Mosunetuzumab in FL

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Disclosures: Laurie Sehn

- **Consulting/honoraria**:
  - Amgen, AbbVie, AstraZeneca, BMS/Celgene, Gilead Sciences, Janssen-Ortho, Kite, Merck, F. Hoffmann-La Roche Ltd/Genentech, Inc., Seagen, Takeda, Teva, TG Therapeutics, Incyte, Sandoz-Novartis, Nurix, Genmab

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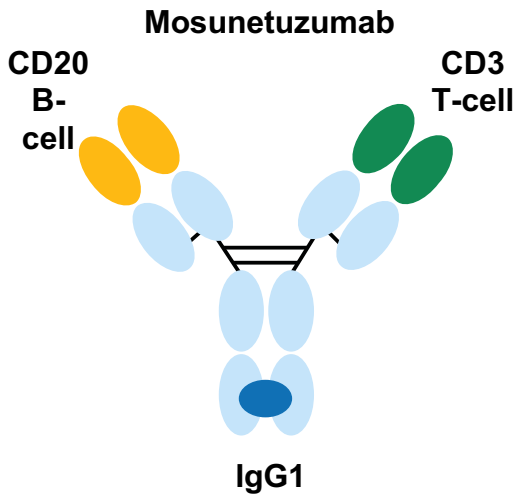
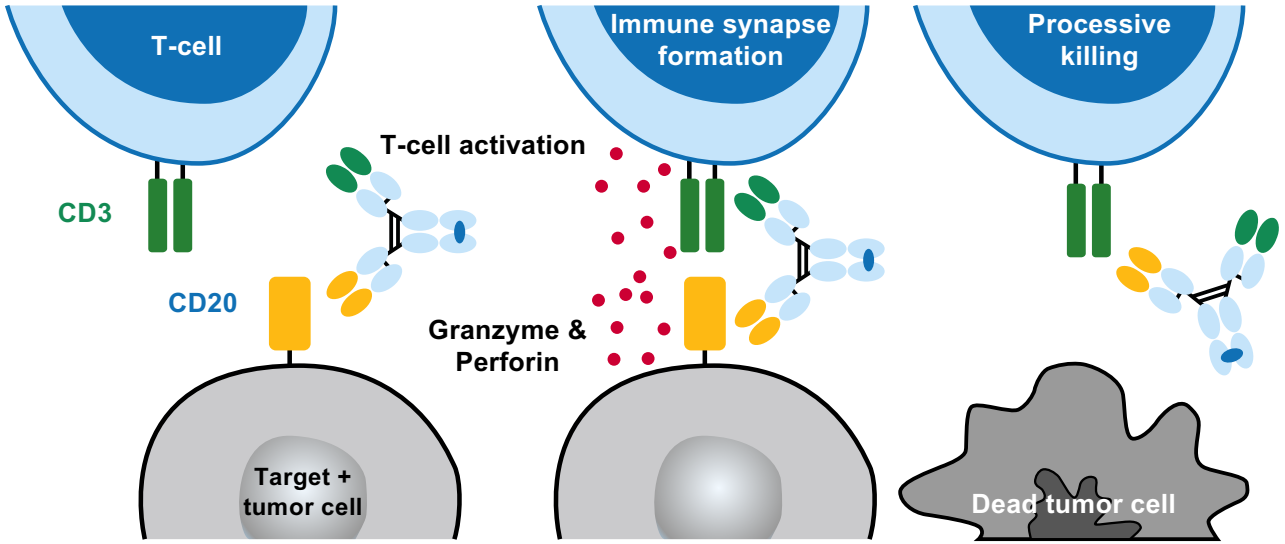
Mosunetuzumab: a bispecific antibody targeting CD3 and CD20

- **Full-length humanized IgG1 antibody**
  - Longer half-life than fragment-based drug formats
  - PK properties enable once weekly to q3w dosing
  - Does not require *ex-vivo* T-cell manipulation
  - Off the shelf, readily available treatment
- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells
  - Conditional agonist: T-cell activation dependent on B-cell engagement
  - Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells





ADCC, antibody-dependent cell-mediated cytotoxicity

Sun et al. Sci Transl Med 2015

Study design

Pivotal, single-arm, multicenter, Phase II expansion in patients with R/R FL and ≥2 prior therapies

Key inclusion criteria

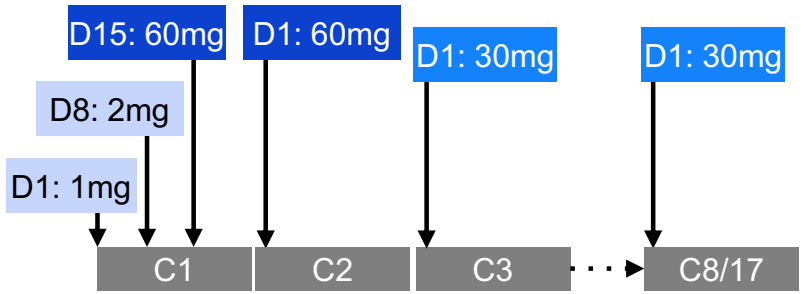
- FL Grade 1–3a
- ECOG PS 0–1
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator

Data analysis

- Study met its primary endpoint: 60% CR rate versus 14% historical control ($p<0.0001$)[1,2]
- Updated efficacy and safety analysis with median 28.3 months of follow up (10 months after the previous report)

Mosunetuzumab administration

- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Re-treatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



Budde LE, et al. Lancet Oncol 2022

Baseline characteristics

	N=90
Median age, years (range)	60 (29–90)
Male	61%
ECOG PS	
0	59%
1	41%
Ann Arbor stage	
I/II	23%
III/IV	77%
Median lines of prior therapy, n (range)	3 (2–10)
Refractory to last prior therapy	69%
Refractory to any prior anti-CD20 therapy	79%
Progression of disease within 24 months from start of first-line therapy (POD24)	52%
Double refractory to prior anti-CD20 and alkylator therapy	53%
Prior autologous stem cell transplant	21%

Budde LE, et al. Lancet Oncol 2022.

Patient disposition and exposure

	N=90
Median time on study, months (range)	28.3 (2–38)
Patients remaining in follow-up	81%
Initial study treatment	
Completed	62%
Discontinued	38%
Due to progressive disease*	27%
Retreatment with mosunetuzumab	4%

	N=90
Number of cycles received	
<8 cycles	23%
8 cycles	59%
>8 and <17 cycles	6%
17 cycles	12%

*Other reasons for discontinuation included: adverse event (4%), physician decision (3%), use of another anti-cancer therapy (2%), and withdrawal by subject (1%).

Bartlett et al, ASH 2022

Response rates

Efficacy endpoint in the overall population by investigator assessment; % (95% CI)	N=90
ORR	**78%** (68–86)
CR	**60%** (49–70)

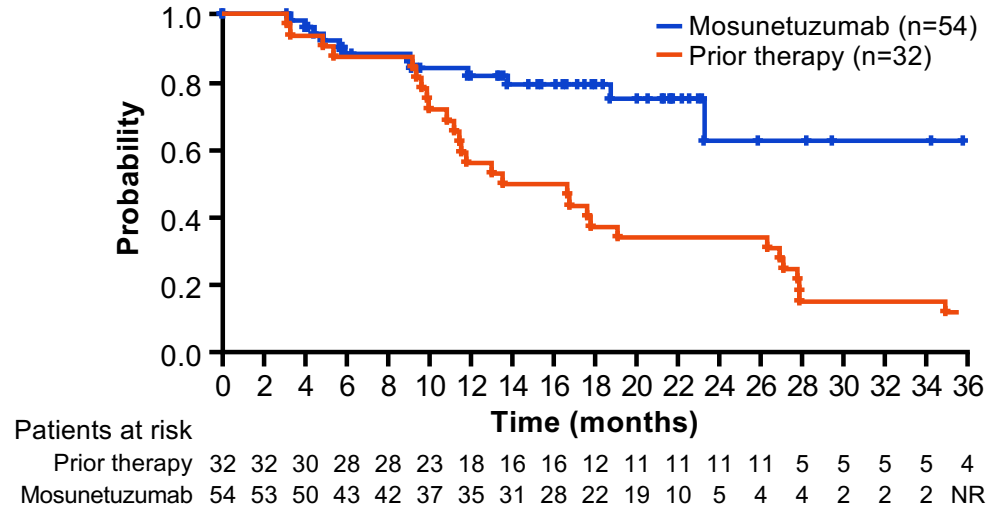
Time to first response (median [range]): **1.4 months** (1.0–11)
Time to first CR (median [range]): **3.0 months** (1.0–19)

