

week 0

13 / 54 → 24%

week 18

1 / 54 → 2%

Kapitel 2

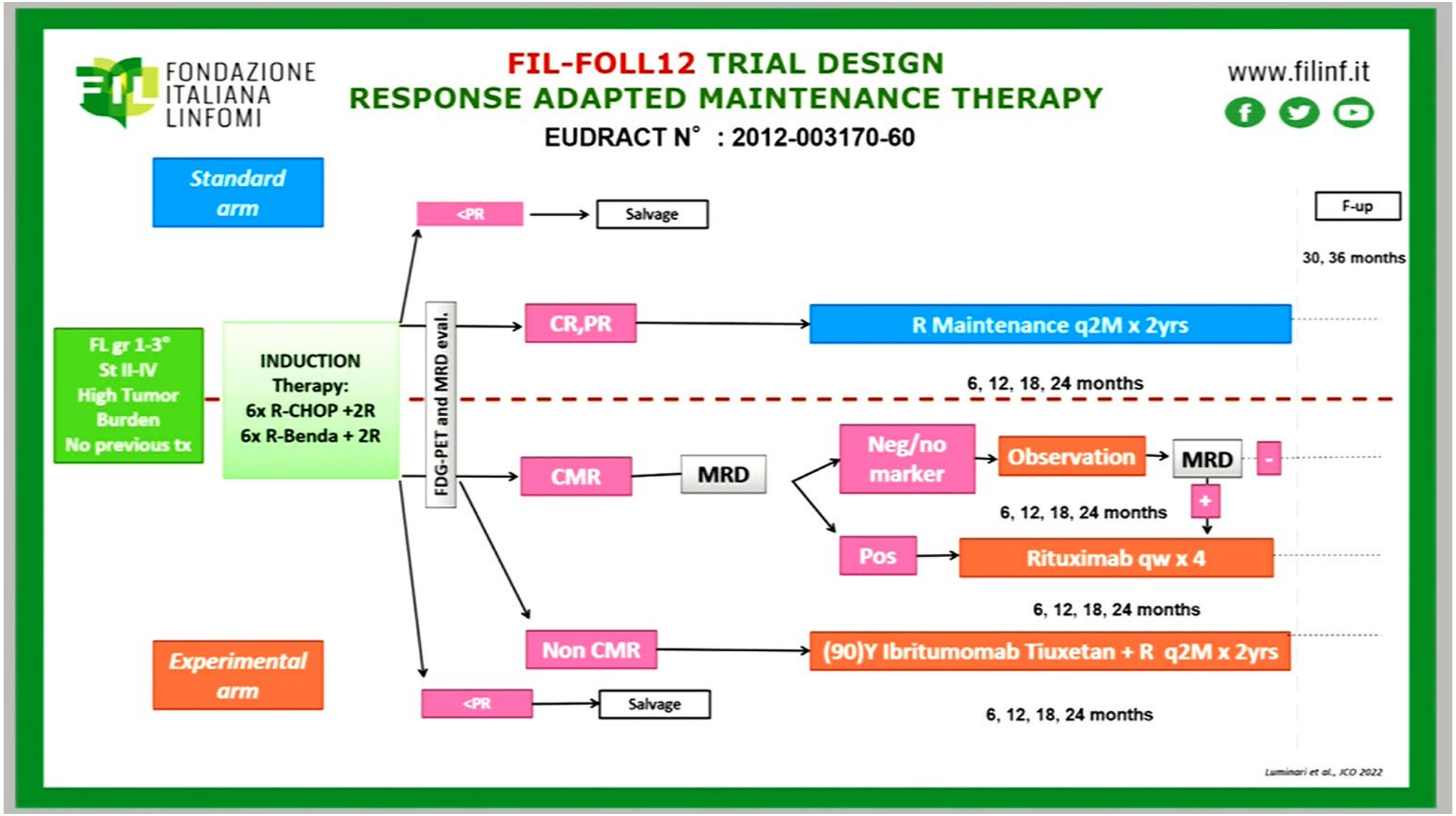
Können wir den Verlauf eines Patienten mit follikulärem Lymphom vorhersagen?

Combined use of minimal residual disease monitoring and FDG-PET for outcome prediction in follicular lymphoma: results from the Fondazione Italiana Linfomi (FIL) FOLL12 trial

Abstract Nr. 115

Simone Ferrero et al.

