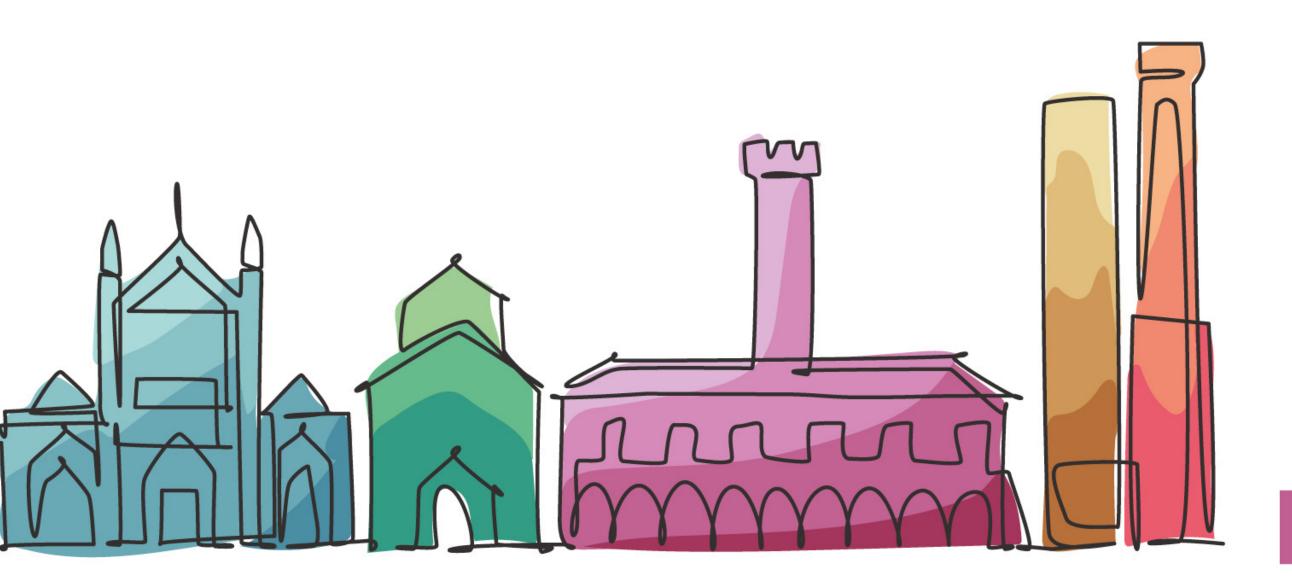
PRECEPTORSHIP



Un confronto sulla gestione delle malattie linfoproliferative al Sant'Orsola di Bologna

Bologna, NH DE LA GARE, 6 ottobre 2025

Linfoma Follicolaredietro l'angolo

Cinzia Pellegrini IRCSS AOU di Bologna

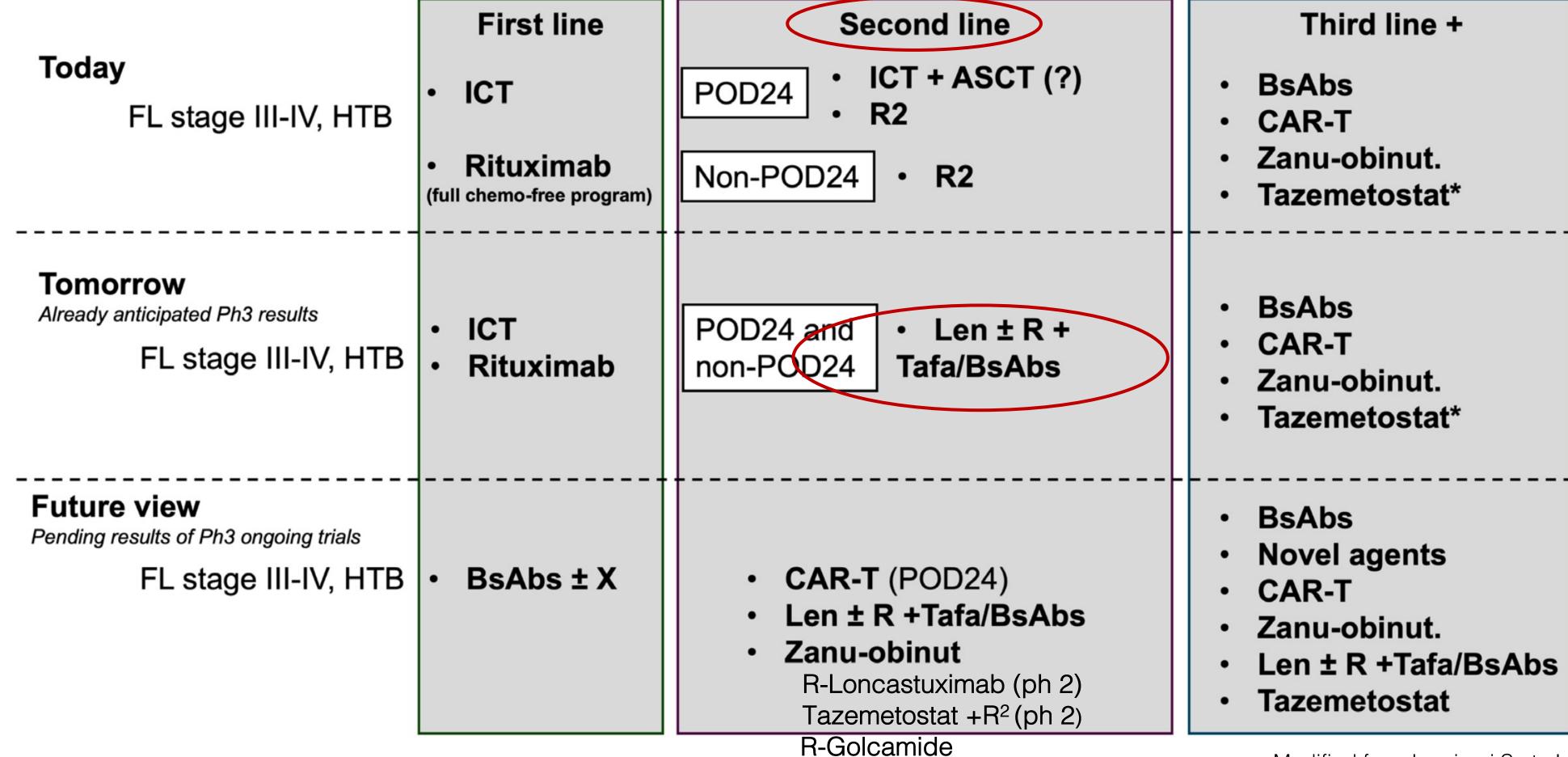


Disclosure

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---------------|---------------------|----------|------------|-------------|--------------------|----------------|-------|
| Roche | | | | | X | | X |
| Gilead | | | | | X | | X |
| Takeda | | | | | | X | |
| Janssen-Cilag | | | | | | X | |
| Abbvie | | | | | X | | X |
| BeOne | | | | | X | | |



HTB FL New Era: Shifting from ICT to Novel Biological Tx





Selected Ph 3 Study Design in 2L FL with R² as

Backbone anti-CD19 **CAR T-cell therapies** anti-CD20xCD3 bsAbs Other targeted therapies **TRANSFORM EPCORE® OLYMPIA-5**⁵ **ZUMA-22**¹ inMIND⁶ SYMPHONY-17 MAHOGANY⁸ Celestimo⁴ FL² FL-1³ axi-cel liso-cel epcoritamab mosunetuzumab odronextamab tafasitamab zanubrutinib tazemetostat + R² + R² + R² + R/O + len + len VS VS **VS** VS Comparator: R-chemo or R² **Primary Endpoint(s): ORR PFS PFS** PFS **PFS** PFS **PFS**



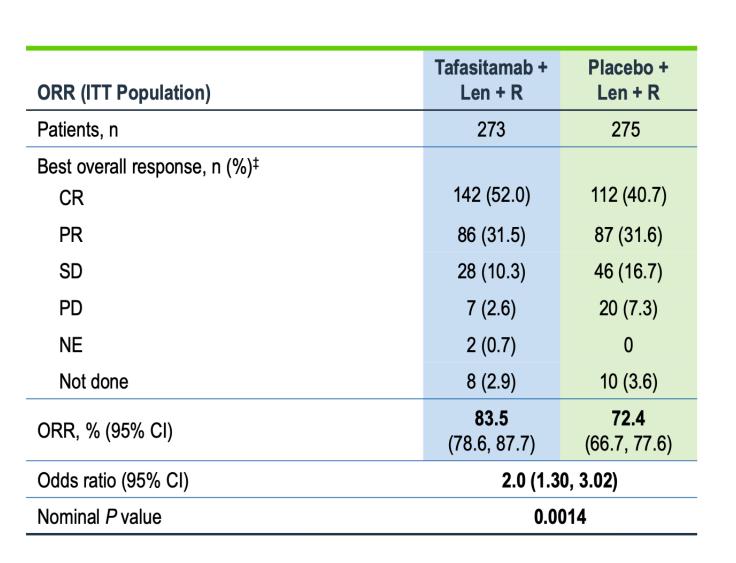
2L FL - inMIND Phase 3 trial: Tafa+R+Lena vs Placebo+R+Lena

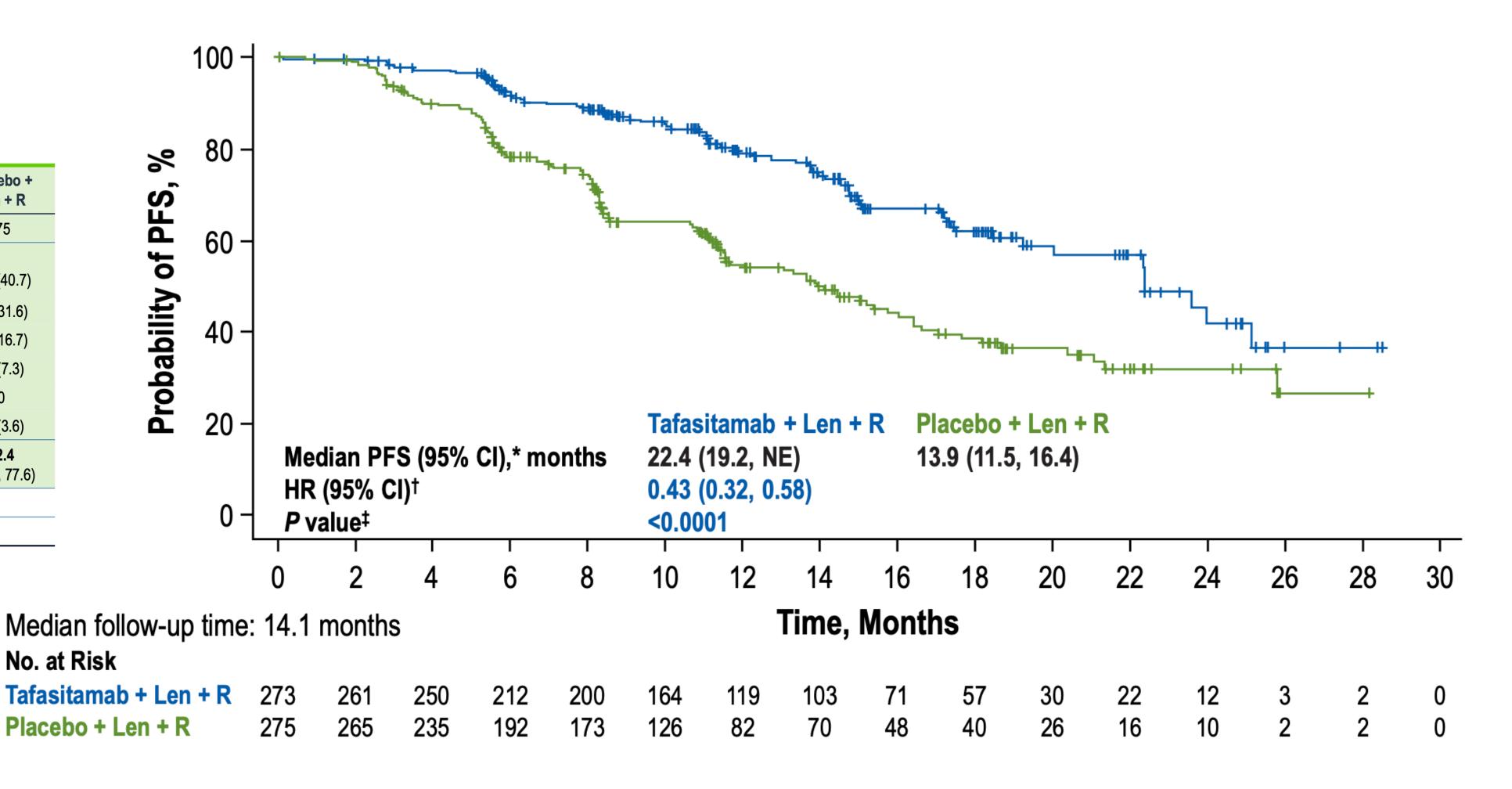
| | ← 4-v | veek treatment cycles ———————————————————————————————————— | —— |
|---|-----------------------|--|-------------|
| | Tafasitamab + Len + R | Placebo + Len + R | Total |
| Variable | (n=273) | (n=275) | (N=548) |
| Median number of prior lines of therapy (range) | 1.0 (1, 7) | 1.0 (1, 10) | 1.0 (1, 10) |
| Number of prior lines of therapy, n (%) | | | |
| 1 | 147 (53.8) | 153 (55.6) | 300 (54.7) |
| 2 | 66 (24.2) | 71 (25.8) | 137 (25.0) |
| 3 | 39 (14.3) | 30 (10.9) | 69 (12.6) |
| ≥4 | 21 (7.7) | 21 (7.6) | 42 (7.7) |
| Time since last anti-lymphoma therapy, n (%) | | | |
| ≤2 years | 147 (53.8) | 157 (57.1) | 304 (55.5) |
| >2 years | 126 (46.2) | 118 (42.9) | 244 (44.5) |
| POD24, n (%) | 85 (31.1) | 88 (32.0) | 173 (31.6) |
| Relapsed/refractory status to last therapy, n (%) | | | |
| Relapsed | 148 (54.2) | 164 (59.6) | 312 (56.9) |
| Refractory | 112 (41.0) | 97 (35.2) | 209 (38.1) |
| Undetermined | 13 (4.8) | 14 (5.1) | 27 (4.9) |
| Refractory to prior anti-CD20 therapy, n (%) | 118 (43.2) | 115 (41.8) | 233 (42.5) |