High ORR and CR rate were consistent with published results[1]

Bartlett et al, ASH 2022

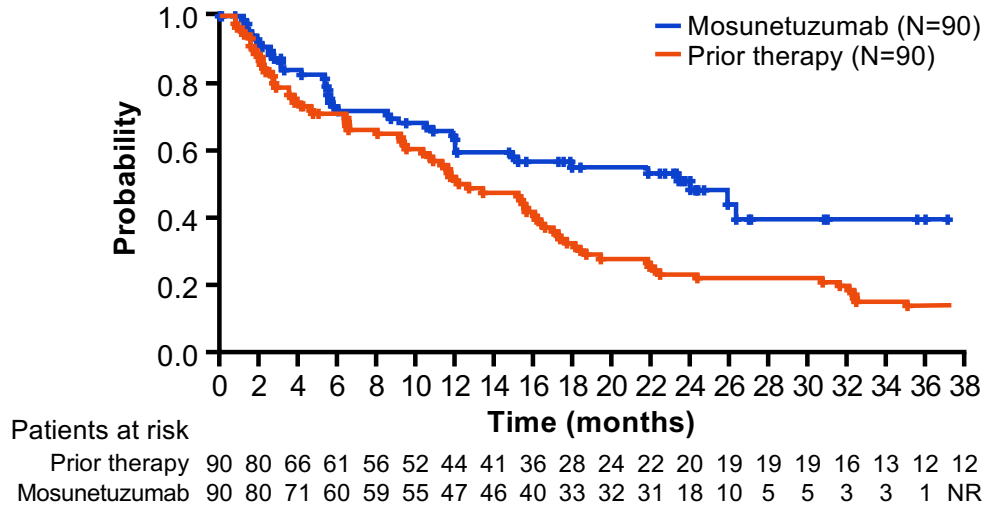
DOCR and PFS with mosunetuzumab versus last prior therapy

DOCR



	Mosunetuzumab (n=54)	Last prior therapy (n=32)
Median DOCR, months (95% CI)	**NR** (23–NR)	**15** (11–26)

PFS

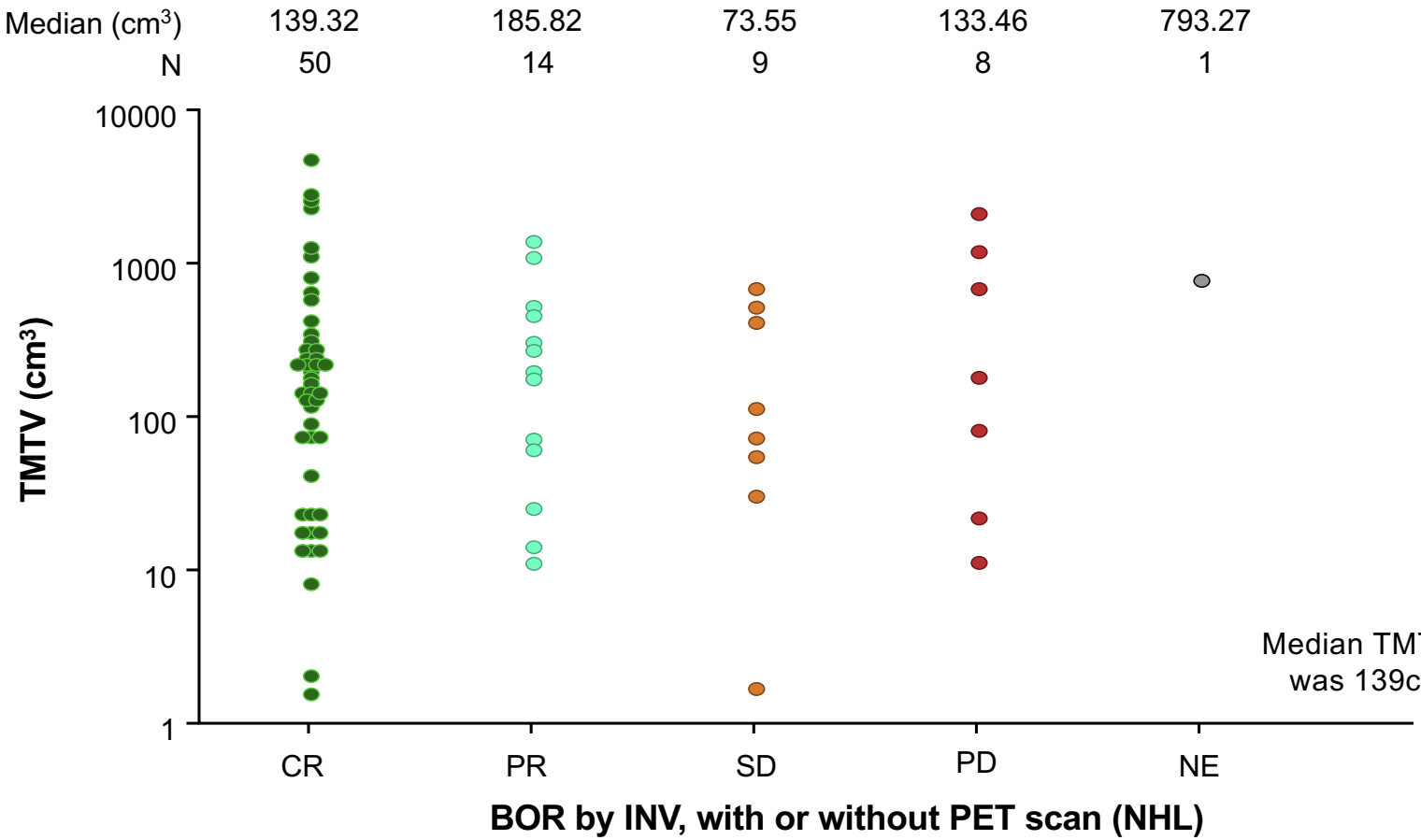


	Mosunetuzumab (N=90)	Last prior therapy (N=90)
Median PFS, months (95% CI)	**24** (12–NR)	**12** (10–16)

Extended DOCR and 12-month improvement in median PFS with mosunetuzumab compared with last prior therapy

Bartlett et al, ASH 2022

No correlation was observed between baseline TMTV and BOR



Median TMTV at baseline (n=82) was 139cm^3 (range: 0–4858)

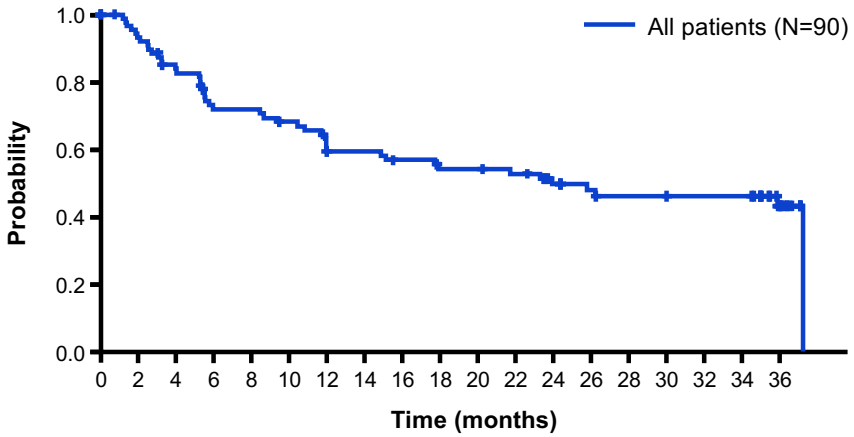
Data cut-off date: July 8, 2022.