FOLL12: Studiendesign



FOLL12: PFS nach PET- und MRD-Status

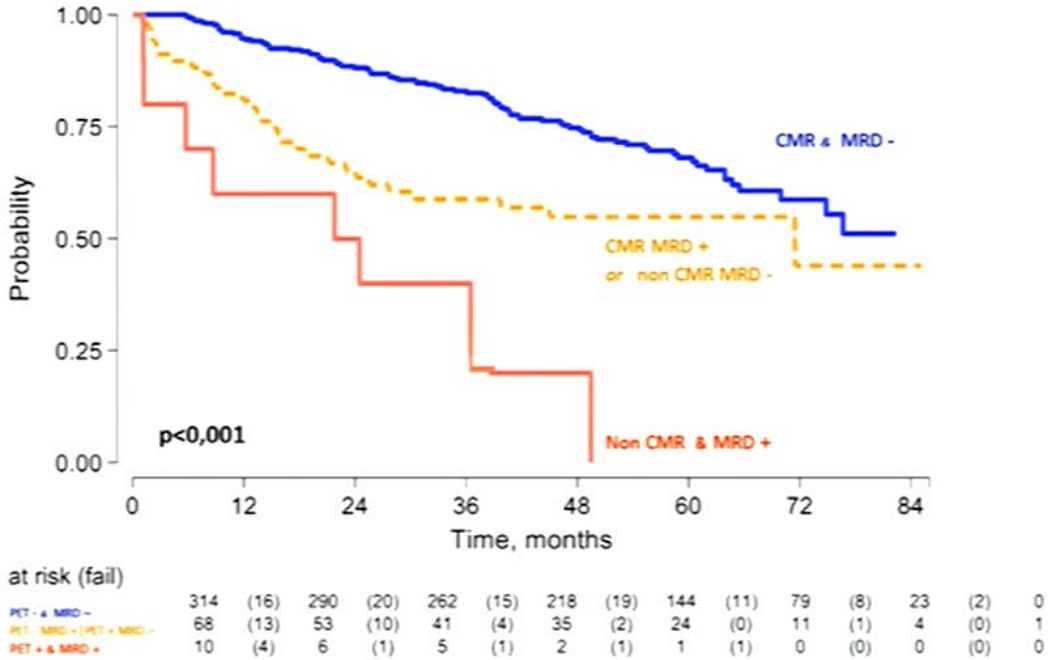
FONDAZIONE ITALIANA LINFOMI

FDG-PET & MRD AT EOI ARE INDEPENDENT PREDICTORS OF PFS

www.filinf.it

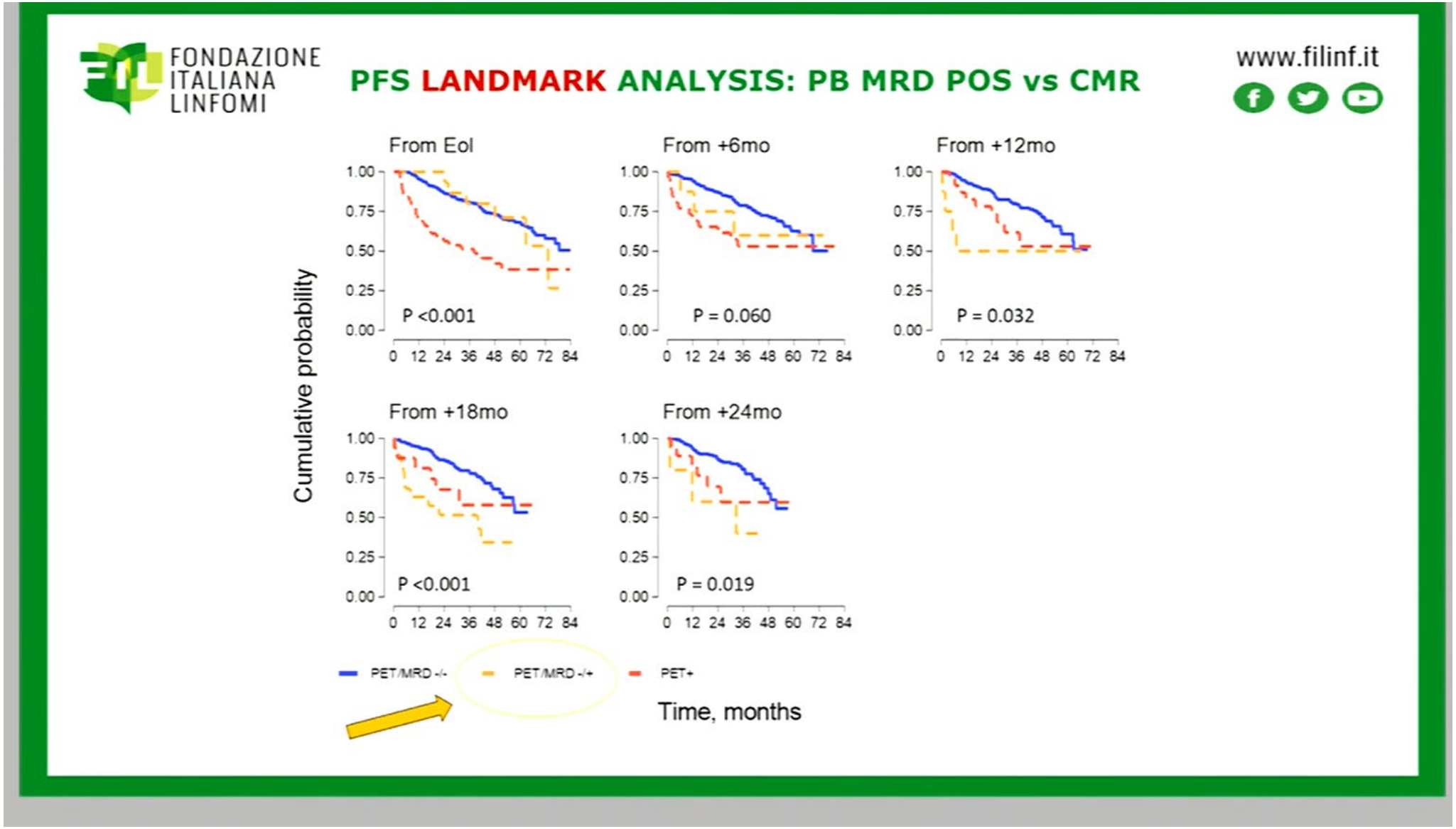
MULTIVARIATE ANALYSIS

Factor	HR (95%CI)	P-value
MRD +	1.66 (1.01-2.71)	0.042
Non CMR (DS 4/5)	2.03 (1.30-3.18)	0.002
FLIPI-2 HR (3/5)	2.30 (1.61-3.30)	<0.001
Exp. Arm	2.20 (1.53-3.18)	<0.001



PFS from EoI stratified by PET and BM MRD results

FOLL12: Verlauf bei PET-Negativität und MRD-Positivität

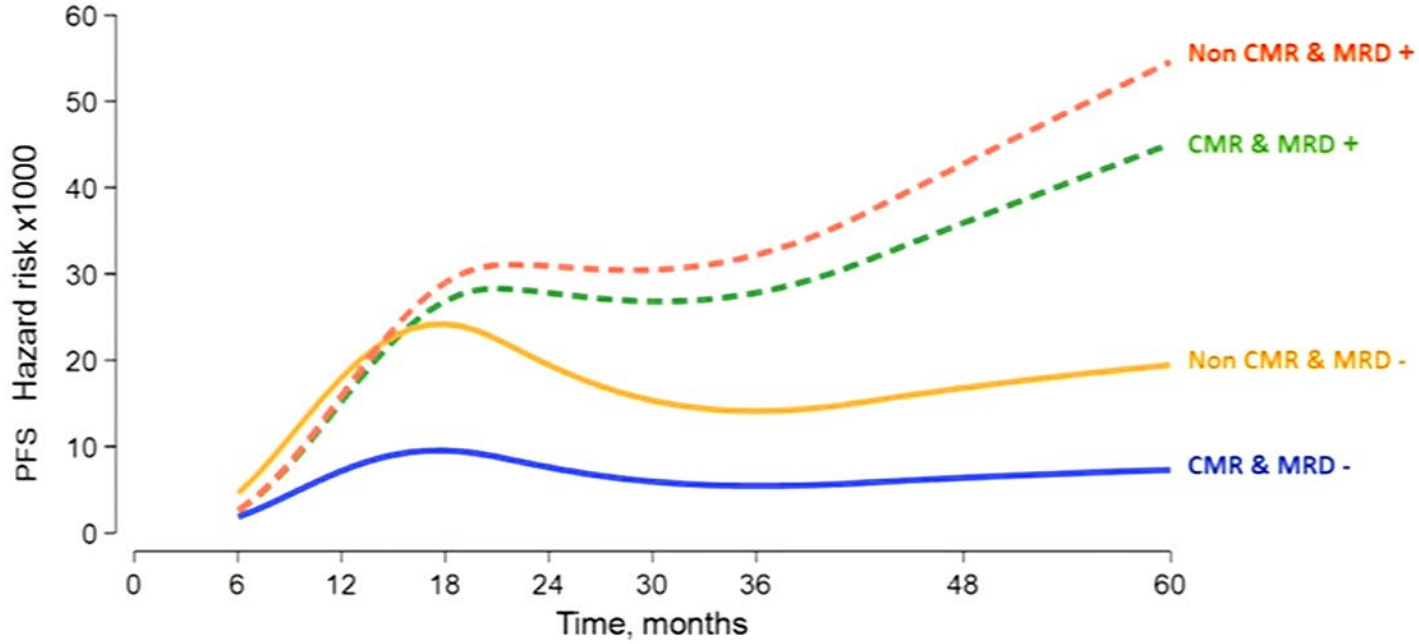


FOLL12: Verlauf bei MRD-negativen Patienten

FONDAZIONE ITALIANA LINFOMI

www.filinf.it

PERSISTENTLY MRD NEG PATIENS HAVE THE BEST OUTCOME, IRRESPECTIVELY OF PREVIOUS EOI CMR STATUS



Kapitel 3

Welchen Stellenwert haben BTK-Inhibitoren beim r/r follikulären Lymphom?