Sehn LH. Blood (ASH annual meeting abstracts), 2024; 144 (S2): LBA-1



inMIND Trial 1st End-Point: PFS

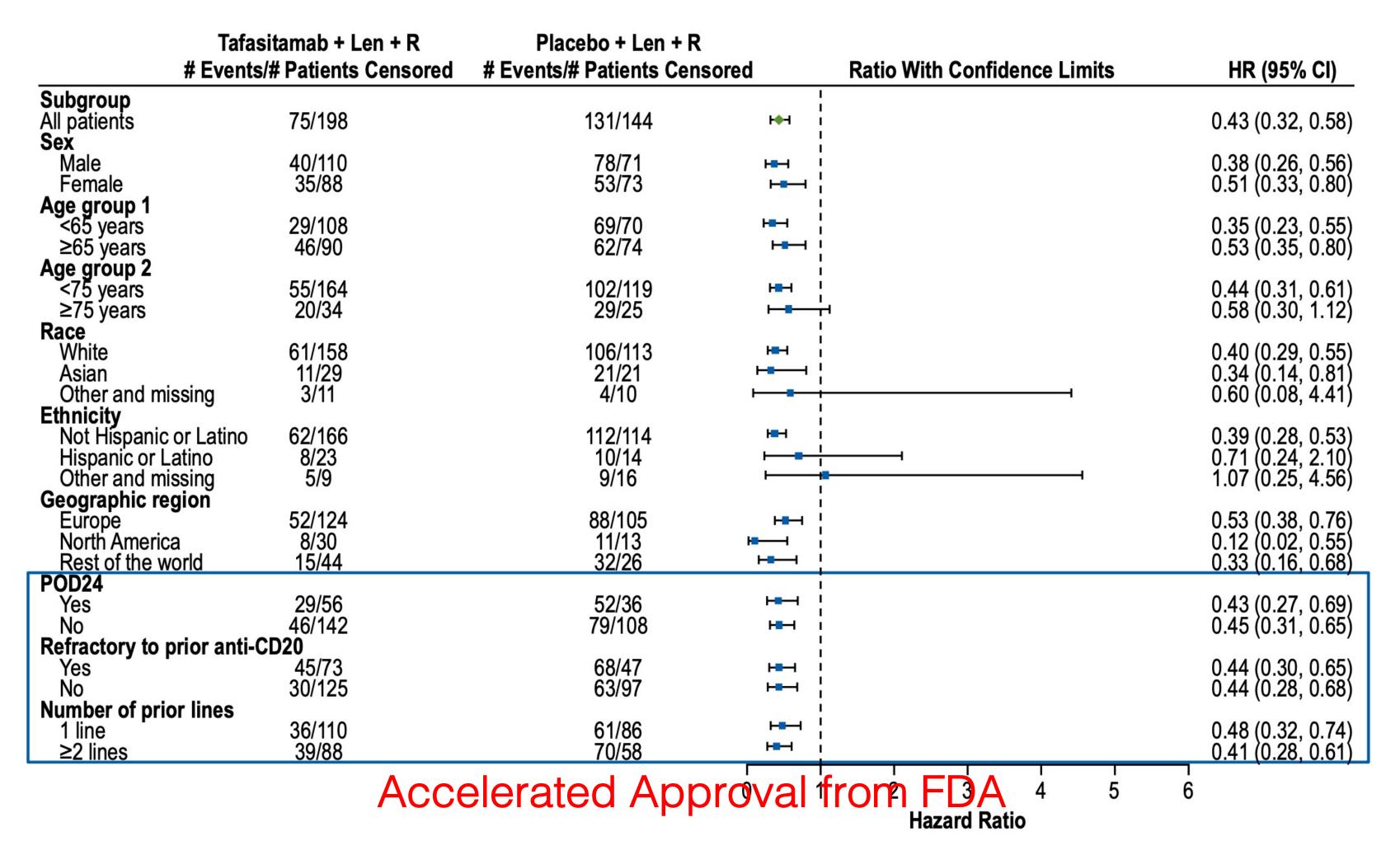




Sehn LH. Blood (ASH annual meeting abstracts), 2024; 144 (S2): LBA-1



inMIND Trial: PFS Benefit is Observed in All Prespecified Subgroups



Sehn LH. Blood (ASH annual meeting abstracts), 2024; 144 (S2): LBA-1



2L Ongoing Ph 3 Trial with BsAbs and Lena as Backbone

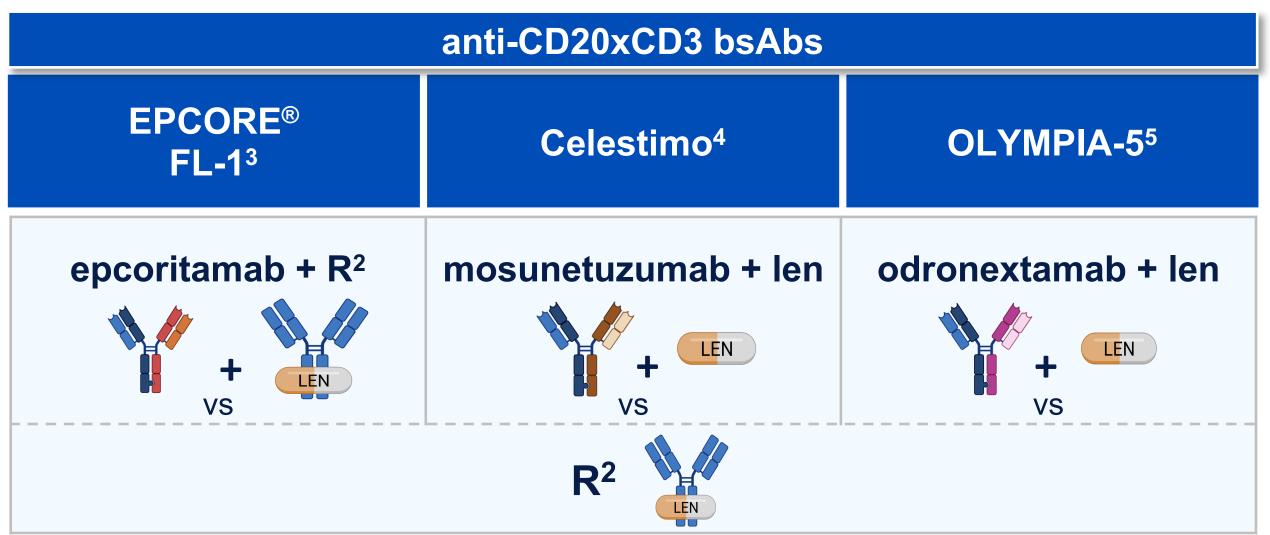
| CAR T-cell therapies | | anti-CD20xCD3 bsAbs | | | anti-CD19 | Other target | ed therapies |
|---------------------------------------|------------------------------|---------------------------------|------------------------|------------------------|---------------------|----------------------------------|-----------------------|
| ZUMA-22 ¹ | TRANSFORM FL ² | EPCORE® FL-1 ³ | Celestimo ⁴ | OLYMPIA-5 ⁵ | inMIND ⁶ | SYMPHONY-17 | MAHOGANY ⁸ |
| axi-cel Output Description: | liso-cel () | epcoritamab + R ² | mosunetuzumab + len | odronextamab + len | tafasitamab + R² | tazemetostat + R² TAZ + LEN VS | zanubrutinib + R/O |
| Comparator: R-chemo or R ² | | | R ² | | | | |
| Primary Endpoint(s): PFS | PFS | ORR PFS | PFS | PFS | PFS | PFS | PFS |

Adapted from: 1. NCT05371093. 2. NCT06313996. 3. NCT05409066. 4. NCT04712097. 5. NCT06149286. 6. NCT04680052. 7. NCT04224493. 8. NCT05100862 ■



2L Ongoing Ph 3 Trial with BsAbs and Lena as Backbone





Data from Phase 1-2 studies available?

Trial

Ν

Most recent publication

| yes | yes | no |
|---|---|----|
| Phase 2 EPCORE® NHL-2 Arm 29 | Phase 1b CO41942 ¹⁰ | |
| 111 | 29 | |
| Falchi L, et al. Abstract 342. ASH Annual Meeting 2024. | Morschhauser, et al. Abstract 128. ASH Annual Meeting 2021. | |



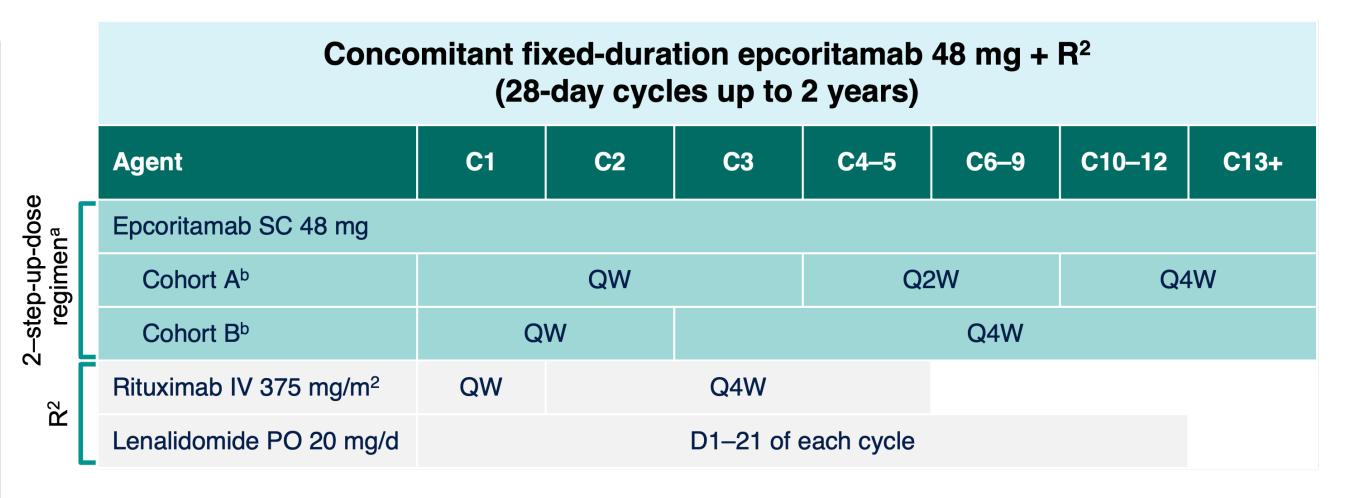
2L FL - Ph 2 EPCORE NHL2 arm 2: Epcoritamab + R²