BOR, best overall response; INV, investigator; TMTV: total metabolic tumor volume.

Sehn et al, ICML 2023

PFS and OS; median follow-up >36 months

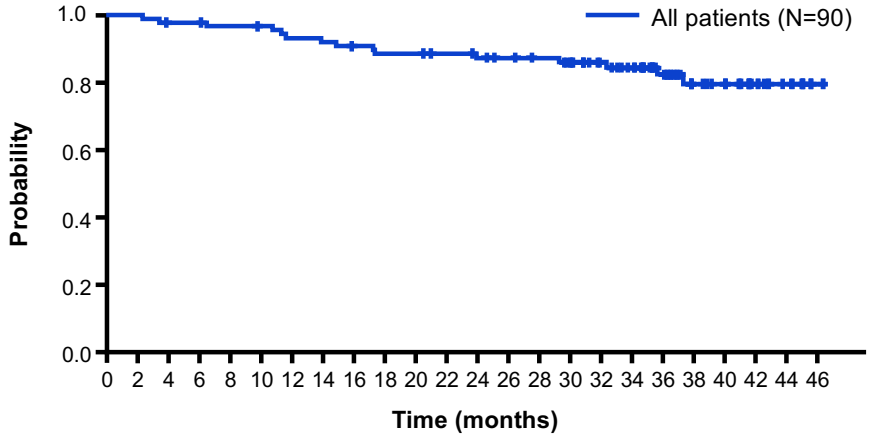
PFS



Patients at risk 90 81 72 60 59 55 47 46 43 40 40 38 30 27 25 25 24 24 13

	N=90
Median PFS, months (95% CI)	**24.0** (12.0–NE)

OS



Patients at risk 90 89 87 86 85 84 81 80 78 76 76 74 72 70 68 62 56 51 39 26 21 14 8 1

	N=90
Median OS, months (95% CI)	**NR** (NE–NE)

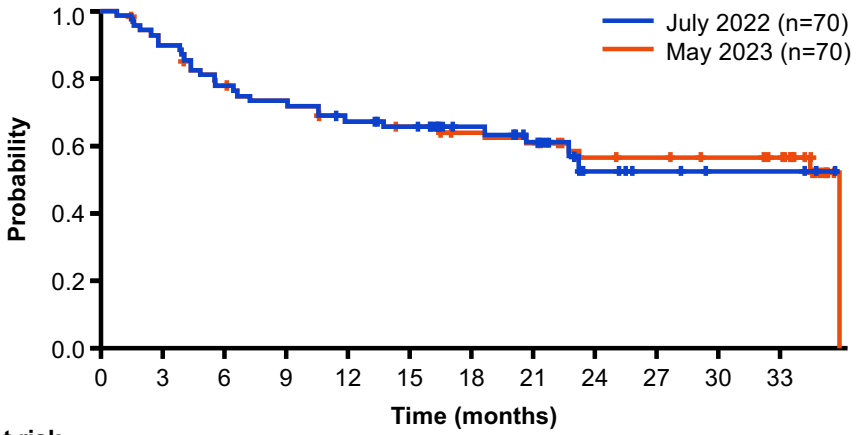
36-month PFS and OS rates were 43.2% (95% CI: 31.3–55.2) and 82.4% (95% CI: 73.8–91.0), respectively

OS, overall survival; PFS, progression-free survival.

Schuster et al, ASH 2023

Durability of responses

DOR (July 2022 vs May 2023 data cut-off)

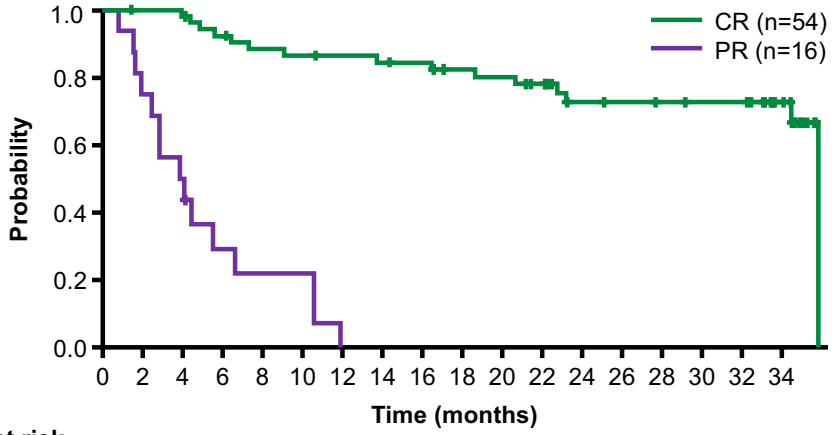


Patients at risk

July 2022	70	62	52	48	42	38	30	25	9	5	3	3
May 2023	70	62	52	48	43	41	38	36	26	25	23	21

	n=70
Median DOR, months (95% CI)*	35.9 (20.7–NE)
30-month DOR rate, % (95% CI)†	56.6% (44.2–68.9)

DOR for CR vs PR (May 2023 data cut-off)



Patients at risk

CR	54	53	52	48	45	44	43	42	41	38	37	34	26	25	24	23	23	15
PR	16	12	8	4	3	3	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Median DOR in patients with CR, months (95% CI); n=54*	NE (NE–NE)
Median DOR in patients with PR, months (95% CI); n=16*	4.0 (2.5–6.7)

72.7% (95% CI: 60.8–86.8) of patients with a CR were estimated to remain alive and progression free 30 months after their first response

*Responders per INV assessment. †36-month DOR data are not available as this analysis was conducted from the first response assessment, therefore the landmark analysis is shorter for the duration outputs.

Schuster et al, ASH 2023

New anti-lymphoma therapy or retreatment with mosunetuzumab

n, unless stated	N=90
Median TTNT, months (95% CI)	37.3 (18.0–NE)
Any new anti-lymphoma therapy	36 (40%)
New systemic treatment	35 (39%)
Chemo +/- immunotherapy	20 (22%)
PI3K inhibitors +/- immunotherapy	10 (11%)
CAR T-cell therapy	9 (10%)
BTK inhibitors +/- venetoclax	5 (6%)
Lenalidomide +/- immunotherapy	4 (4%)
Radiotherapy	9 (10%)
Excision of tumor	2 (2%)
Allogeneic stem cell transplant	2 (2%)
Autologous stem cell transplant	2 (2%)

5 patients received mosunetuzumab retreatment

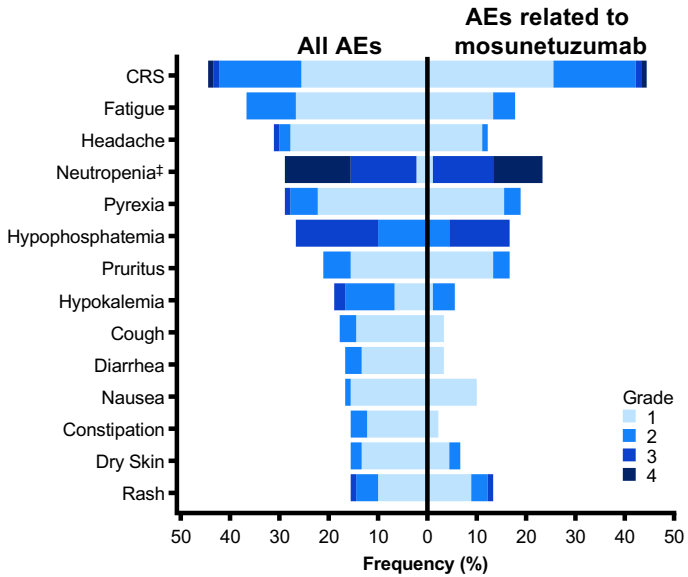
Response to mosunetuzumab retreatment; n	n=5
CR	3 (60%)
PR	0
SD	2 (40%)
PD	0

BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; chemo, chemotherapy; PD, progressive disease; PI3K, phosphoinositide 3-kinase; TTNT, time to next therapy or death.