Zanubrutinib plus obinutuzumab versus obinutuzumab in patients with relapsed/refractory follicular lymphoma: Updated analysis of the ROSEWOOD study

Abstract Nr. 81

Pier Luigi Zinzani et al.

ROSEWOOD: Studiendesign

A Phase 2, Multicenter, Open-Label, Randomized Trial for Patients with Relapsed or Refractory Follicular Lymphoma

Eligibility

- Adult patients with histologically confirmed grade 1-3a FL
- Patients with R/R disease, previously treated with ≥ 2 prior systemic treatments including an anti-CD20 antibody and an appropriate alkylator-based combination therapy
- Measurable disease
- ECOG-PS 0-2
- Adequate organ functions
- No prior BTK inhibitor exposure

Stratification factors
- Number of prior lines
- Rituximab refractory status
- Geographic region

ARM A
Zanubrutinib plus obinutuzumab
N = 140
Until PD/unacceptable toxicity

ARM B
Obinutuzumab
N = 70
Option to crossover to arm A if PD/SD centrally confirmed at 12 months

Assuming $ORR_A = 0.55$ and $ORR_B = 0.30$, 210 patients will be enrolled in a 2:1 ratio to provide a power of approximately 91% in testing ORR_A versus ORR_B using a normal approximation to binomial distribution with a 2-sided significance level of 0.05 with continuity correction

Primary Endpoint:
ORR assessed by ICR according to Lugano classification

Secondary Endpoints:
- ORR assessed by investigator
- DOR and PFS determined by ICR review and investigator assessment
- Overall survival
- CR and CMR rate assessed by ICR and investigator assessment
- TTR assessed by ICR and investigator assessment
- Patient-reported outcome measured by EORTC QLQ-C30 and EQ-5D-5L questionnaires
- Safety/Tolerability
- Pharmacokinetics parameters (combination arm only)

Exploratory Endpoint:
- ORR after crossover to arm A

ROSEWOOD: Patientencharakteristika

	Zanubrutinib + Obinutuzumab N=145	Obinutuzumab N=72
Median age, years (min, max)	63.0 (31, 84)	65.5 (32, 88)
ECOG PS 0-1, n (%)	140 (96.6)	71 (98.6)
High FLIPI score, n (%)	77 (53.1)	37 (51.4)
Ann Arbor stage III-IV, n (%)	119 (82.1)	60 (83.3)
Bulky disease (≥7 cm), n (%)	23 (15.9)	12 (16.7)
High LDH level (>ULN), n (%)	49 (33.8)	29 (40.3)
High tumor burden per GELF criteria, n (%)	83 (57.2)	40 (55.6)
Median number of prior lines of therapy, n (min, max)	3 (2, 11)	3 (2, 9)
Refractory to rituximab, n (%)	78 (53.8)	36 (50.0)
Refractory to most recent line of therapy, n (%)	47 (32.4)	29 (40.3)
PD ≤24 months of starting first line of therapy, n (%)	50 (34.5)	30 (41.7)

FLIPI, follicular lymphoma international prognostic index; ITT, intention to treat; LDH, lactate dehydrogenase.

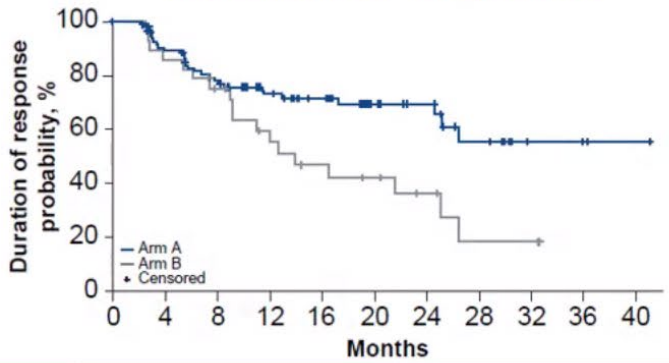
ROSEWOOD: Therapieansprechen

	Zanubrutinib + Obinutuzumab N=145	Obinutuzumab N=72
Best Overall Response, n (%)		
Complete response	57 (39.3)	14 (19.4)
Partial response	43 (29.7)	19 (26.4)
Stable disease	24 (16.6)	14 (19.4)
Non-progressive disease	3 (2.1)	4 (5.6)
Progressive disease	13 (9.0)	15 (20.8)
Discontinued prior to first tumor assessment/Not Evaluable	5 (3.4)	6 (8.3)
Overall Response Rate, n (%)	100 (69.0)	33 (45.8)
(95% CI)	(60.8, 76.4)	(34.0, 58.0)
Risk Difference, % (95% CI)	22.7 (9.0, 36.5)	
2-sided p-value	0.0012	
Disease Control Rate, n (%)	124 (85.5)	47 (65.3)

ITT, intent to treat.

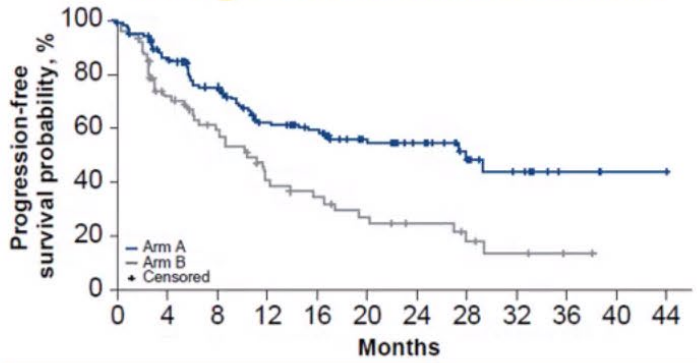
ROSEWOOD: Verlauf

Duration of response



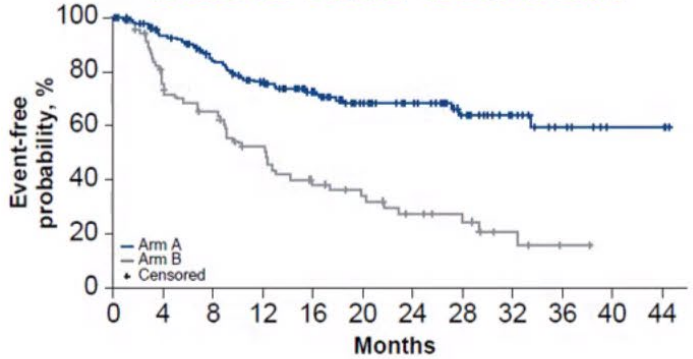
	Zanubrutinib + Obinutuzumab N=145	Obinutuzumab N=72
Median Duration of Response, months (95% CI)	NE (25.3, NE)	14.0 (9.2, 25.1)
DOR Rate at 18 months, % (95% CI)	69.3 (57.8, 78.2)	41.9 (22.6, 60.1)