Fixed Duration Regimen (2 Years)

Key inclusion criteria

- R/R CD20+ FL
 - Grade 1-3A
 - Stage II-IV
- ≥1 prior treatment, including an anti-CD20 antibody
- Need for treatment per GELF criteria¹
- ECOG PS 0-2
- Measurable disease by CT or MRI
- Adequate organ function

Median fup: 28.2 mo (2,4-39)



Primary endpoint: ORR per Lugano criteria^c

Key secondary endpoints: CR rate, DOR, DOCR, PFS, TTNT, OS, MRD analysis, and safety and tolerability

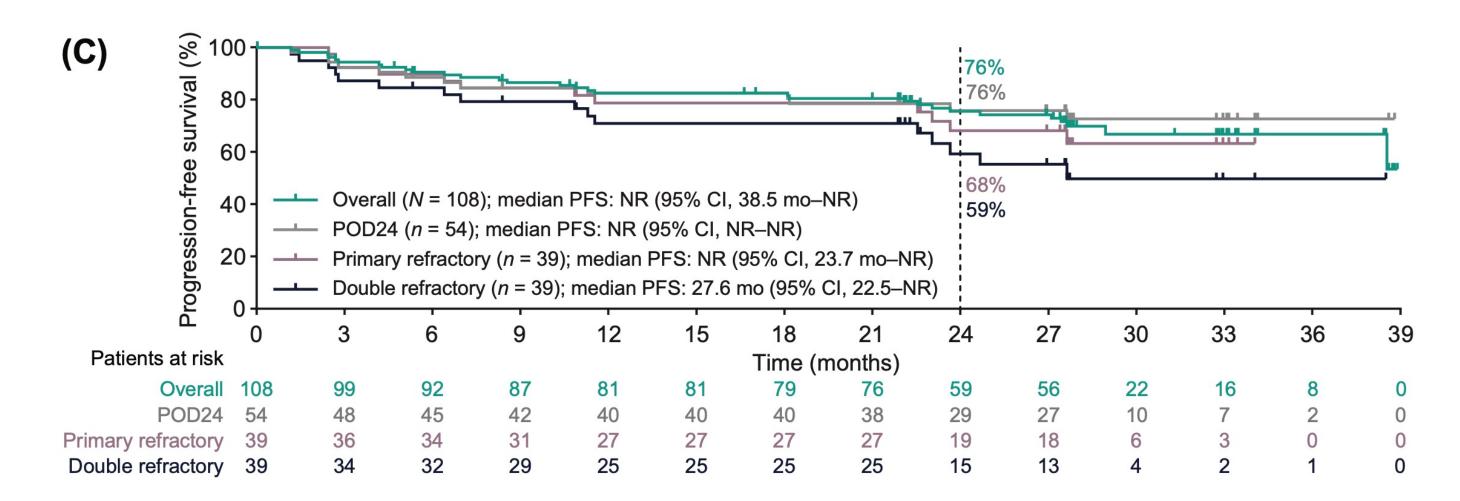
NCT04663347. ^aPatients received epcoritamab with 2 step-up doses (0.16 mg on C1D1 and 0.8 mg on C1D8) before the first full dose on C1D15, corticosteroid prophylaxis to mitigate CRS, and protocol-mandated hospitalization for 24 h after the first full dose. ^bCohorts A and B enrolled 27 and 84 patients, respectively. ^cTumor response was evaluated by PET-CT (or separate PET and CT/MRI when PET-CT was not available) obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression. ^dMRD was assessed in PBMCs using the clonoSEQ[®] assay (Adaptive Biotechnologies) with a cutoff of 10⁻⁶. 1. Brice P, et al. *J Clin Oncol*. 1997;15:1110-7.

- 108 pts (efficacy + safety)
 - Median pLOT: 1 (1-7)
 - POD24: 50%
- Primary refractory: 36%
- Double refractory: 36%



2L FL - Ph 2 EPCORE NHL2 arm 2: Epcoritamab + R²

| Outcomes, n (%) | Epcor + R ² (N=108) |
|-----------------------------|-----------------------------------|
| ORR | 96% |
| CR | 88% |
| MRD-negativity, any time | 88% |
| Median Time to response, mo | 1.4 |
| Median DoCR, mo | NR |



| Common TEAEs, All Grades Gr ≥3 | Epcor + R ² (N=108) |
|-------------------------------------|-----------------------------------|
| Neutropenia | 62% 53% |
| COVID-19 ^b | 57% 24% |
| CRS | 52% 2% |
| Diarrhea | 46% 4% |
| ISR ^c | 44% 0% |
| Fatigue | 39% 3% |
| Constipation | 36% 1% |



CELESTIMO (GO42909): Study design

Randomised, open-label, multicentre Phase III study of mosunezutumab (IV) and lenalidomide compared with rituximab and lenalidomide in patients with R/R FL

Eligibility

- Age ≥18 years
- Grade 1-3a CD20+ FL
- ECOG PS 0-2
- ≥1 prior systemic antilymphoma therapy
- Target enrolment (Randomised cohort): 400

Stratification factors

- POD 24 status
- Prior lines of therapy $(1 \text{ vs } \ge 2)$
- Refractoriness to anti-CD20 therapy

Mosunetuzumab + lenalidomide Arm A Mosunetuzumab IV on C1 [D1 (1 mg), D8 (2 mg), D15 (30 mg)] q3w and C2-12 D1 (30 mg) q4w Lenalidomide on C2-12 D1 (20 mg) q4w Randomised 1:1* Rituximab + lenalidomide Rituximab IV on C1 D1/D8/D15/22 and C3, 5, 7, 11 D1

 $(375 \text{ mg/m}^2) \text{ q4w}$

Arm C

Mosunetuzumab + lenalidomide (US extension cohort, n=54 pts)

Lenalidomide on C2-12 D1 (20 mg) q4w

1º endpoint

PFS (IRC-assessed) in ITT

Efficacy follow-up: 5 years from time of randomisation

Secondary and other endpoints[†]

Arm B

PFS (INV-assessed) in ITT, CR rate (by PET-CT), ORR, OS, DOR, DOCR, time to deterioration in physical functioning and fatigue by EORTC QLQC30, safety, PK, immunogenicity, biomarker

https://clinicaltrials.gov/study/NCT04712097

Nastoupil L, et al. EHA 2022; Poster presentation (#P1125);



CO41942: Mosunetuzumab (IV) + Len in 2L+ FL

Open-label, multicenter, Phase Ib study of mosunetuzumab + lenalidomide in patients with R/R FL

Eligibility

- CD20+ FL Grade 1-3a
- R/R to ≥1 prior chemoimmunotherapy regimen including an a CD20 antibody; prior lenalidomide allowed
- ECOG PS 0-2

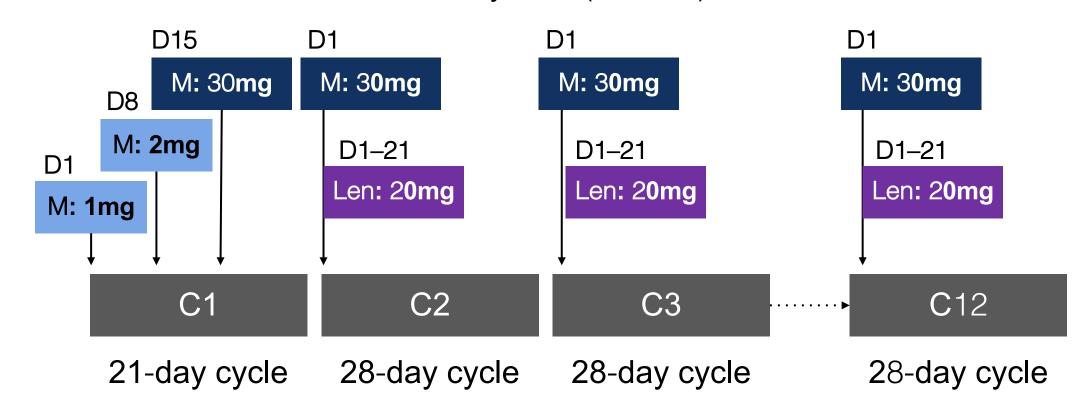
Mosun-Len administration (n=29)*

Mosunetuzumab

Intravenous administration for 12 cycles (C1: Q3W; C2–12: Q4W)

Lenalidomide

Oral administration for 11 cycles (C2–12)



- C1 step-up dosing for CRS mitigation
- No mandatory hospitalization

Endpoints

Primary:

- DLTs
- AE rate

Secondary:

- CR rate
- ORR
- DOR
- DOCR

2L, second line; AE, adverse event; CRS, cytokine release syndrome; Q3W, once every 3 weeks; Q4W, once every 4 weeks.

Morschhauser F, et al. ASH 2021; Oral presentation (abstract #129); Bishton M, et al. ASH 2022; Poster presentation (abstract #1544).

^{*}One patient from dose escalation, all other patients from dose expansion.



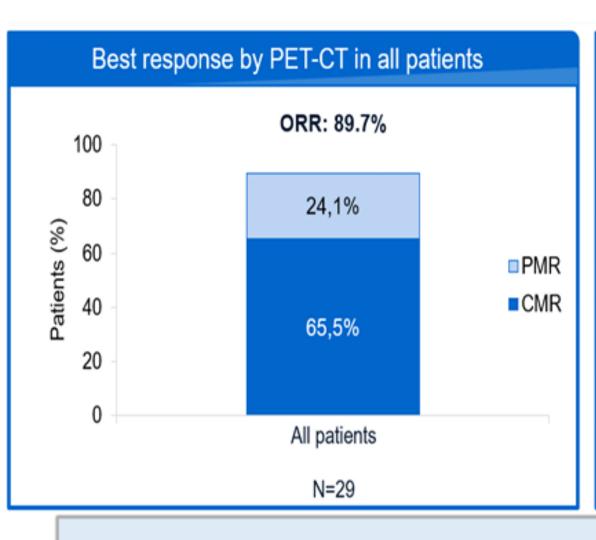
CO41942: Mosunetuzumab (IV) + Len in 2L+ FL

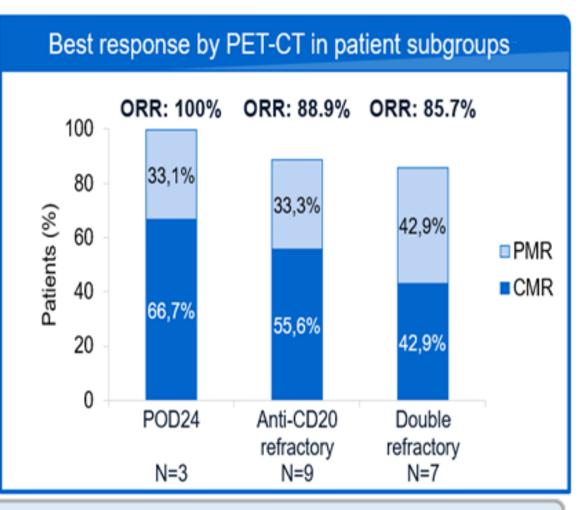
Baseline Characteristics

| | N=29 |
|--|--------------------------------------|
| Age in years, median (range) | 59 (30–79) |
| Male | 13 (44.8%) |
| Ann Arbor stage at study entry I–II III–IV | 2 (6.8%) 27 (93.1%) |
| FLIPI risk factors at study entry 0-1 2 3-5 | 7 (24.1%) 8 (27.6%) 14 (48.3%) |
| Number of prior lines of therapy, median (range) 1 prior line ≥2 prior lines | 1 (1–6) 16 (55.2%) 13 (44.8%) |
| Refractory to any prior aCD20 therapy | 9 (31.0%) |
| Refractory to any prior aCD20 therapy AND an alkylating agent (double refractory) | 7 (24.1%) |
| POD24 | 3 (10.3%) |

Median duration of follow-up: 5.4 months (range: 3-12)