Safety profile

Adverse events (AEs), n	N=90
AE	90 (100%)
Mosunetuzumab-related	83 (92%)
Grade 3/4 AE	63 (70%)
Mosunetuzumab-related	46 (51%)
Serious AE	42 (47%)
Mosunetuzumab-related	30 (33%)
Grade 5 (fatal) AE	2 (2%)*
Mosunetuzumab-related	0
AE leading to treatment discontinuation	4 (4%)†
Mosunetuzumab-related	2 (2%)

AEs (≥15%) by grade and relationship with mosunetuzumab



No new AEs were reported since the previous data cut-off§; incidence of AEs and serious AEs remains unchanged with this extended follow-up

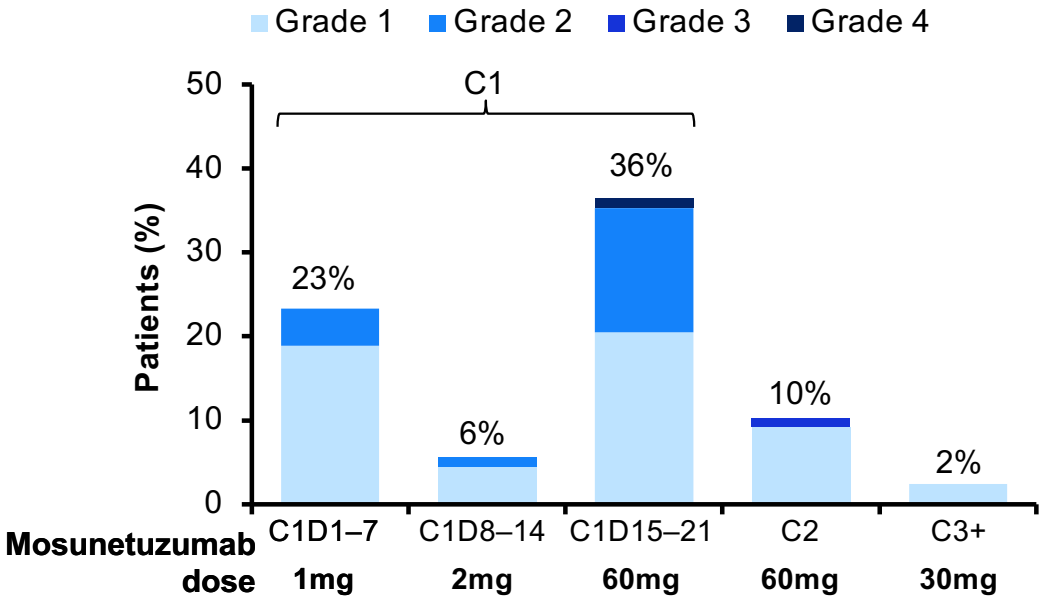
*Malignant neoplasm progression (n=1, onset study D94) and unexplained death (n=1, onset study D60). †Mosunetuzumab related: CRS (n=2, onset study D15 and D22 [both recovered]); mosunetuzumab unrelated: Epstein-Barr viremia (n=1, onset study D11, recovered) and Hodgkin's disease (n=1, onset study D193, not recovered). ‡Preferred terms neutropenia and neutrophil count decreased are combined. §One non-serious, unrelated AE was reported outside of the AE-reporting window and was subsequently inactivated.

Schuster et al, ASH 2023

CRS summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade), n	40 (44%)
Grade 1	23 (26%)
Grade 2	15 (17%)
Grade 3	1 (1%)
Grade 4	1 (1%)
Median time to CRS onset, hours (range)	
C1D1	5 (1–24)
C1D15	27 (0–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management, n	10 (11%)*
Tocilizumab for CRS management, n	7 (8%)*
Events resolved	100%

CRS by cycle and grade

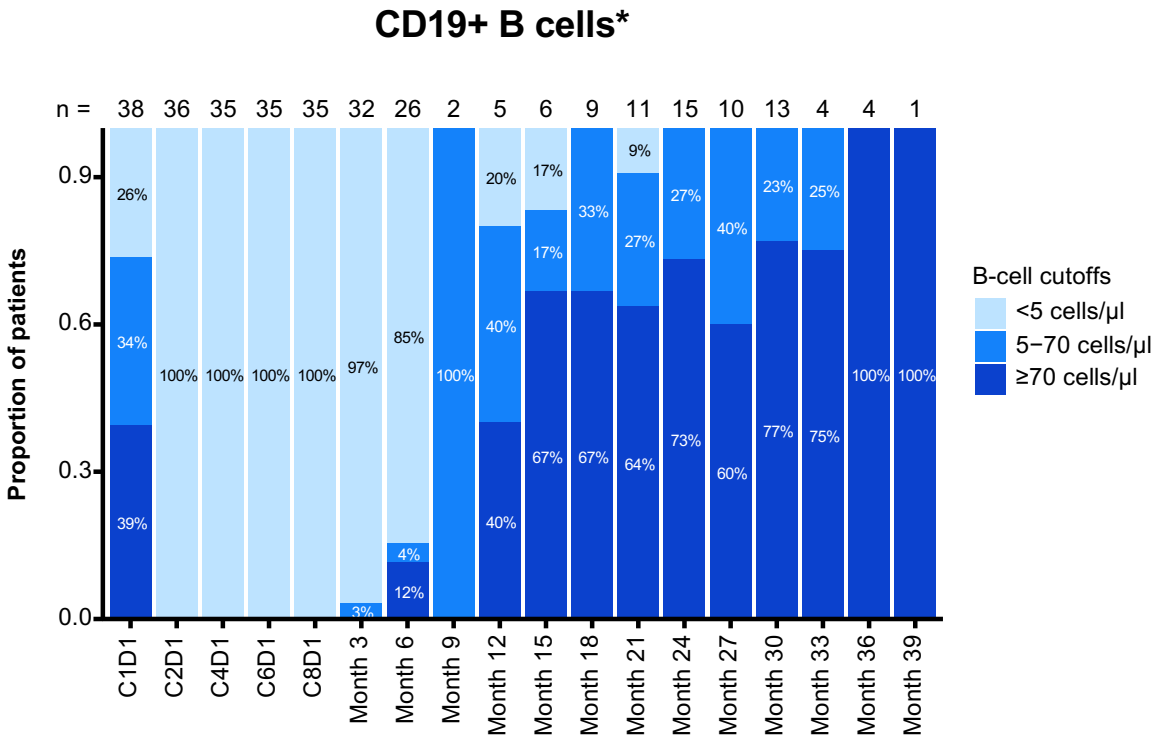


CRS was predominantly low grade and occurred during C1
All CRS events resolved; no new events were reported in this extended follow-up

Data cut-off: August 27, 2021, as no new CRS events occurred subsequently.*Four patients received both corticosteroids and tocilizumab for CRS management. ASTCT, American Society for Transplantation and Cellular Therapy.