Progression-free survival



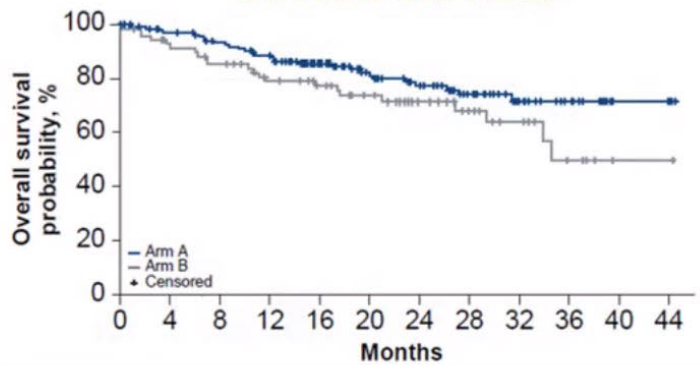
	Zanubrutinib + Obinutuzumab N=145	Obinutuzumab N=72
Median Progression-free survival, months (95% CI)	28.0 (16.1, NE)	10.4 (6.5, 13.8)
Rate at 18 months, % (95% CI)	56.3 (46.7, 64.8)	29.7 (17.6, 42.7)

Time to Next Treatment



	Zanubrutinib + Obinutuzumab N=145	Obinutuzumab N=72
Median Time To Next Treatment, months (95% CI)	NE (33.4, NE)	12.2 (8.5, 17.3)
Rate at 18 months, % (95% CI)	69.5 (60.4, 76.9)	36.2 (24.2, 48.2)

Overall survival



	Zanubrutinib + Obinutuzumab N=145	Obinutuzumab N=72
Median Overall survival, months (95% CI)	NE (NE, NE)	34.6 (29.3, NE)
Rate at 18 months, % (95% CI)	84.6 (77.1, 89.8)	73.5 (60.7, 82.7)

ROSEWOOD: Sicherheitsanalyse

	Zanubrutinib + Obinutuzumab N=143	Obinutuzumab N=71
Patients With at Least One Treatment-Emergent Adverse Event	135 (94.4)	64 (90.1)
Grade 3 or Higher	90 (62.9)	34 (47.9)
Serious	58 (40.6)	22 (31.0)
Leading to Death	12 (8.4)	7 (9.9)
Leading to Treatment Discontinuation	23 (16.1)	8 (11.3)
Leading to Dose Modification	75 (52.4)	31 (43.7)
Leading to Dose Interruption	65 (45.5)	18 (25.4)
Leading to Dose Reduction	13 (9.1)	NA
Leading to Dose Delay	40 (28.0)	18 (25.4)

Kapitel 4

Bispezifische Antikörper und CAR-T-Zelltherapien beim r/r follikulären Lymphom

Epcoritamab with rituximab + lenalidomide (R2) provides durable responses in high-risk follicular lymphoma, regardless of POD24 status

Abstract Nr. 84

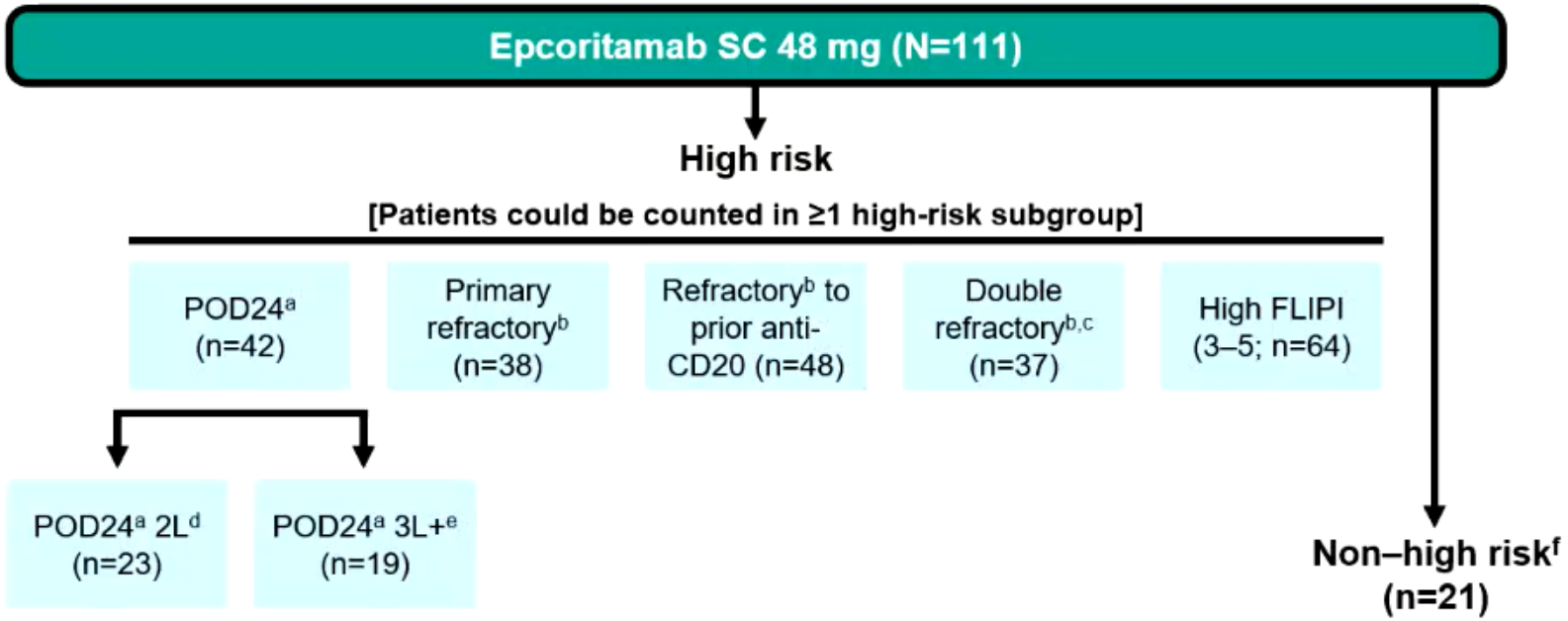
David Belada et al.