Best response





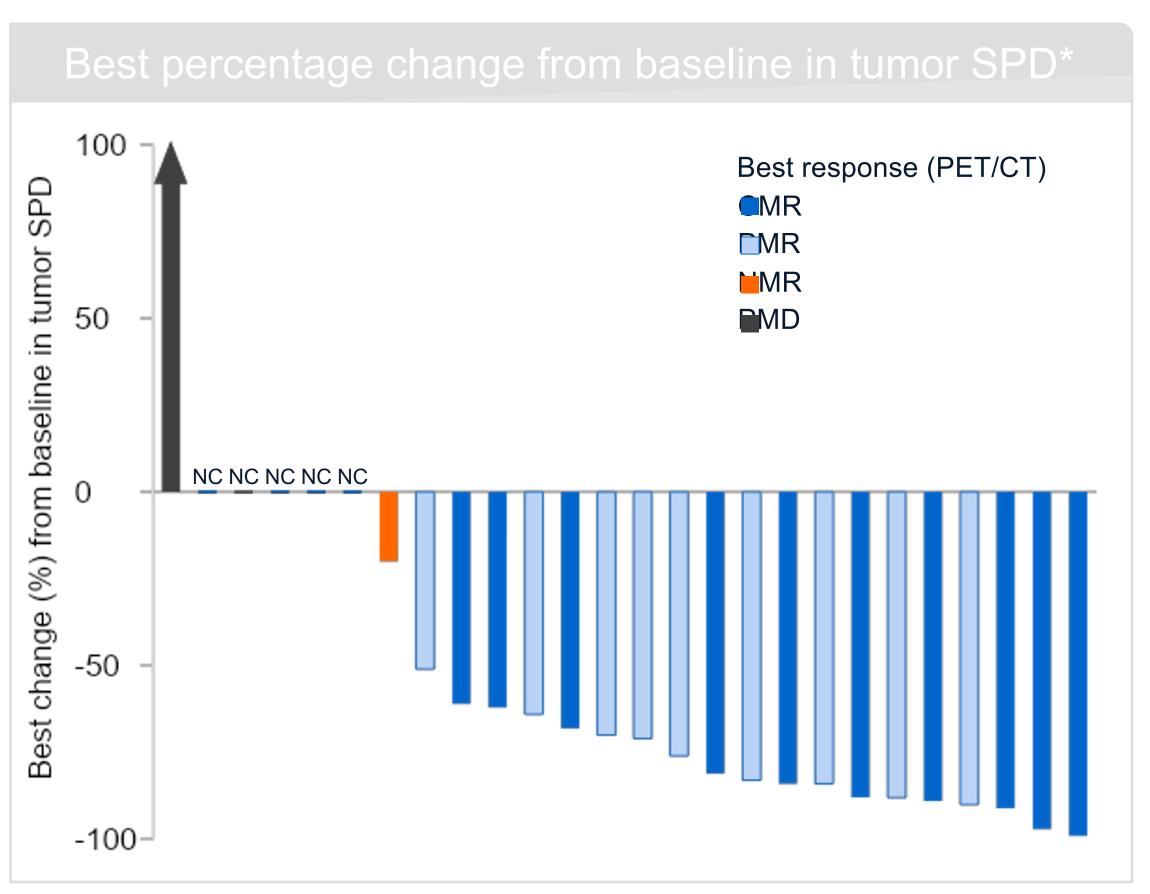
Median time to first / best response: 2.5 mo (range: 1.4–5.3) / 2.5 mo (range: 1.4–10.7)

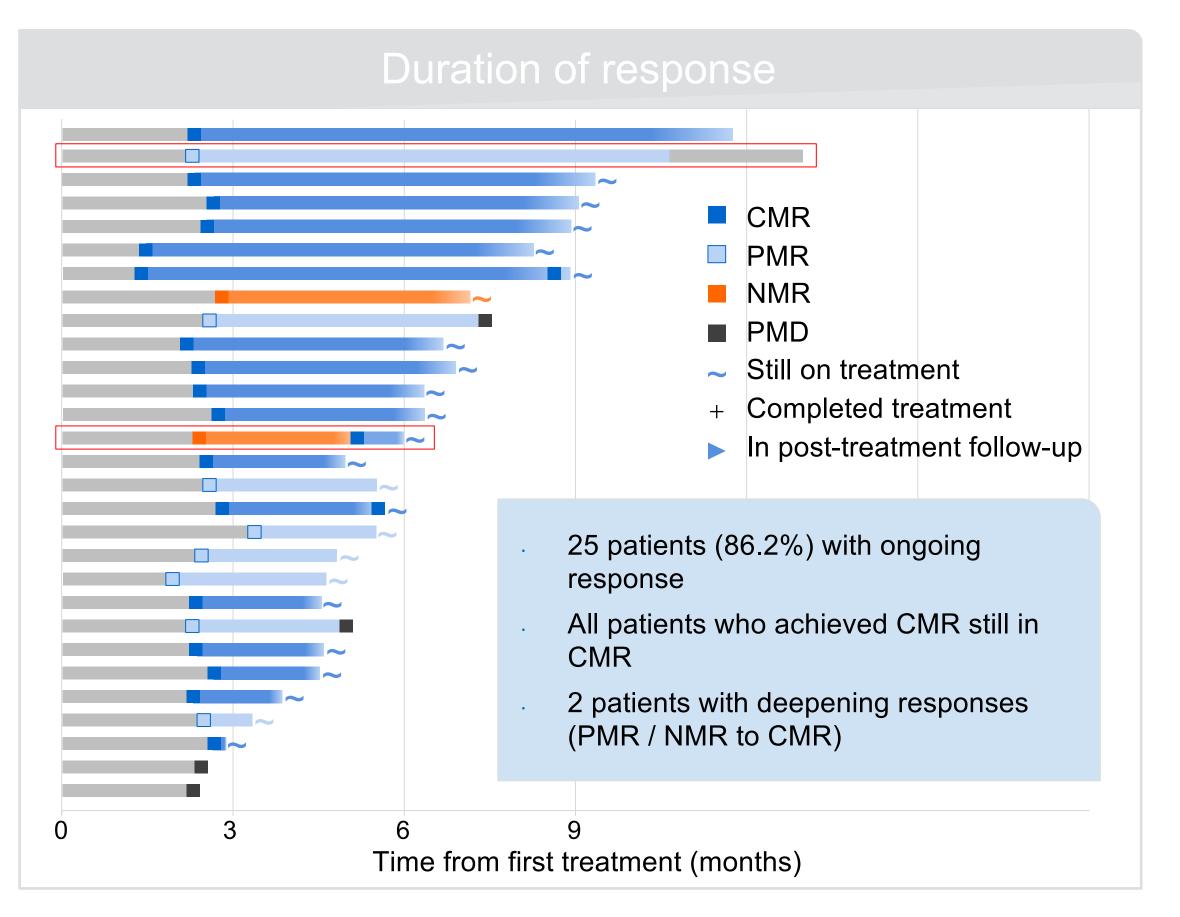
Morschhauser F. British Society of Hematology BSH meeting, 2022



Change in tumour SPD and duration of response

Median duration of follow-up: 5.2 months (range: 1-10); most patients (92.5%) had 3-9 months of follow-up at CCOD





Data cut-off date: September 13, 2021.

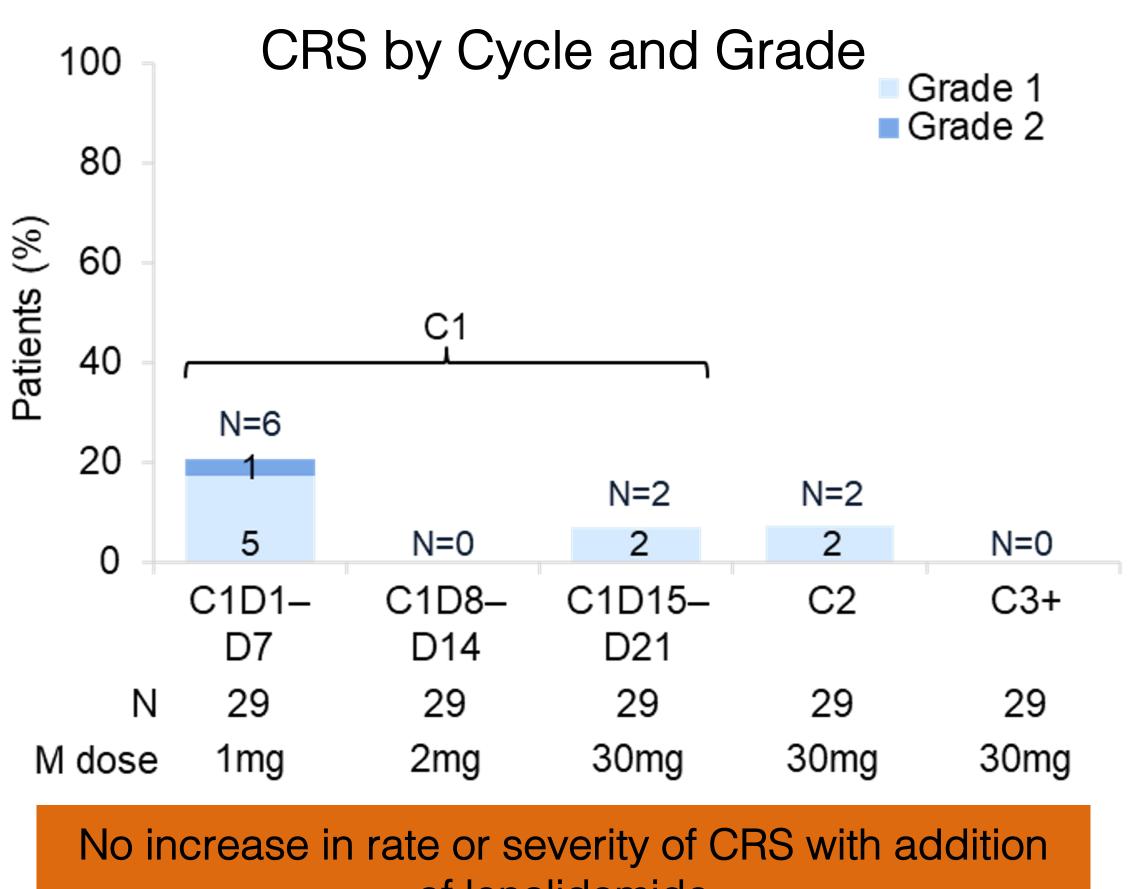
Morschhauser F, et al. ASH 2021; Oral presentation (abstract #129).

^{*}In all patients with ≥1 diagnostic CT scan at response assessment (N=26). CCOD, clinical cut-off date; NC, no change; NMR, no metabolic response; PMD, progressive metabolic disease; SPD, sum of product diameters.



CRS was low grade and predominantly confined to C1

| | N=29 |
|---|---|
| CRS (any grade), n (%)* Grade 1 Grade 2 Grade ≥3 | 8 (27.6) 7 (24.1) 1 (3.4) [†] 0 |
| Serious AE of CRS (any Grade), n (%) | 4 (13.8)‡ |
| Median time to first CRS onset, days (range) | 1 (1–28) |
| Median CRS duration, days (range) | 3 (2–5) |
| Corticosteroids for CRS management, n (%) | 0 |
| Tocilizumab for CRS management, n (%) | 0 |
| CRS leading to mosunetuzumab discontinuation, n (%) | 0 |
| CRS resolved, n (%) | 8 (100) |



of lenalidomide

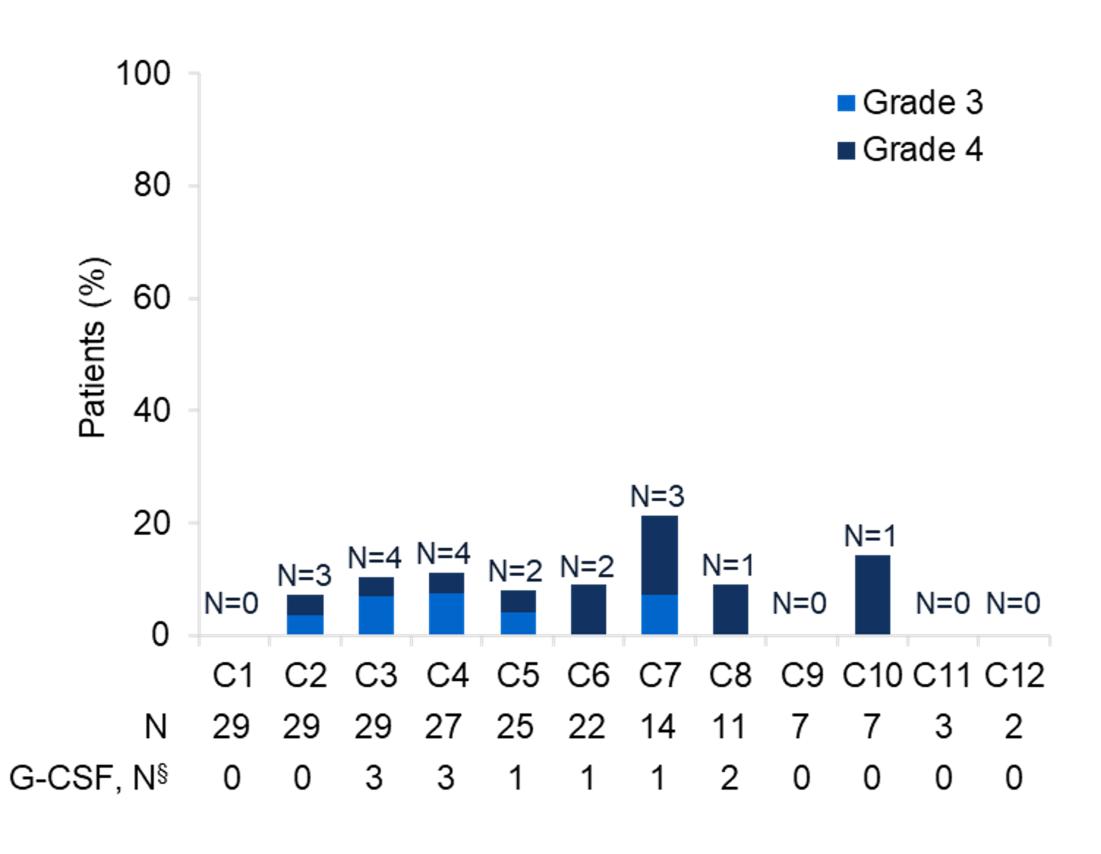
Morschhauser F, et al. ASH 2021; Oral presentation (abstract #129).