Schuster et al, ASH 2023

B-cell depletion and recovery

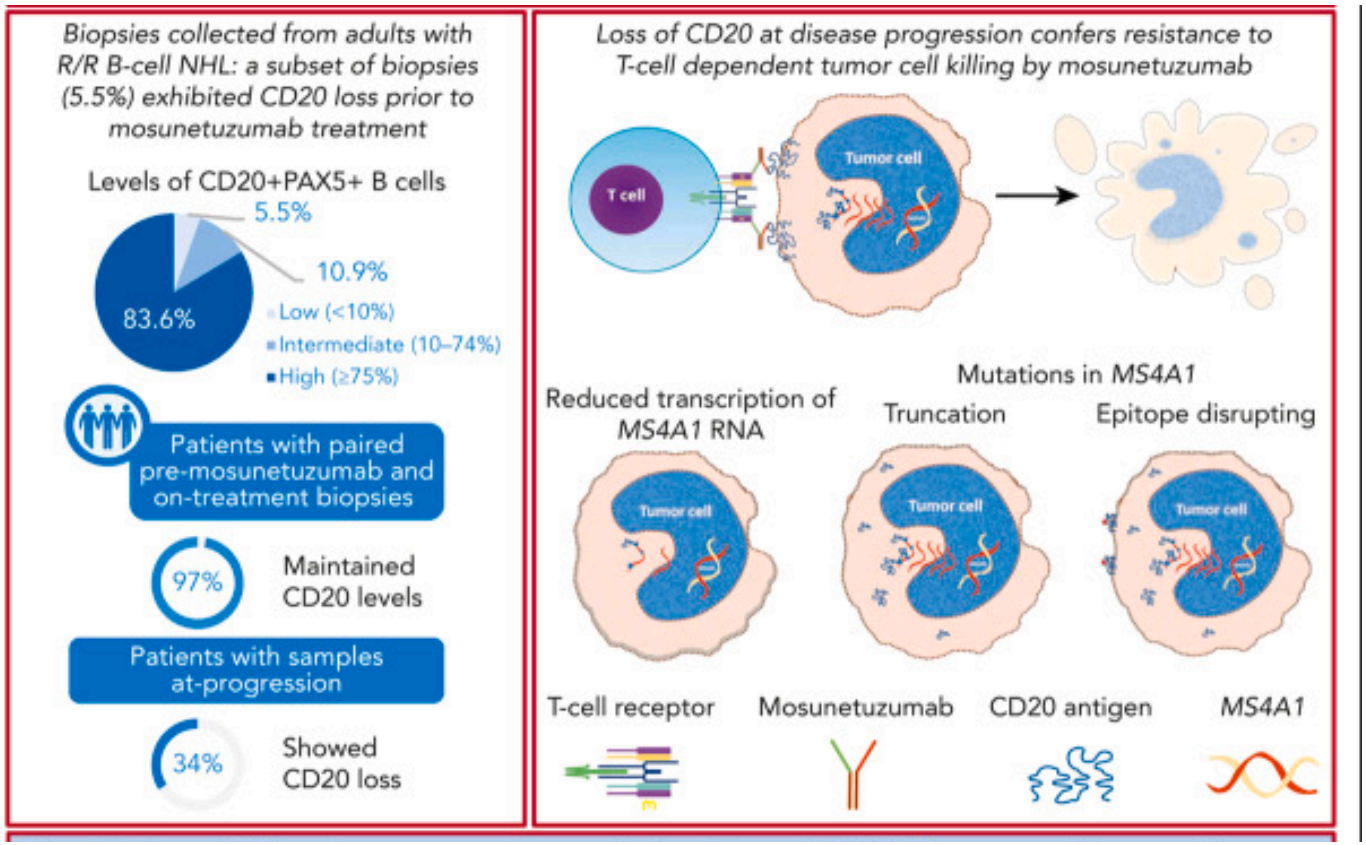


- Peripheral blood B-cell depletion following treatment with mosunetuzumab occurred rapidly by the initiation of C2 dosing in all patients (n=74)
- Time-to-event analysis in patients with end-of-treatment (C8) and follow-up samples (n=38) was performed to assess B-cell recovery
  - Median time to recovery to quantitative levels was 18.4 months (95% CI: 12.8–25.0)
  - Median time to recover to the lower level of normal was 25.1 months (95% CI: 19.0–NE)

*CD19+ B cells were monitored by flow cytometry at C1, C2, C4, and C8, and every 3 months during follow-up or until progression or next lymphoma treatment. The lower limit of quantitation was 5 cells/µl and the lower limit of normal was 70 cells/µl. Depletion was analyzed in all patients with a pre-dose and at least one on-treatment sample. Recovery was analyzed in patients with a CR and at least one follow-up sample.

Schuster et al, ASH 2023

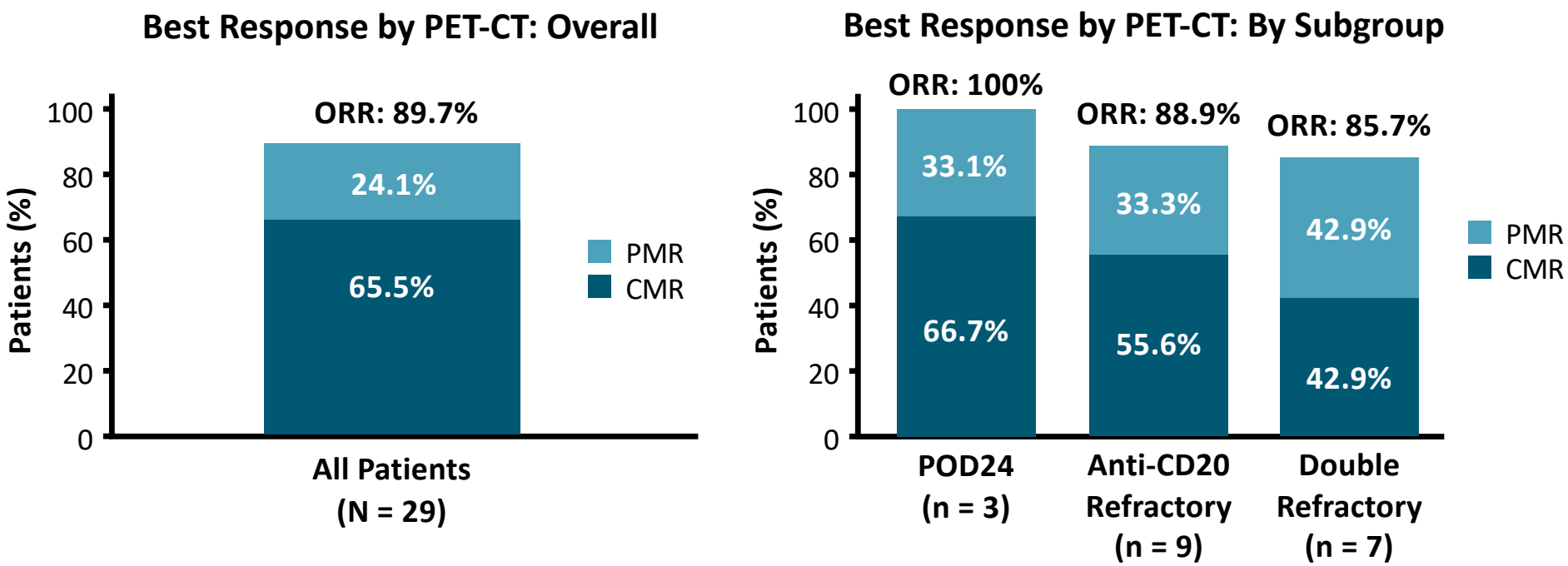
Loss of CD20 following Mosunetuzumab



*Observed in up to 34% of patients tested at progression

Schuster, S et al Blood 2023

Mosunetuzumab + Lenalidomide in R/R FL: Response



- Median time to first/best response: 2.5 mo (range: 1.4-5.3)/2.5 mo (range: 1.4-10.7)
- High ORR and CMR rate in overall population, including those with high-risk disease

Morschhauser et al, ASH 2021

CELESTIMO Study Design

Eligibility

- Histologically confirmed diagnosis of FL (Grade 1, 2 or 3a)
- >=1 prior systemic therapy for FL

Stratification:

- POD24 vs non POD24
- 1 prior therapy vs >1 prior therapy
- CD20 therapy refractory vs not

1:1

Arm A
M + Len
N=200 FL patients

Arm B
R+ Len
N=200 FL patients

Endpoints

1° EP: PFS by IRC

2° EP:

- PFS by INV
- ORR, CR
- OS
- DOR
- DOCR
- QoL
- Safety
- Pharmacokinetics
- Biomarkers

Exploratory:

- TTNLT
- TTR
- PFS2
- EFS
- Histologic transformation rate

Mosunetuzumab/Lenalidomide in Untreated FL

Key inclusion criteria

- CD20+ FL Grade 1–3a
- Previously untreated and require therapy*
- ECOG PS 0–2

Objectives

- Primary: Safety and tolerability of Mosun-Len
- Other: Efficacy (response assessed every 3 cycles,† durability of response), biomarkers, and PK

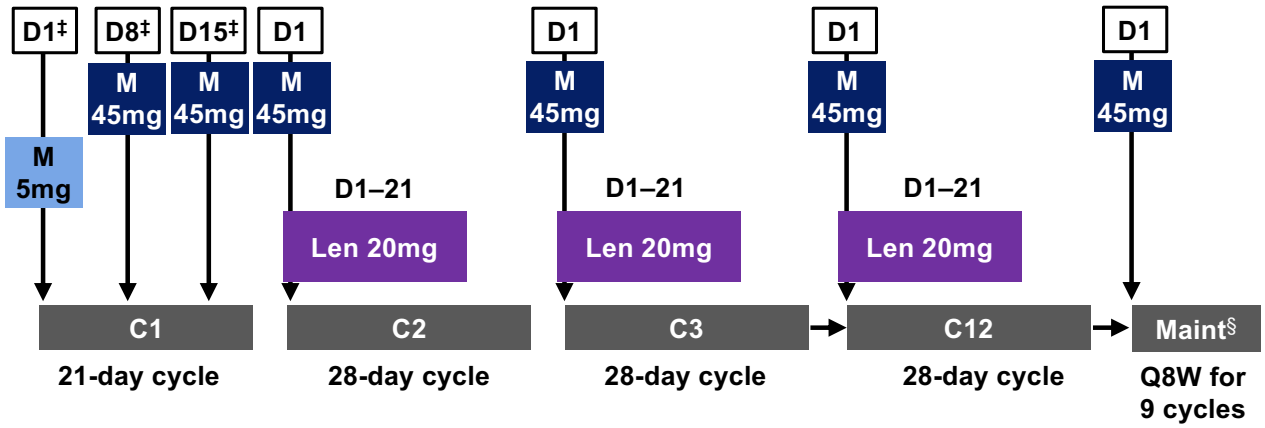
Mosun-Len administration

Mosun

- SC administration for 12 cycles (C1: Q3W; C2–12: Q4W)
- C1 step-up dosing (CRS mitigation)
- No mandatory hospitalization

Len

- Oral administration for 11 cycles (C2–12)



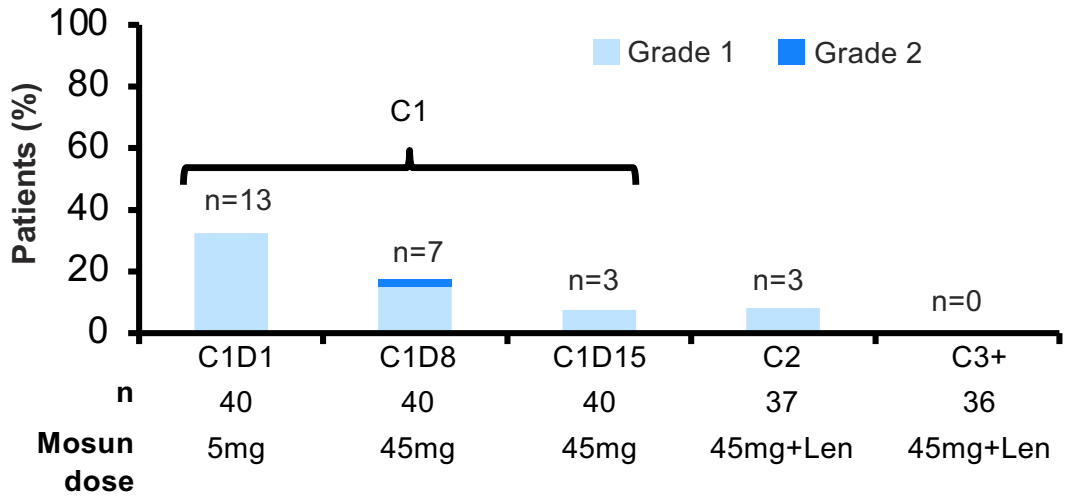
CCOD: July 20, 2023.*Investigator-assessed based on Groupe d'Etude des Lymphomes Folliculaires criteria. †During induction C1–C12. ‡A single dose of oral or IV dexamethasone or methylprednisolone as pre-medication to mitigate risk of CRS was required during C1 and optional after C1. §Mosun monotherapy maintenance option for patients who achieved complete or partial metabolic response after 12 cycles of induction therapy with Mosun-Len.
C, cycle; CCOD, clinical cut-off date; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; M, mosunetuzumab; Q3W, once every 3 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; maint, maintenance; PK, pharmacokinetics.

Morschhauser et al, ASH 2023

Cytokine release syndrome

	N=40; n (%)*
CRS† (any grade) Grade 1 Grade 2	20 (50.0) 19 (47.5) 1 (2.5)
Serious AE of CRS‡ (any grade)	6 (15.0)
Median time to first CRS onset,§ days (range)	2.5 (1–27)
Median CRS duration, days (range)	2.0 (1–26)
CRS resolved	20 (100)
Corticosteroids for CRS management	0
Tocilizumab for CRS management	2 (5.0)¶
CRS leading to Mosun discontinuation	0

Patients with CRS† by cycle and grade



CRS occurred in 50% of patients (predominantly Grade 1 with one Grade 2 event) and was confined to C1–C2
None of the CRS cases required vasopressors, supplemental oxygen, or ICU admission
All events resolved

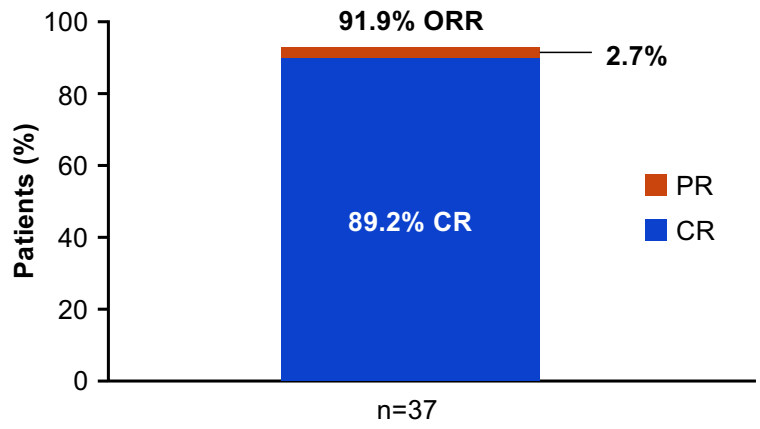
CCOD: July 20, 2023. *Unless otherwise specified. †Assessed using American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria. ‡Serious AE due to hospitalization. §First occurrence of CRS from start of study (C1D1). ¶Grade 1 (fever, shortness of breath) and Grade 2 (fever, hypotension) CRS.