EPCORE NHL-2: Studiendesign

Key inclusion criteria

- R/R CD20+ FL
  - Grade 1, 2, or 3A
  - Stage II–IV
- Need for treatment based on symptoms or disease burden, as determined by GELF criteria[1]
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

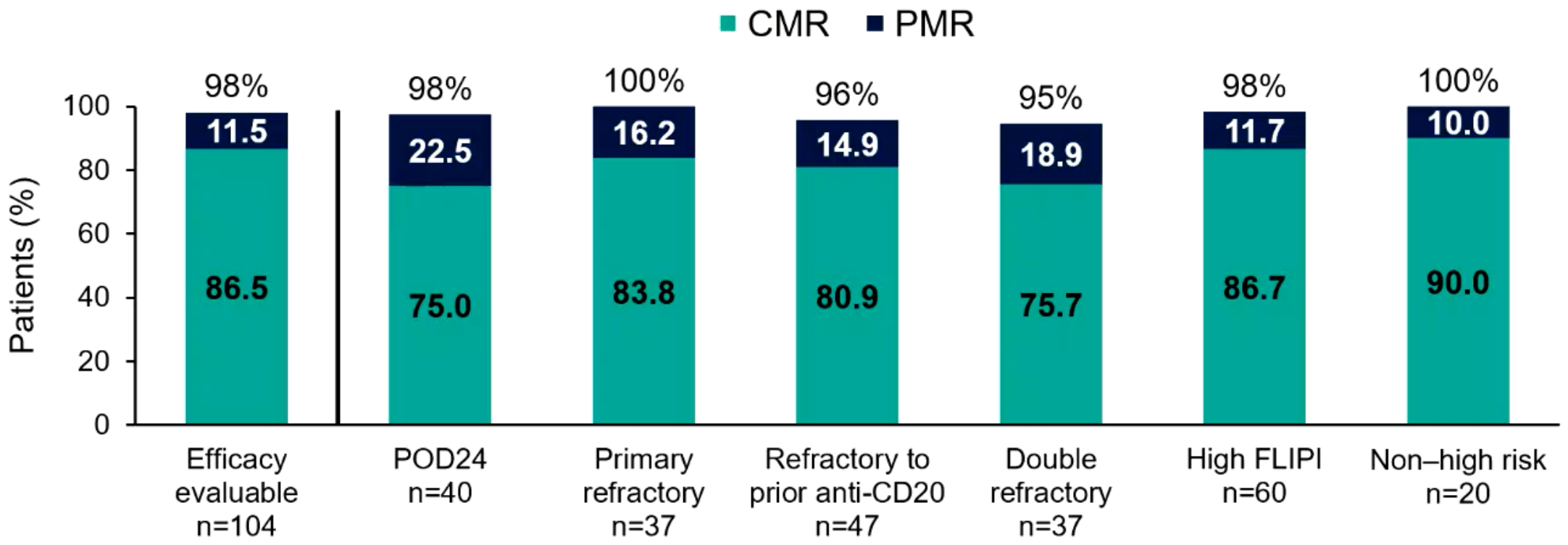
Data cutoff: January 31, 2023
Median follow-up: 11.4 mo
Primary objectives: Safety and antitumor activity[g]



First pooled analysis for epcoritamab SC + R² in R/R FL patients

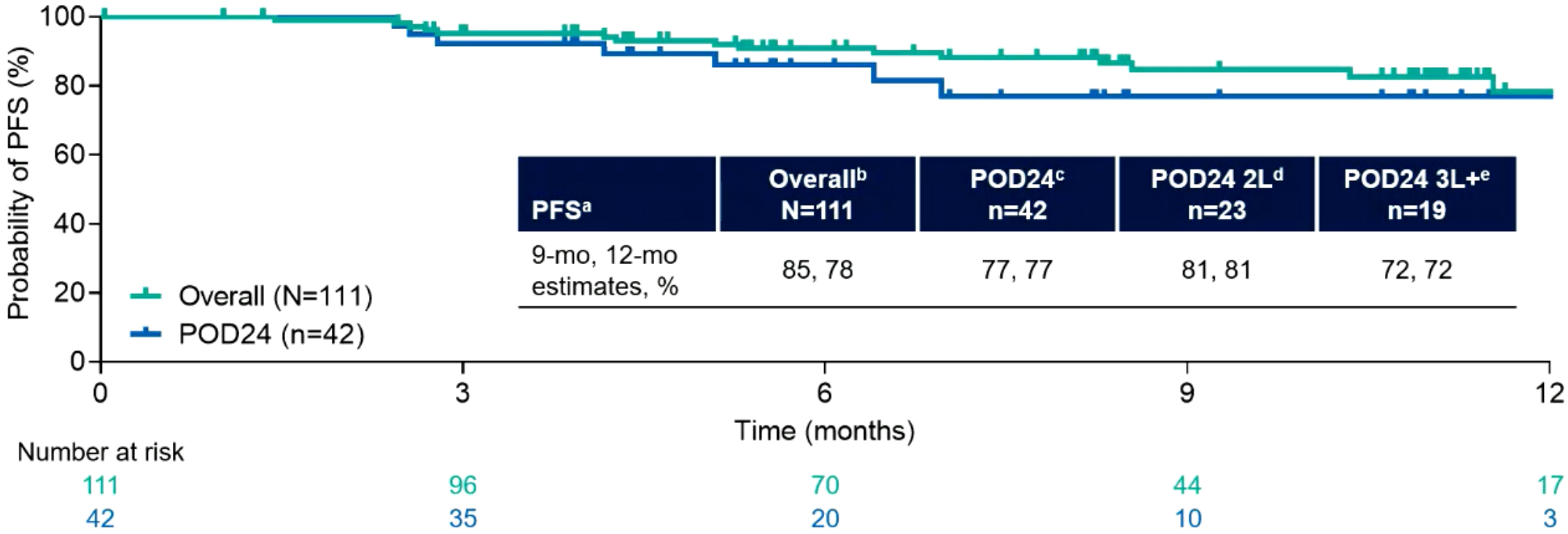
[a]POD24: Progression within 2 y of initiating first-line treatment that included chemoimmunotherapy. [b]Refractory: No response or relapse within 6 mo after therapy. [c]Double refractory: Refractory to both anti-CD20 and an alkylating agent. [d]Patients received epcoritamab SC in second line. [e]Patients received epcoritamab SC in third line or beyond. [f]Non–high risk: Patients who do not meet criteria for any of the predefined high-risk factors (eg, POD24, primary refractory, refractory to prior anti-CD20, double refractory, and high FLIPI). [g]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression. **1.** Brice P, et al. *J Clin Oncol*. 1997;15:1110-7.