ICANS* and serious infections were uncommon

| | N=29 | |
|---|----------------------------------|--|
| ICANS,* n (%) Grade 3 | 1 (3.4) 0 | Amnesia (3.4%; Grade 1†). Ongoing No aphasia, seizures, encephalopathy or cerebral edema |
| Serious AE of infection,‡n (%) Grade 3 | 2 (6.9) 2 (6.9) | Grade 3 pneumonia and Grade 3 urinary tract infection in 1 patient each. All resolved |
| Any neutropenia (all Grades), n (%) Grade 3 Grade 4 | 7 (24.1) 4 (13.8) 3 (10.3) | Febrile neutropenia (Grade 3) in 1 patient (duration: 5 days) was considered treatment related |
| Median time to neutropenia onset, days (range) | 86 (41– 189) | _ |
| Median duration of neutropenia, days (range) | 9 (4–29) | All neutropenia/febrile neutropenia resolved |

Neutropenia by Cycle and Grade



Data cut-off date: September 13, 2021.

CTCAE, Common Terminology Criteria for Adverse Events; G-CSF, granulocyte-colony stimulating factor;

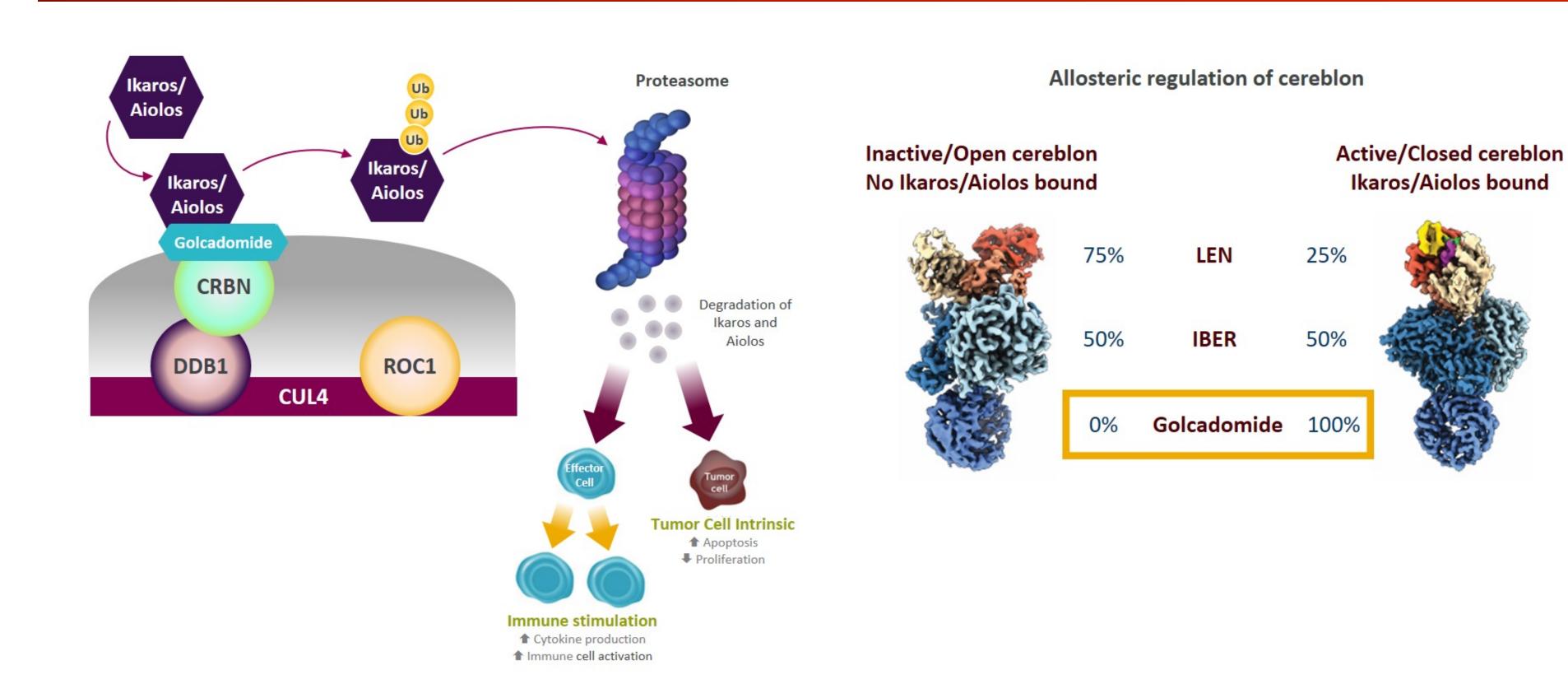
ICANS, Immune effector cell-associated neurotoxicity syndrome.

Morschhauser F, et al. ASH 2021; Oral presentation (abstract #129).

^{*}Mosunetuzumab-related neurological AEs potentially consistent with ICANS. †Graded per CTCAE;‡System Organ Class 'infections and infestations'. §One patient received G-CSF prophylaxis.



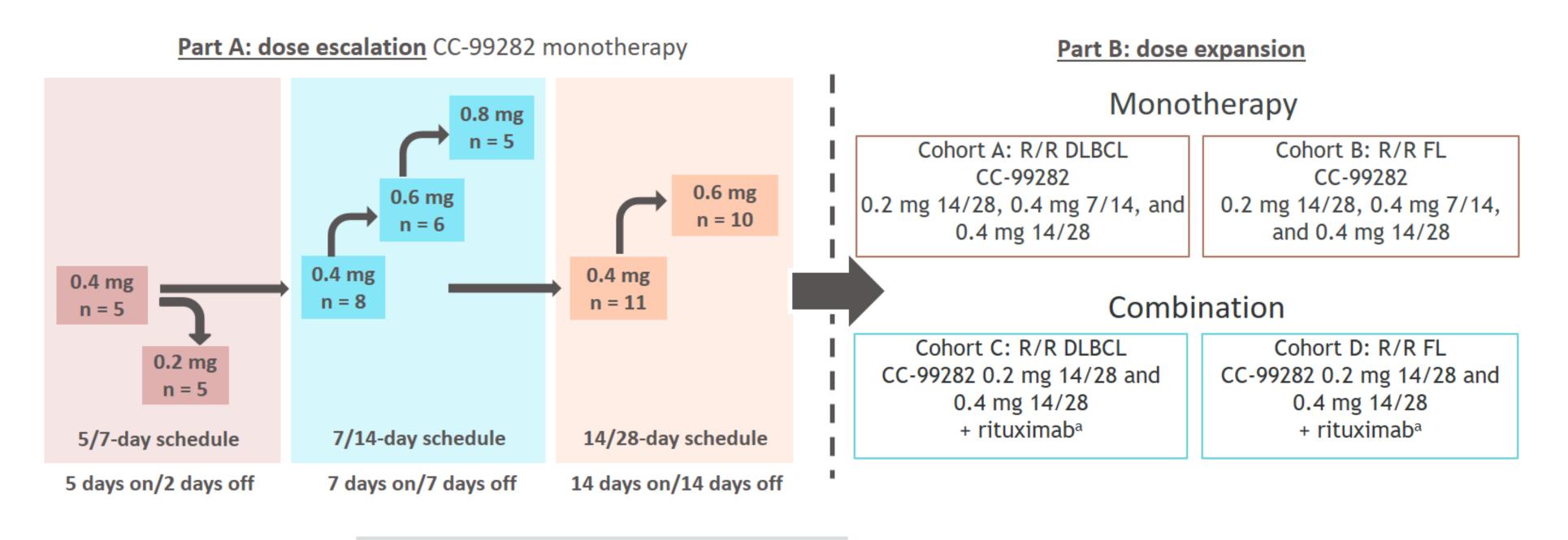
GOLCADOMIDE



Watson ER. Science, 2022; 378: 549-553



Golcadomide (GOLCA) ± Rituximab (RTX) Demonstrates
Durable Efficacy and Is Well Tolerated in Patients (pts) with
Relapsed/Refractory Follicular Lymphoma (R/R FL): Updated
Results from the Phase 1/2 CC-99282-NHL-001 Study



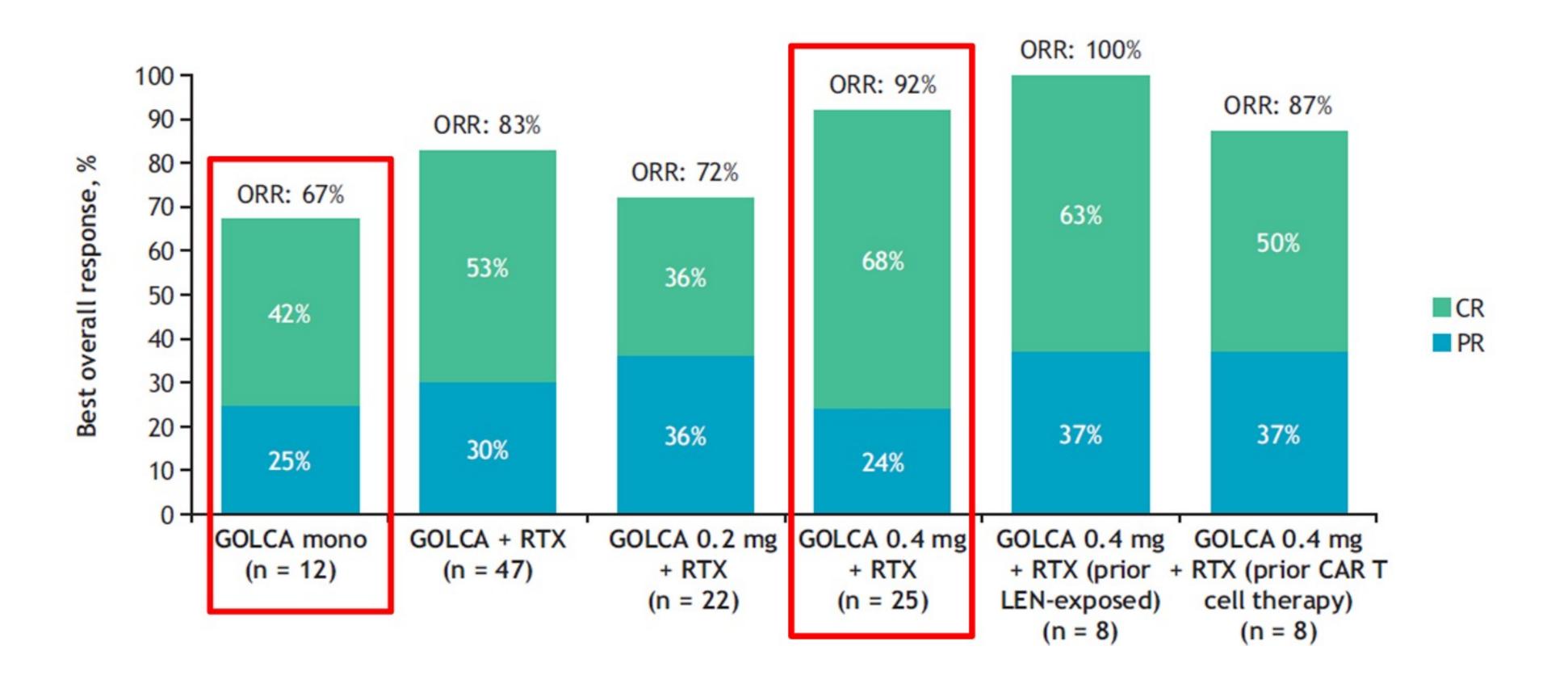
Duration of treatment is up to 2 years

^aRituximab dosing was 375 mg/m² on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of Cycles 2-5.