Morschhauser et al, ASH 2023

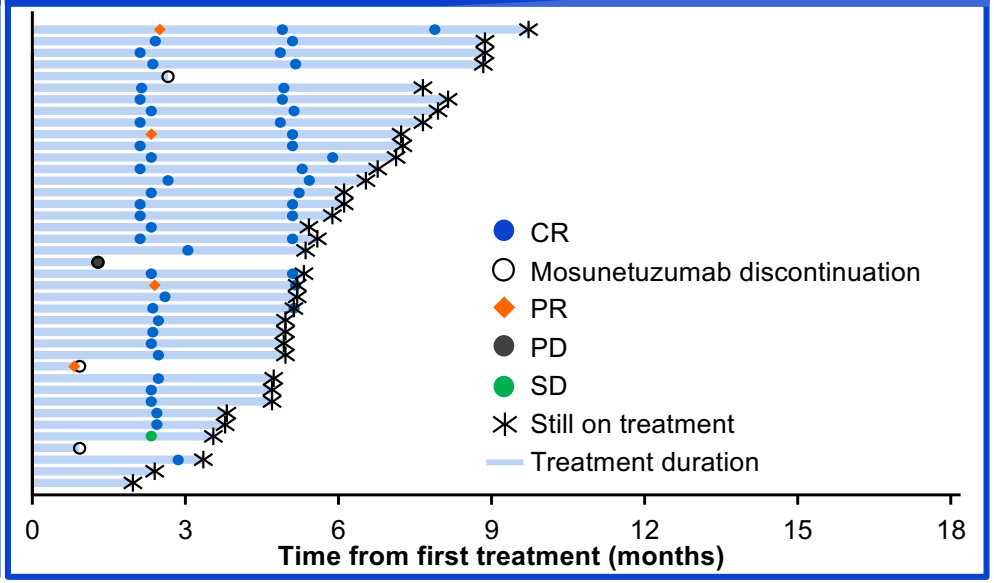
Response

- Median duration of follow-up: 5.2 months (range: 1–10); most patients (95%) had 3–9 months of follow-up at CCOD

Best overall response*



Response timing and duration†

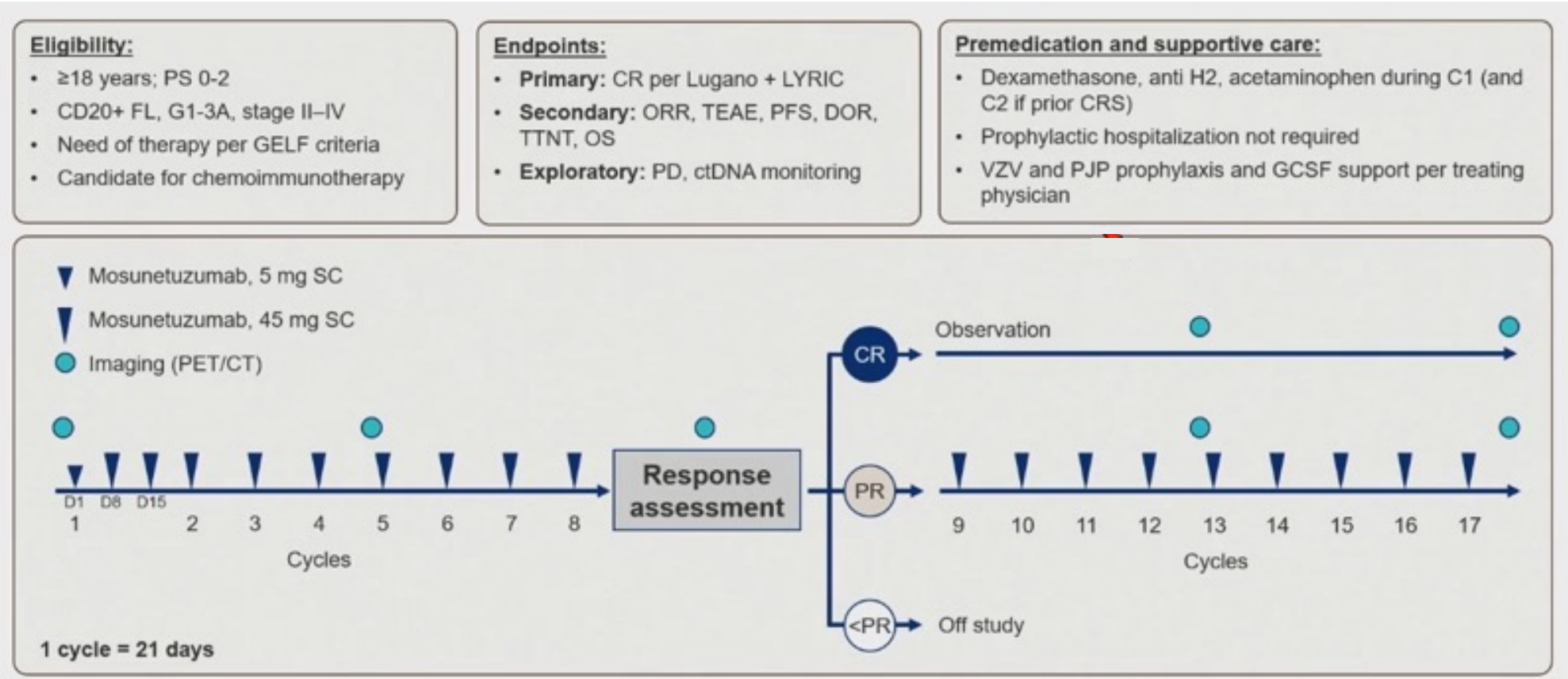


ORR and CR rates were high. All patients who responded were still in response at the CCOD

CCOD: July 20, 2023.
*Thirty-seven patients reached the first treatment assessment (by PET-CT using Lugano 2014 criteria) and were efficacy evaluable. In the efficacy evaluable population one patient (2.7%) each had SD and PD; one patient (2.7%) did not have a response assessment due to early treatment discontinuation for uveitis. Transformed disease was observed in one patient with PR and another with PD during Cycles 1 and 2, respectively.
†Responses were with or without PET.
ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