EPCORE NHL-2: Therapieansprechen in Subgruppen



High overall response and CMR rates regardless of subgroup

EPCORE NHL-2: PFS, Gesamtkollektiv und POD24-Patienten



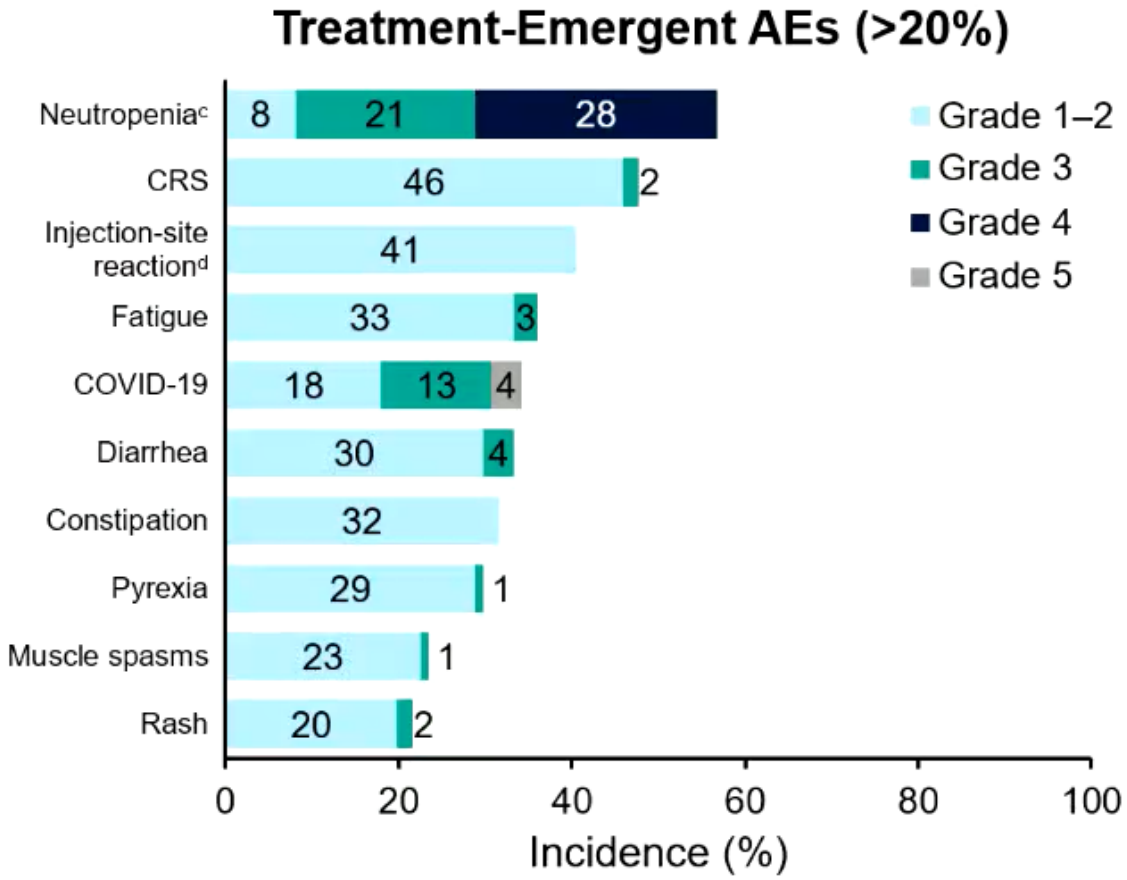
PFS[a]	Overall[b] N=111	POD24[c] n=42	POD24 2L[d] n=23	POD24 3L+[e] n=19
9-mo, 12-mo estimates, %	85, 78	77, 77	81, 81	72, 72

Epcoritamab SC + R^2 led to durable remissions, including in POD24 patients

Data cutoff: January 31, 2023. Definitions for all subgroups available in Study Design and Patient Disposition. [a]PFS is among full analysis set. [b]Median follow-up: 11.4 mo (range, 2.1–22.1). [c]Median follow-up: 9.5 mo (range, 2.4+ to 19.4). [d]Median follow-up: 9.2 mo (range, 3.0–19.4). [e]Median follow-up: 9.5 mo (range, 2.4+ to 16.7).

EPCORE NHL-2: Toxizitäten

	Total N=111
Grade ≥3 TEAE, n (%)	84 (76)
Related to epcoritamab SC	45 (41)
ICANS, n (%)[a]	2 (2)
Median time to resolution, d (range)[b]	5.5 (4–7)
CTLS, n (%)	0
Epcoritamab SC dose delay due to TEAE, n (%)	68 (61)
Related to epcoritamab SC	32 (29)
Epcoritamab SC discontinuation due to TEAE, n (%)	14 (13)
Related to epcoritamab SC	**5 (5)**
Fatal TEAE (all COVID-19), n (%)	4 (4)



Findings are consistent with previous reports

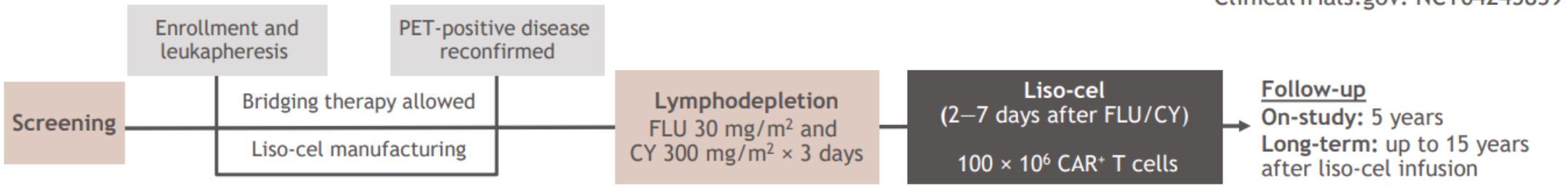
TRANSCEND FL: PHASE 2 STUDY RESULTS OF LISOCABTAGENE MARALEUCEL (LISO-CEL) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL)

Abstract Nr. LBA4

Franck Morschhauser et al.

TRANSCEND FL: Studiendesign

ClinicalTrials.gov: NCT04245839



Key patient eligibility criteria

- Age ≥ 18 years
- R/R FL
  - 4L+ cohort
  - 3L cohort
  - 2L cohort (POD24 and/or GELF)
- FL histologically confirmed ≤ 6 months before screening with PET-positive and measurable disease
- Received combination of anti-CD20 antibody and alkylator
- ECOG PS ≤ 1
- Adequate bone marrow, kidney, liver, and cardiac function

Primary endpoint

- ORR (BOR of CR or PR) per IRC by PET/CT using Lugano 2014 criteria[1] in the efficacy set

Secondary endpoints

- CR rate, DOR, DOR if BOR is CR, and PFS per IRC by PET/CT using Lugano 2014 criteria[1] in the efficacy set
- OS
- Safety, cellular kinetics, HRQOL

Exploratory endpoint

- B-cell aplasia

- Study endpoints of ORR and CR rate were tested hierarchically with null hypotheses in the following order at 1-sided α = 0.025 significance: 3L+ FL (ORR ≤ 60%), 4L+ FL (ORR ≤ 50%), 3L+ FL (CR rate ≤ 30%), and 4L+ FL (CR rate ≤ 20%)

2L, second line; 3L, third line; 4L+, fourth line or later; CT, computed tomography; CY, cyclophosphamide; DOR, duration of response; FLU, fludarabine; GELF, Groupe d'Etude des Lymphomes Folliculaires; HRQOL, health-related quality of life; IRC, independent review committee; POD24 (per protocol), disease progression within 24 months of diagnosis and treated with combination systemic therapy with an anti-CD20 antibody and alkylator within 6 months of initial FL diagnosis.[2]