Chavez JC. Blood (ASH annual meeting abstracts), 2024; 144 (S1): 3018a



Golcadomide (GOLCA) ± Rituximab (RTX) Demonstrates Durable Efficacy and Is Well Tolerated in Patients (pts) with Relapsed/Refractory Follicular Lymphoma (R/R FL): Updated Results from the Phase 1/2 CC-99282-NHL-001 Study



Chavez JC. Blood (ASH annual meeting abstracts), 2024; 144 (S1): 3018a

• FL gr 1-3A

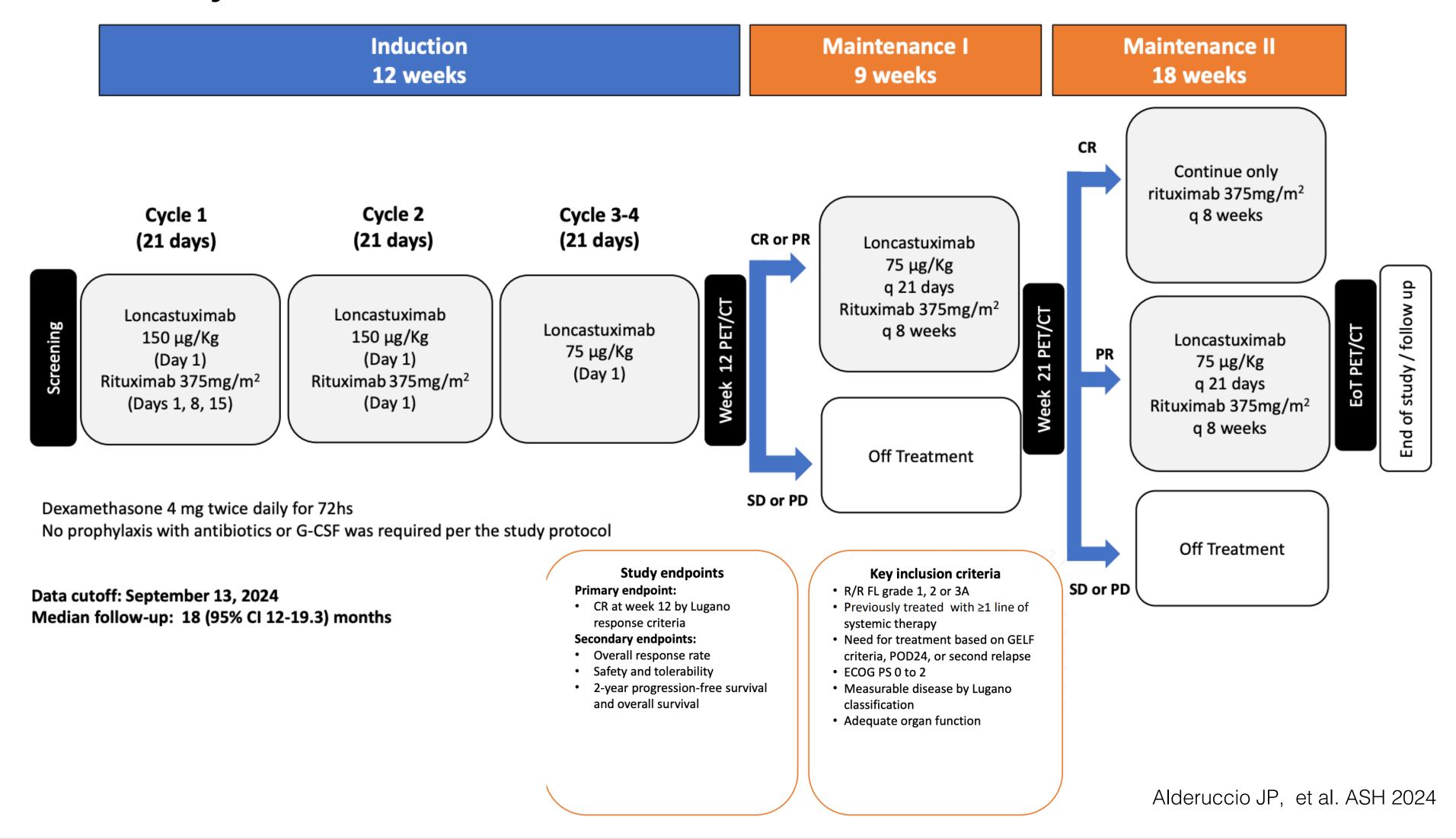
tx

RR to at least 1

previous systemic

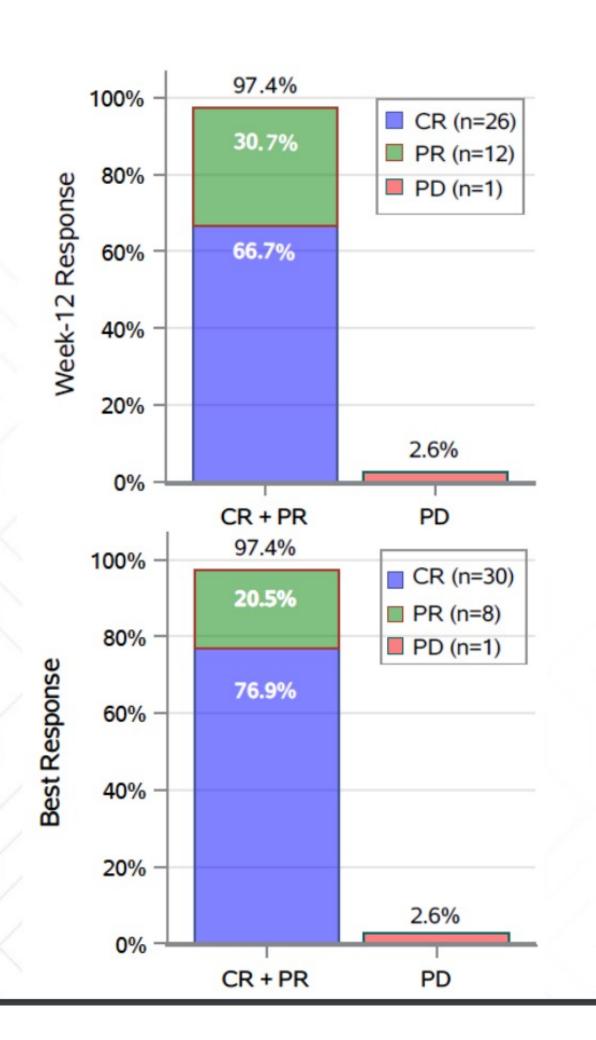


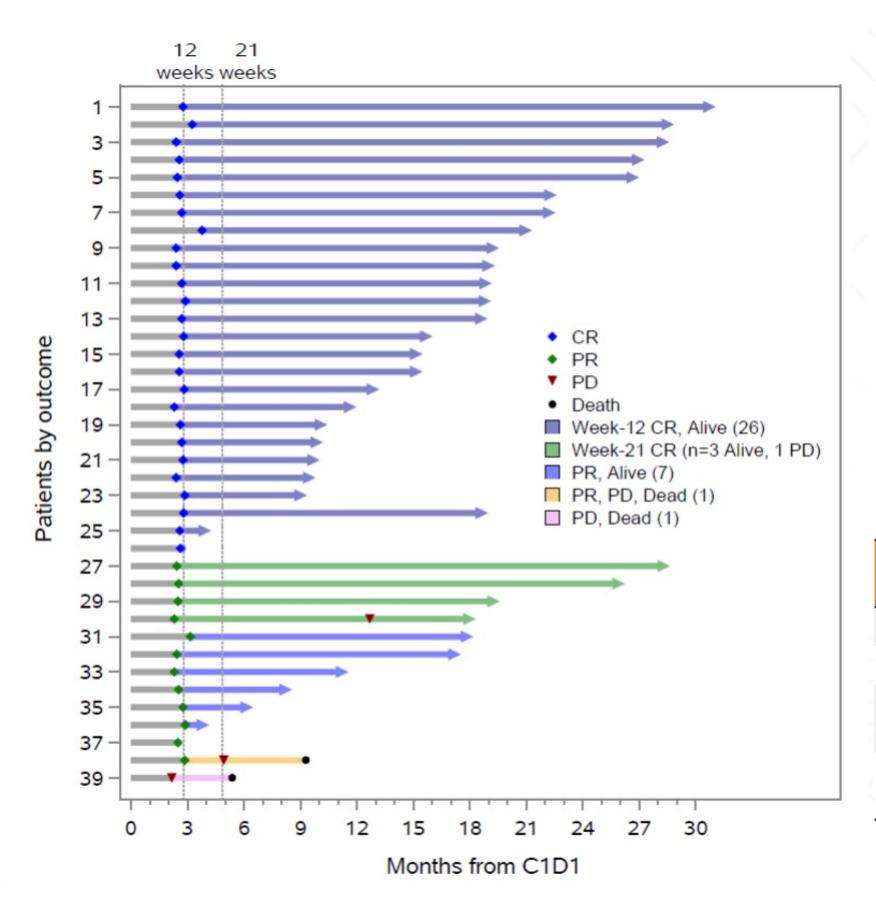
Phase 2 study in 2L FL – Loncastuximab + Rituximab





2L – Loncastuximab + Rituximab





| | n = 39 | % |
|---|---------|----|
| Refractory to last therapy | 20 | 51 |
| Relapsed FL | 19 | 49 |
| Median no, of prior lines, n (range) | 1 (1-6) | |
| ≥3 lines of therapy | 11 | 28 |
| Prior frontline regimens | | |
| • R-CHOP | 22 | 56 |
| Bendamustine with rituximab | 10 | 26 |
| Rituximab | 6 | 15 |
| Fludarabine, mitoxantrone, dexamethasone with rituximab | 1 | 3 |

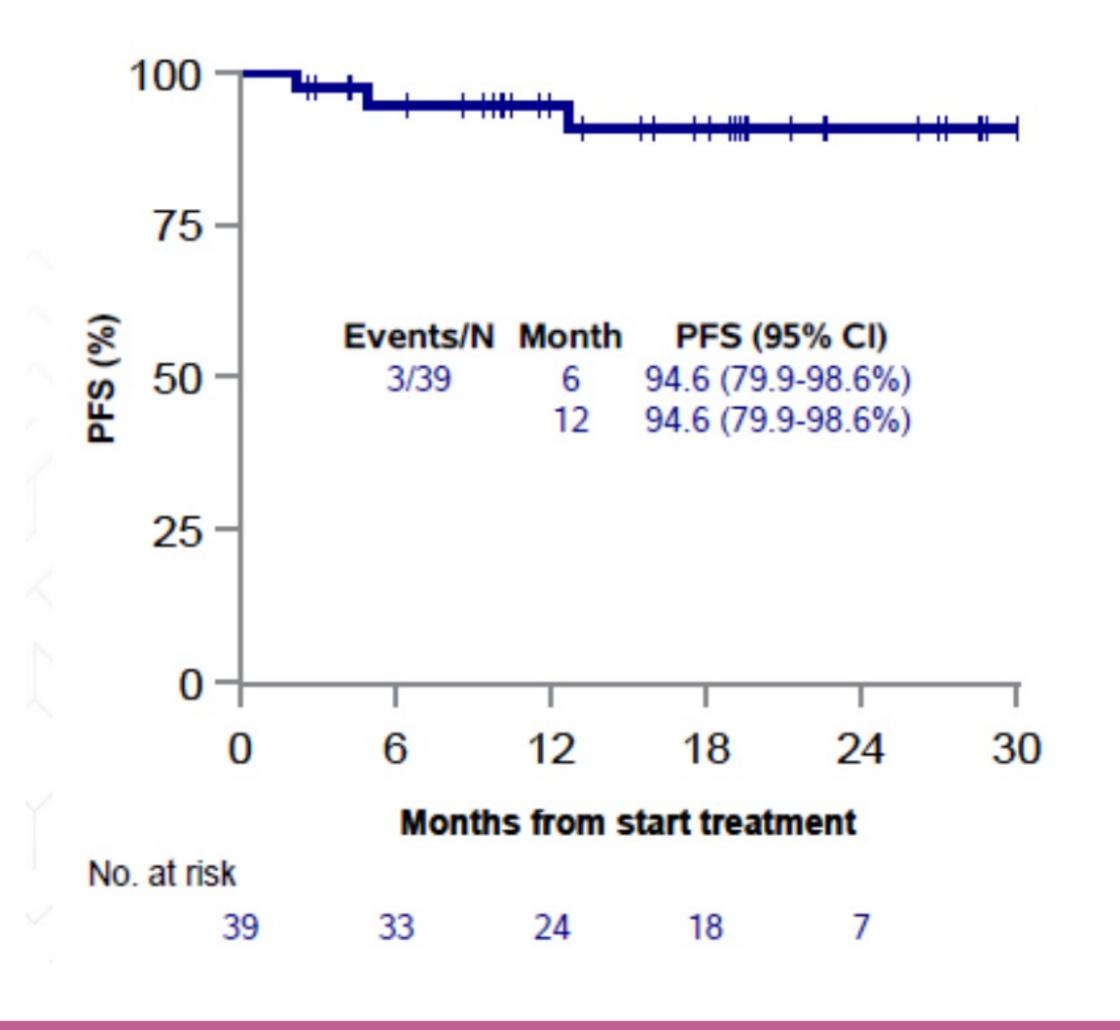
| | n | Best ORR | Best CR rate |
|------------------------------------|----|----------|--------------|
| POD24 | 20 | 100% | 85% |
| High risk FLIPI score | 24 | 96% | 67% |
| Prior transformed FL | 11 | 100% | 73% |
| Rituximab with an alkylating agent | 32 | 100% | 75% |