Morschhauser et al, ASH 2023

Phase 2 Trial of Subcutaneous Mosunetuzumab As First-Line Therapy in FL

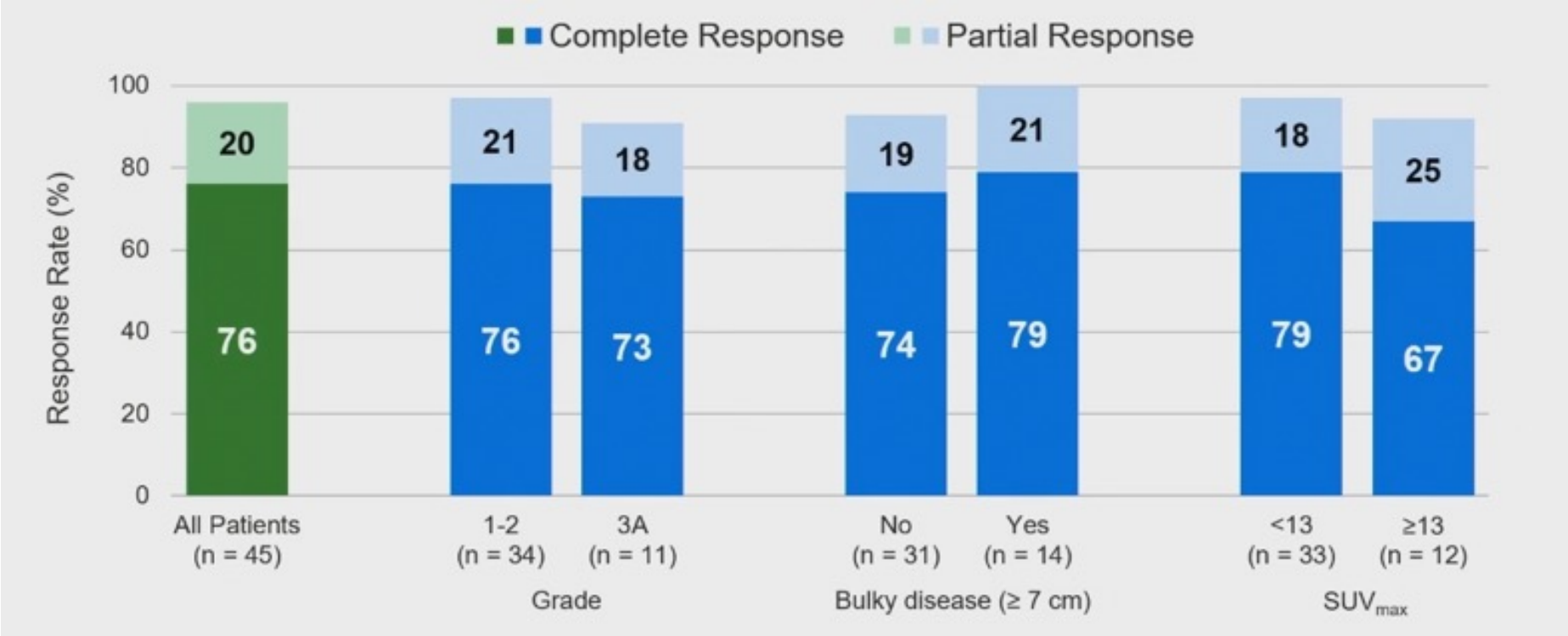


CT, computed tomography; ctDNA, circulating tumor DNA; GCSF, granulocyte-colony stimulating factor; GELF, Groupe d'Etude des Lymphomes Folliculaires; H2, histamine 2; LYRIC, Lymphoma Response to Immunomodulatory Therapy Criteria; PFP, Pneumocystis jirovecii pneumonia; SC, subcutaneously; VZV, varicella-zoster virus.

Falchi L, et al. Blood. 2023;142(Suppl 1): Abstract 604.

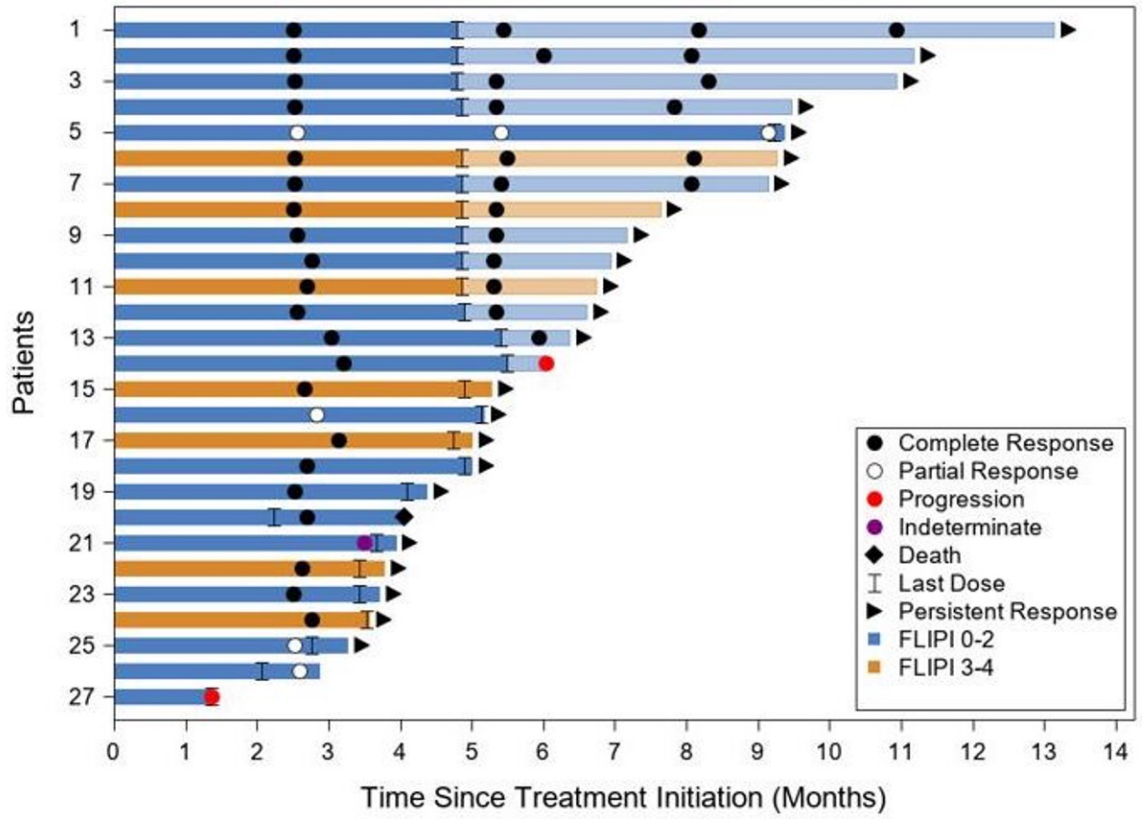
Falchi L, et al. ASH. 2023; Abstract 604.

Mosunetuzumab in FL
Response Rates by Risk Group



Falchi L, et al. ASH. 2023; Abstract 604.

Subcutaneous Mosunetuzumab As First-Line Therapy in High Tumor-Burden FL: Patient Characteristics



Falchi L, et al. ASH. 2023; Abstract 604.

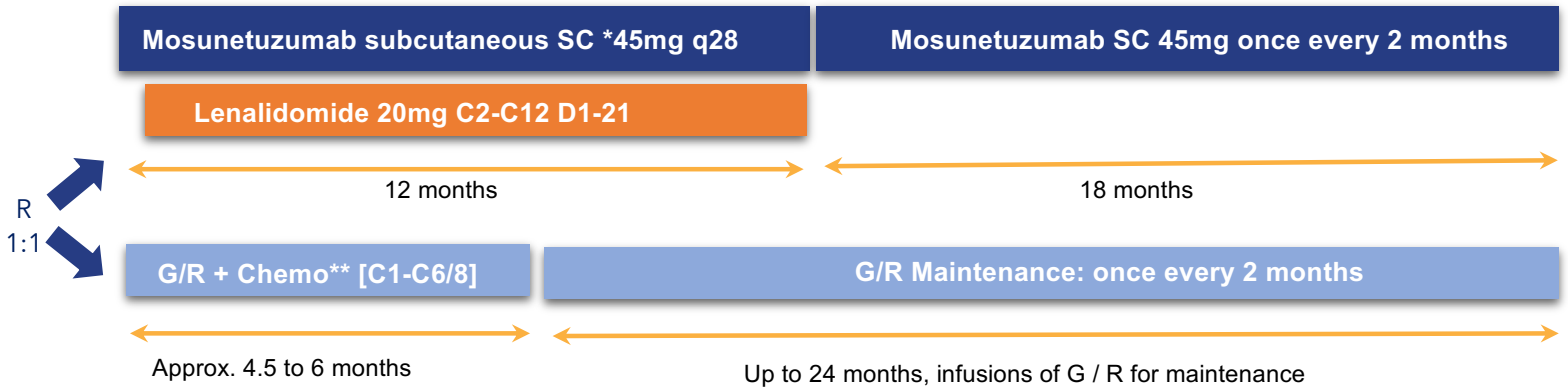
MorningLyte Study Design

Eligibility

- **Symptomatic 1L FL**
- **FLIPI 2-5**
- **N = 790**

Stratification

- **FLIPI 2 versus 3−5**
- **Diameter of the largest lesion (<6 vs. ≥6 cm)**



Superiority Study:

- **HR = 0.65**
- **Primary EP:** PFS (IRC)
- **Secondary EP:** ORR, POD24, PFS by Inv, EFS, TTNT, DOR, OS, Safety, QOL, etc.
- **Exploratory EP**: Biomarkers

*Step up dosing for CRS mitigation during C1: D1 5mg, D8 45mg, D15 45mg
** CHOP or Bendamustine; mAb+chemo regimen→ dealers choice

Conclusions

- Mosunetuzumab is a first-in-class bispecific antibody approved for R/R FL
- In highly pretreated patients, fixed duration therapy induces a high rate of durable remissions
- Manageable safety profile allows out-patient treatment
- Encouraging efficacy with re-treatment
- Phase 3 trials in combination with lenalidomide in second and first-line setting underway