1. Cheson BD, et al. *J Clin Oncol* 2014;32:3059–3068.; 2. Casulo C, et al. *J Clin Oncol* 2015;33:2516–2522.

TRANSCEND FL: Patientencharakteristika

	Liso-cel–treated set[a]	
	2L+ FL (n = 130)	3L+ FL (n = 107)
Median (range) age, y	60 (23–80)	62 (23–80)
Male, n (%)	83 (64)	66 (62)
FL subtype/grade at screening, n(%) Grade 1/2 Grade 3A Unknown	 15 (12) / 83 (64) 31 (24) 1 (1)	 9 (8) / 72 (67) 25 (23) 1 (1)
Ann Arbor stage at screening, n (%) Stage I/II Stage III/IV	 2 (2) / 16 (12) 45 (35) / 67 (52)	 1 (1) / 11 (10) 39 (36) / 56 (52)
FL International Prognostic Index at screening, n (%) Low risk (0–1) Intermediate risk (2) High risk (3–5)	 23 (18) 38 (29) 69 (53)	 12 (11) 34 (32) 61 (57)
Lactate dehydrogenase > ULN, n (%)	53 (41)	47 (44)
Met modified GELF criteria at most recent relapse, n (%)	73 (56)	57 (53)
Prior lines of systemic therapy, median (range)	2 (1–10)	3 (2–10)
Prior HSCT,[b] n (%)	33 (25)	33 (31)
Received prior rituximab and lenalidomide, n (%)	23 (18)	23 (21)
Refractory to last systemic therapy,[c] n (%)	86 (66)	72 (67)
Double refractory (anti-CD20 and alkylator), n (%)	80 (62)	69 (64)
POD24,[d] n (%)	73 (56)	58 (54)
Received bridging therapy, n (%)	49 (38)	44 (41)

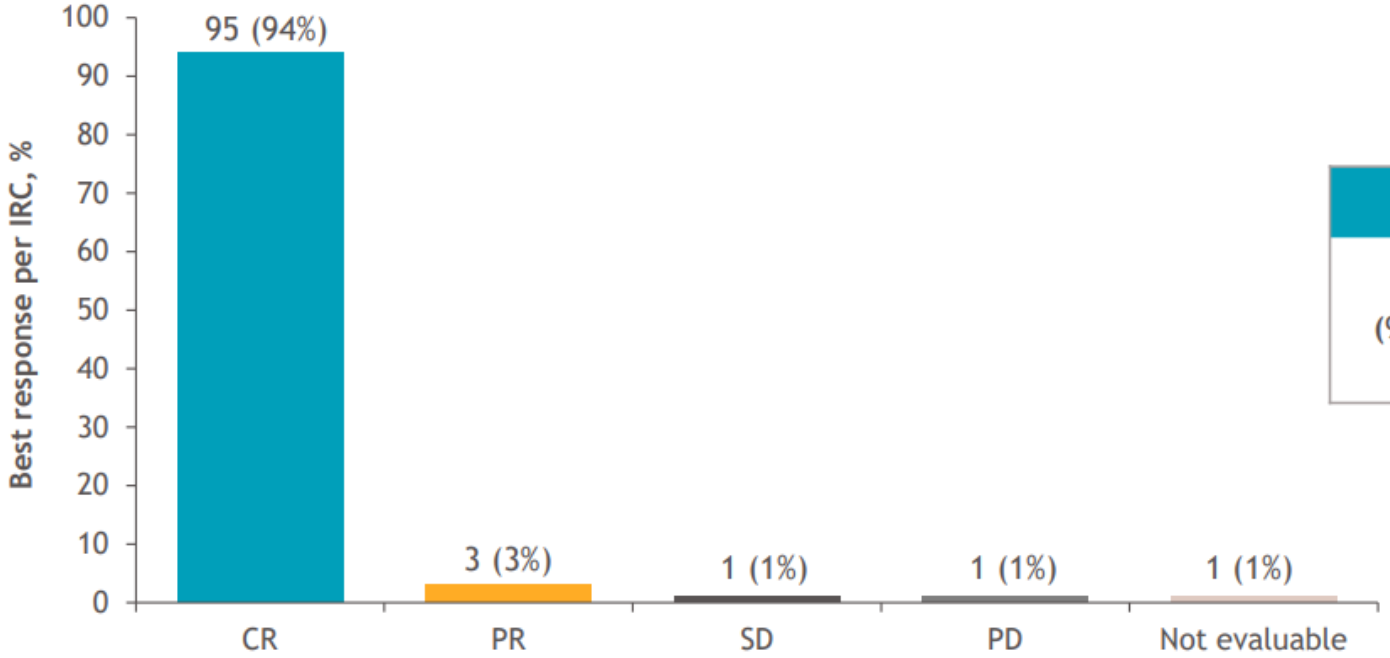
[a]Percentages may not add up to 100% due to rounding; [b]All prior HSCT was autologous HSCT; [c]Defined as progression or stable disease while on last line of therapy or within 6 months of completing the last line of therapy; [d]Defined as progression within 24 months from initiation of chemoimmunotherapy. HSCT, hematopoietic stem cell transplantation; ULN, upper limit of normal.

Morschhauser F. et al. ICML 2023 [Abstract #LBA4]

6

TRANSCEND FL: Therapieansprechen

3L+ FL efficacy set (n = 101)



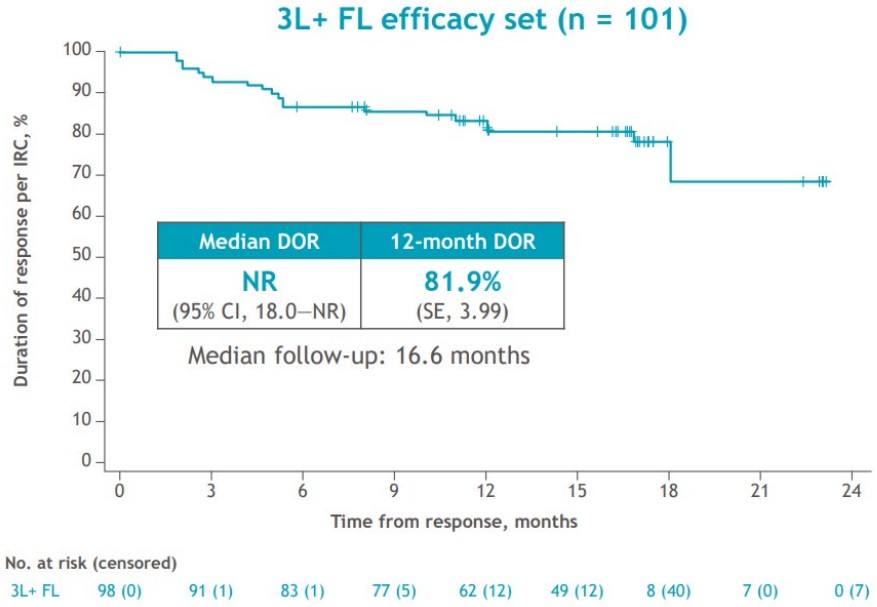
ORR	CR rate
97% (95% CI, 91.6–99.4) *P* < 0.0001[a]	**94%** (95% CI, 87.5–97.8) *P* < 0.0001[a]

- **Primary and key secondary endpoints were met**; all null hypotheses were rejected
- ORR was 97%, with all responders (except 3) achieving CR
- ORR remained high across subgroups