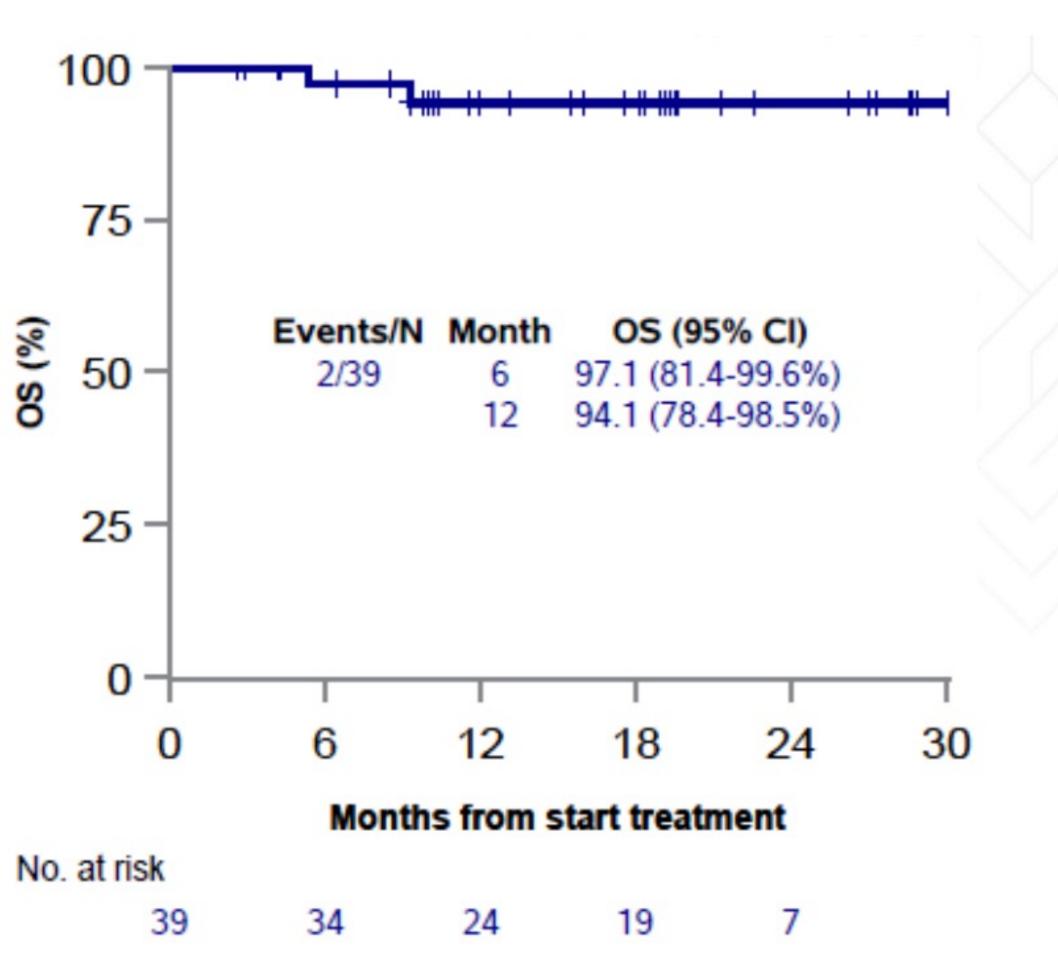
The null hypothesis was rejected (one-sided p<0.0001)

Alderuccio JP, et al. ASH 2024



2L – Loncastuximab + Rituximab

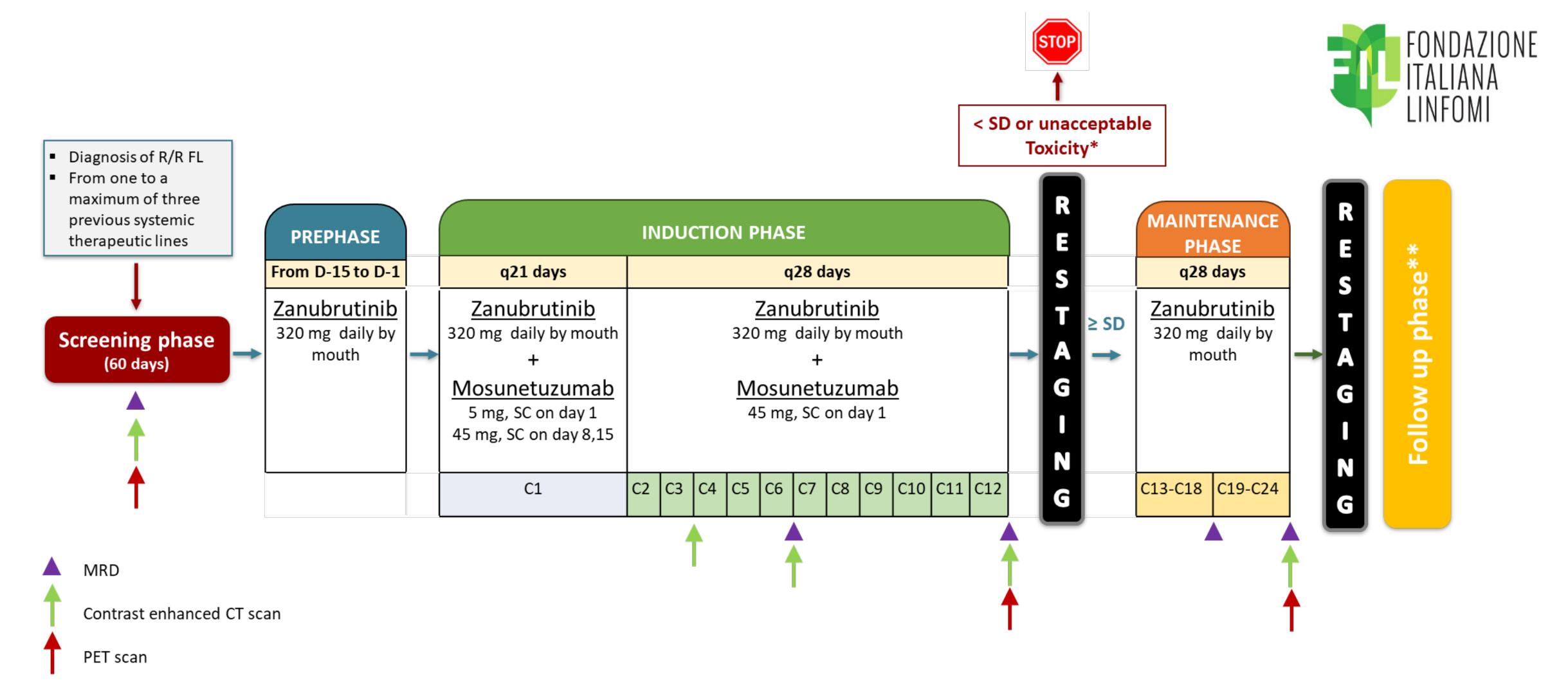




Alderuccio JP, et al. ASH 2024



Phase 2 study in 2L FL – MOZART Study by FIL





Phase 1B study in 2L FL – Symphony-1 (Tazemetostat+R²)

Dose-escalating 3+3 design

Patients
with
R/R FL
(N=44)

TAZ (12 cycles):
400/600/800 mg PO BID*
Rituximab (5 cycles):
375 mg/m² IV†
Lenalidomide (12 cycles):
20/10 mg PO QD‡

RP3D:

800 mg BID TAZ (24 cycles)§

- **Primary endpoints:** Safety and tolerability, RP3D of TAZ in combination with R²
 - Secondary endpoints: PK parameters
- Efficacy analysis (ITT): Best overall response, PFS and DOR (investigator assessment, according to Lugano 2014 response criteria)¹

- EZH2 is an important regulator of B cell development; gain of function mutations (MT EZH2) or uncontrolled upregulation of wild type (WT) EZH2 may lead to the development of FL, making EZH2 a therapeutic target in FL²⁻⁴
- TAZ is a small molecule inhibitor of the epigenetic enzyme EZH2^{2–4}

- TAZ is FDA-approved⁵ for treatment of adult patients with:
 - R/R FL with MT EZH2 and ≥2 prior therapies
 - R/R FL with no satisfactory alternative treatment options



HTB FL New Era: Shifting from ICT to Novel Biological Tx

| | First line | Second line | Third line + |
|--|-------------------------------------|---|---|
| Today FL stage III-IV, HTB | · ICT | • ICT + ASCT (?) • R2 | BsAbs CAR-T |
| | Rituximab (full chemo-free program) | Non-POD24 • R2 | Zanu-obinut.Tazemetostat* |
| Tomorrow Already anticipated Ph3 results FL stage III-IV, HTB | • ICT • Rituximab | POD24 and non-POD24 • Len ± R + Tafa/BsAbs | BsAbs CAR-T Zanu-obinut. Tazemetostat* |
| Future view Pending results of Ph3 ongoing trials FL stage III-IV, HTB | BsAbs ± X | CAR-T (POD24) Len ± R +Tafa/BsAbs Zanu-obinut | BsAbs Novel agents CAR-T Zanu-obinut. Len ± R +Tafa/BsAbs Tazemetostat |



Selected Ph 3 Study Design in 1L FL

| | anti-CD19xCD3 bsAb | | | |
|--|---------------------------|-------------------------|---------------------------|---|
| EPCORE FL-2 ¹ | OLYMPIA-1 ^{2*} | OLYMPIA-2 ^{3*} | MorningLyte ⁴ | SOUNDTRACK-F15 |
| Induction: | | + chemo | + LEN | |
| Epcor + R ² | Odron monotherapy | Odron + CHOP/CVP | Mosun + Len | AZD0486 + R |
| Maintenance: ± epcor maintenance | + odron maintenance | ± odron maintenance | + mosun maintenance | + R maintenance |
| VS | VS | VS | VS | vs |
| Induction: • R/G-CHOP • R/G-Benda • R ² | • R-CHOP/CVP • R-Benda | • R-CHOP | • R/G-CHOP • R/G-Benda | • R-CHOP/CVP • R/Benda |
| Maintenance: + R maintenance | + R maintenance | + R maintenance | + R maintenance | + R maintenance (with R-CHOP/CVP only) |
| Primary Endpoint(s): CR30, PFS | CR30 | CR30 | PFS | PFS |

Adapted from: 1. NCT06191744. 2. NCT06091254. 3. NCT06097364. 4. NCT06284122. 5. NCT06549595



Epcoritamab with rituximab + lenalidomide (R2) in previously untreated (1L) follicular lymphoma (FL) and epcoritamab maintenance therapy in FL: novel results from EPCORE NHL-2 arms 6 and 7

Key inclusion criteria

- 1L CD20+ FL, G1-3a
- ECOG PS 0-2
- Measurable disease
- Adequate organ function

| Arm 6 (1L FL) expansion, N=41 | | | | | | |
|--|--|--|--|--|--|--|
| Epcoritamab (SC) 48 mg QW C1–2, Q4W C3+ (28 d/C) Treatment up to 2 y | Rituximab (IV) 375 mg/m ² QW C1, Q4W C2–6 | Lenalidomide (oral) 20 mg QD for 21 d in C1–12 | | | | |

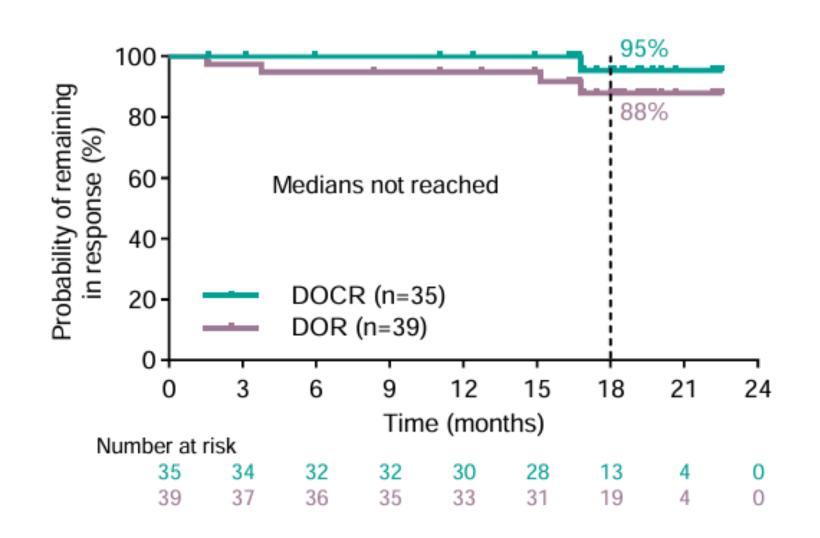
Median follow-up: 22.8 mo Primary objective: Antitumor

activity (ORR)

Key secondary endpoints: Safety, DOR, DOCR, PFS, OS

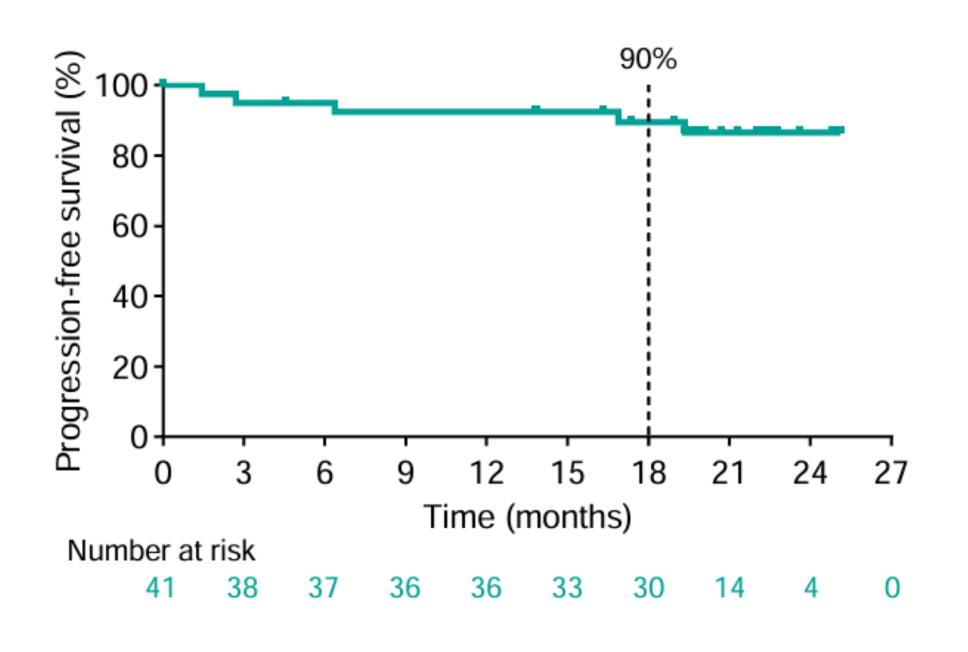
| | N=41a |
|-------------------------------------|----------------|
| Overall response, n (%) | 39 (95) |
| Complete response, n (%) | 35 (85) |
| Partial response, n (%) | 4 (10) |
| Progressive disease, n | 0 |
| Median time to response, mo (range) | 2.7 (1.2–5.5) |
| Median time to CR, mo (range) | 2.8 (1.4–11.4) |

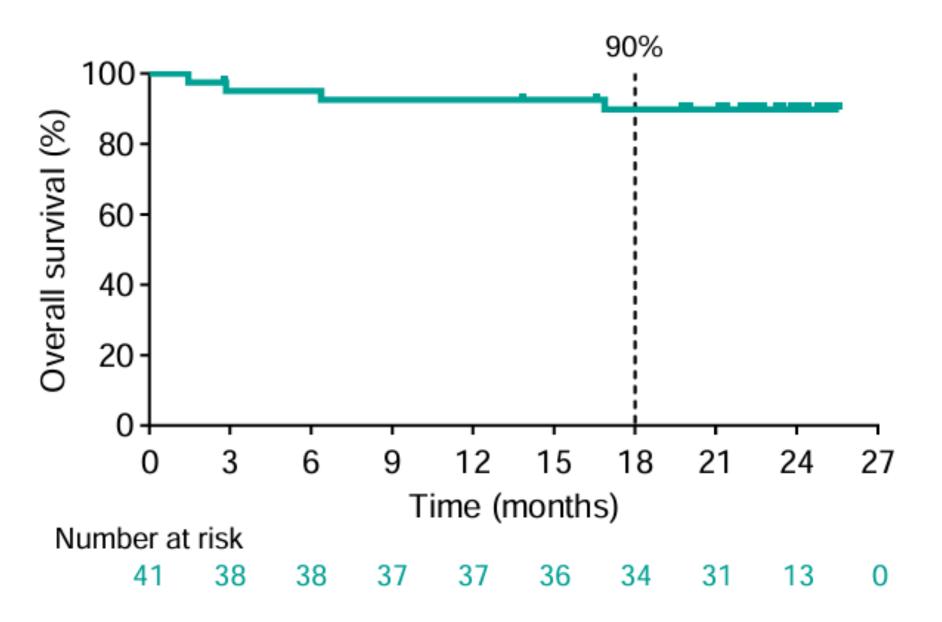
¹L, previously untreated; DOCR, duration of complete response; DOR, duration of response; FL, follicular lymphoma; mo, month(s); R², rituximab + lenalidomide. Kaplan–Meier estimates of DOR and DOCR assessed by investigator. ^aA total of 2 patients were not evaluable.





Epcoritamab with rituximab + lenalidomide (R2) in previously untreated (1L) follicular lymphoma (FL) and epcoritamab maintenance therapy in FL: novel results from EPCORE NHL-2 arms 6 and 7

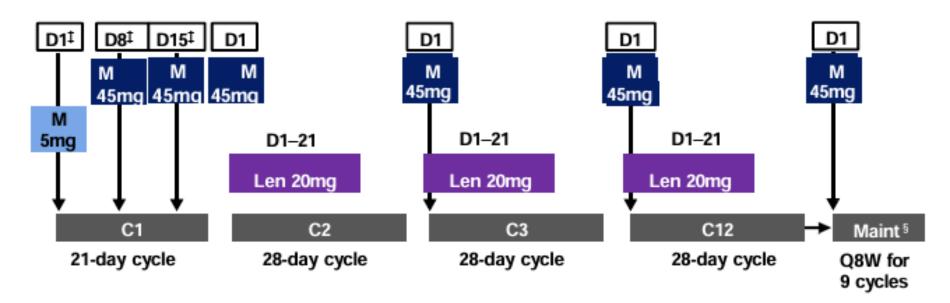


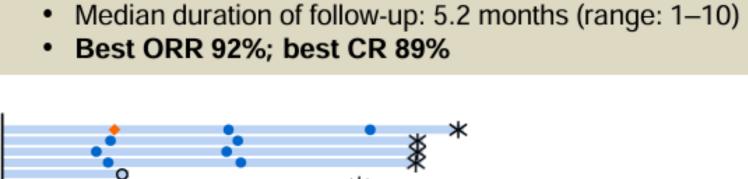


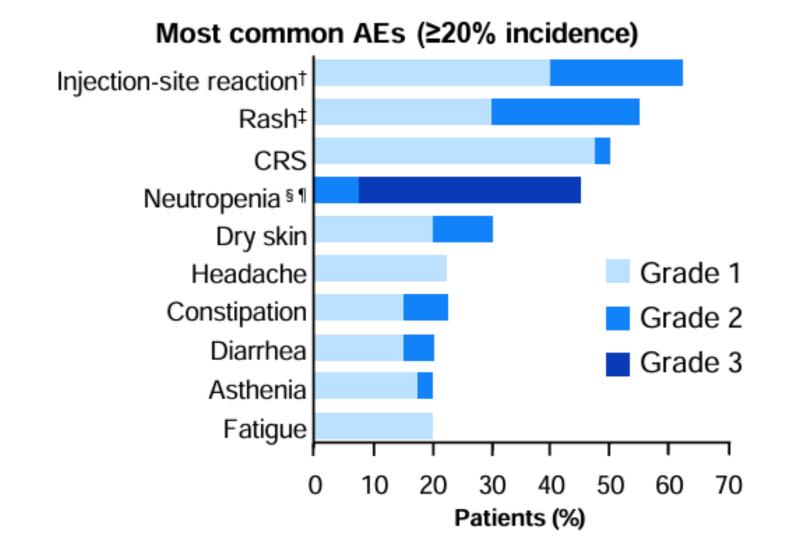


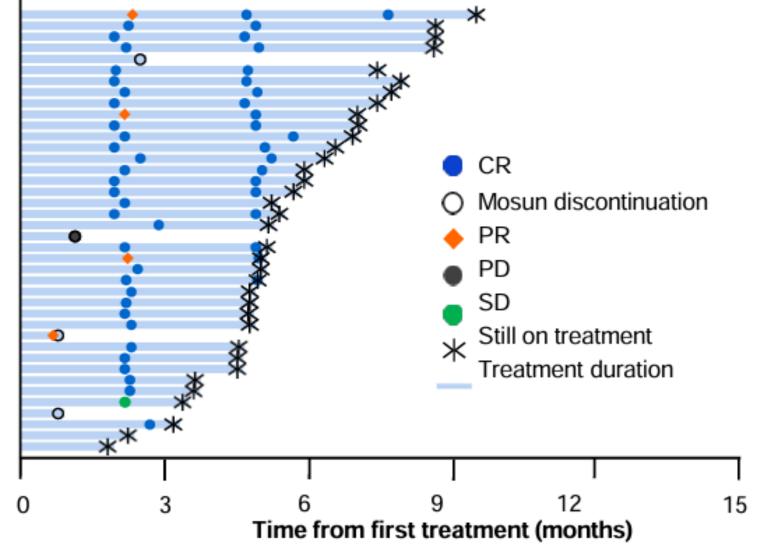
Preliminary Findings of a Phase Ib/II Trial Indicate
Manageable Safety and Promising Efficacy for
Mosunetuzumab in Combination with Lenalidomide
(M+Len) in Previously Untreated (1L) Follicular











Morschhauser F. Blood (ASH annual meeting abstracts), 2023; 142 (S1): 605a



First Line- Ongoing trial

| NCT | Name | Phase | N. | Experimental arm | Control arm | Duration of therapy | Primary endpoint |
|-------------|---------------|-------|------|--|---|---------------------------|------------------|
| NCT04663347 | EPCORE FL-2 | 3 | 1095 | Epcoritamab R ² | G/R-CHOP G/R-benda R ² | 2.5 y | CR30, PFS |
| NCT06284122 | MorningLyte | 3 | 790 | Mosunetuzumab- Lenalidomide | G/R-CHOP G/R-benda | 1.5 y | PFS |
| NCT06091254 | OLYMPIA-1 | 3 | 478 | Odronextamab | R-CHOP R-CVP R-benda | 2 y | CR30 |
| NCT06097364 | OLYMPIA-2 | 3 | 733 | Odronextamab-CHOP/ CVP +/- O-maintenance | R-CHOP/CVP + R- maintenance | 6 m vs 2.5 y | CR30 |
| NCT06549595 | SOUNDTRACK-F1 | 3 | 1015 | AZD0486-rituximab +/- AZD0486 maintenance | R-CHOP/CVP + R- maintenance R-benda | 6-12 m vs. up to 2.5 y | PFS |
| NCT06425302 | Golseek 2 | 2 | 90 | Rituximab-golcadomide (0.2 mg or 0.4 mg) | R-CHOP R-benda | Up to 2 y | CR |