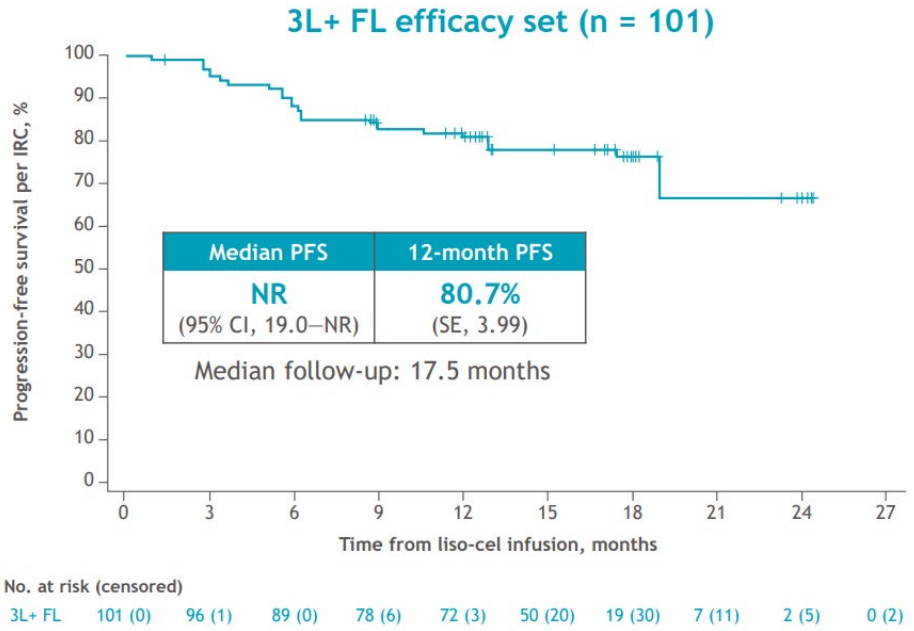
[a]One-sided *P* value (H_0 of ORR ≤ 60%; H_0 of CR rate ≤ 30%).
H_0, null hypothesis; SD, stable disease.

TRANSCEND FL: DOR und PFS

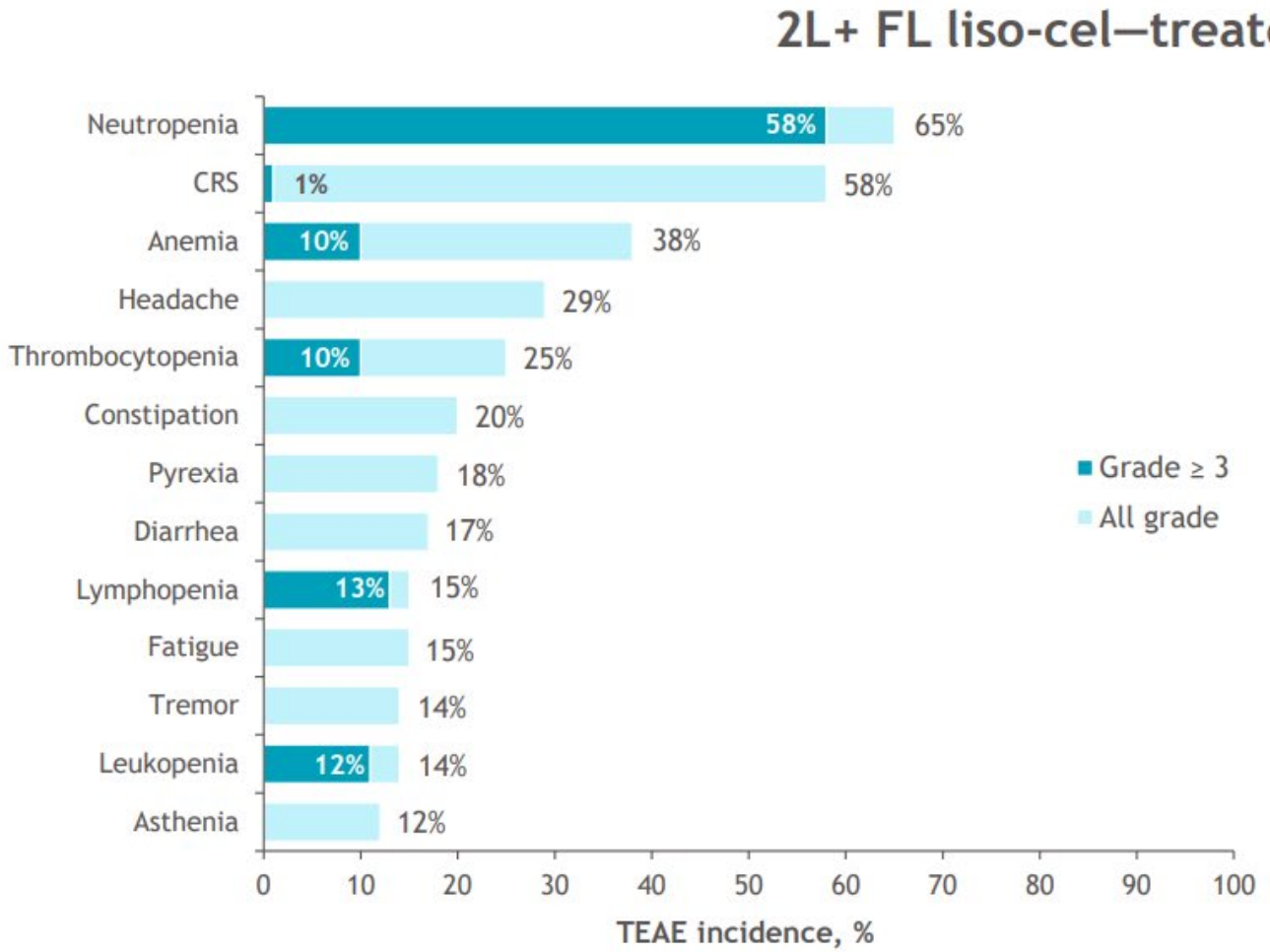
Duration of response per IRC



Progression free survival per IRC



TRANSCEND FL: Toxizitäten



- Most common grade ≥ 3 TEAEs were cytopenias
  - Febrile neutropenia, n = 8 (6%)
- Serious TEAEs were reported in 25% of patients

Zusammenfassung | Take-Home-Messages

- Eine mit 2x2 Gy deutlich reduzierte Strahlendosis plus Obinutuzumab zeigt eine hohe Effektivität in den frühen Stadien des FL, die Verlaufsdaten (PFS) stehen aber noch aus.
- PET und MRD sind unabhängige prognostische Faktoren für das PFS. Konstant MRD-negative Patienten haben das geringste Rezidivrisiko.
- Mit Zanubrutinib werden sich die Therapieoptionen beim follikulären Lymphom weiter verbessern.
- Die Hinzunahme von R^2 zu Epcoritamab verbessert die Effektivität auch in Risikogruppen bei akzeptabler Toxizität.
- Mit Liso-Cel wird demnächst ein weiteres, effektives CAR-T-Zell-Produkt beim r/r FL zur Verfügung stehen.

Die Kurzpräsentationen sind online unter

www.lymphome.de/icml2023

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