Lymphoma Updates from ASH Annual Meeting 2023 (continued)

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Disclosures

- Gilead Sciences – spouse's employment
- Astra Zeneca – site PI on clinical studies

Outline

- Follicular Lymphoma (FL)
- Mantle Cell Lymphoma (MCL)

- Cellular therapies
- Bispecific Antibodies
- Targeted Agents
- Other Advances

FOLLICULAR LYMPHOMA

TRANSCEND FL : Liso-cel for 2nd line tx of high-risk FL

TRANSCEND FL	
Patients	Relapsed/Refractory FL (≥1L of prior tx)
Phase	2
Sites	Multinational
Design	Open label, single tx arm, multiple disease cohorts
Arms	Lisocabtagene maraleucel (100×10^6 cells)
Endpoints	ORR (1°), CR, DOR, PFS, OS, safety, cellular kinetics
Registration	NCT04245839

* Bridging therapy allowed, but residual disease post-bridging required to proceed

- Reported on 23 patients in FL cohort with:
  - POD24 (52%) and/or high tumor burden by mGELF (70%)
  - Prior aCD20 + alkylator
  - Only 1 prior L of therapy
- mFU 18.1 months

[Franck Morschhauser…Loretta Nastoupil]

TRANSCEND FL : Liso-cel for 2nd line tx of high-risk FL

Efficacy	Patients with 2L FL (n = 23)
ORR, n (%)	22 (95.7)
95% CI; 1-sided *P* value	78.1–99.9; < 0.0001
CR rate, n (%)	22 (95.7)
95% CI; 1-sided *P* value	78.1–99.9; < 0.0001
PR, n (%)	0
Stable disease, n (%)	0
PD, n (%)	1 (4.3)
DOR, median (95% CI)	NR (19.3–NR)
Probability of continued response at 12 months, % (SE)	89.8 (6.866)
PFS, median (95% CI)	NR (20.2–NR)
PFS rate at 12 months, % (SE)	91.3 (5.875)
Safety	**Patients with 2L FL (n = 23)**
AEs of special interest, n (%)	
Any-grade CRS[a]	12 (52.2)
Grade 1	7 (30.4)
Grade 2	5 (21.7)
Grade 3	0
Grade 4 or 5	0
Any-grade NEs[b]	4 (17.4)
Grade 1	3 (13.0)
Grade 2	0
Grade 3	1 (4.3)
Grade 4 or 5	0
Prolonged cytopenia[c]	3 (13.0)
Grade ≥ 3 infection	0
MAS	1 (4.3)
Hypogammaglobulinemia	1 (4.3)

[a]CRS was graded based on Lee 2014 criteria; [b]NEs were defined as investigator-identified neurological AEs related to liso-cel and were graded per the NCI CTCAE, version 5.0; [c]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia on Day 29. NR, not reached; SE, standard error.

Summary

- Effective in high risk FL in 2nd line

- "2L" is not always post aCD20+chemo in FL → extrapolation to 2L in general?
- Need long-term (>~5y) follow-up in this disease to know true/full impact

[Franck Morschhauser…Loretta Nastoupil]

ELARA Study : Tisa-cel for 3L FL, extended follow-up

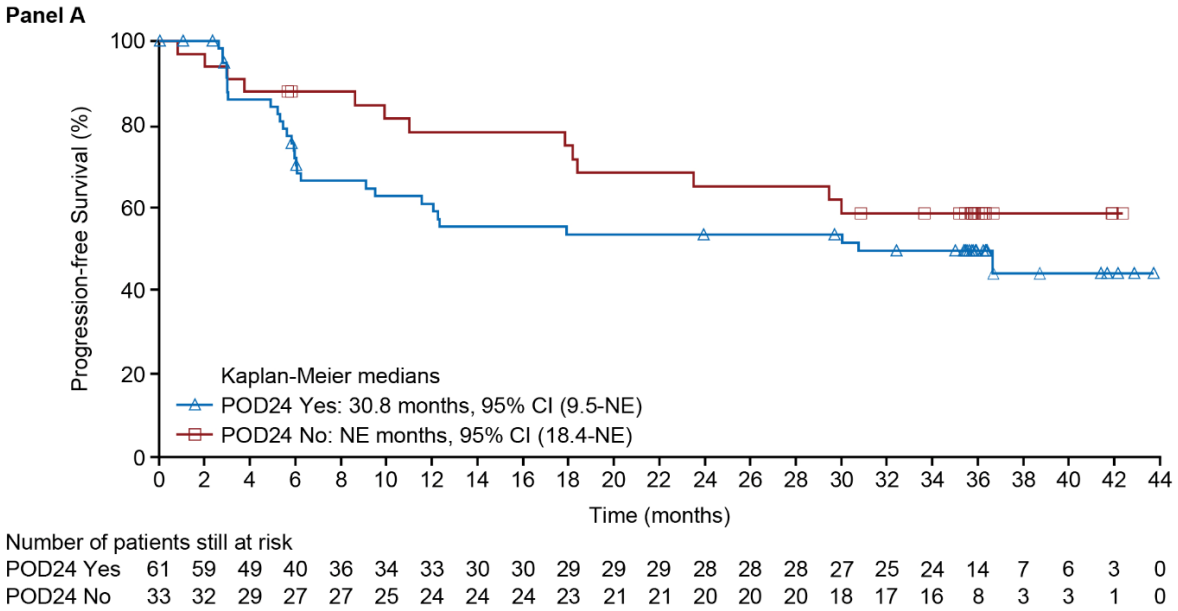
	ELARA
Patients	Relapsed/Refractory FL (≥ 2L of prior tx)
Phase	2
Sites	Multinational
Design	Open label, single tx arm
Arms	Tisagenlecleucel (60-600 x 10^6 cells)
Endpoints	ORR (1°), CR, DOR, PFS, OS, safety, cellular kinetics
Registration	NCT04245839

- 97 patients
- mFU 41m [34.2-49.7]
- 65% bulky, 63% POD24
- Grade ≥3 AEs:
  - Any = 81.4%
  - Neutropenia – 43%
  - Anemia = 19%
- SAEs:
  - Any = 46%; Tx-related = 29%
  - CRS 20%
  - Pneumonia 11%
  - Febrile neutropenia 8%
- Neuro AE ≥G3 = 3%
- 18 deaths: 9 due to PD, 9 due to AEs, 1 due to euthanasia in the setting of a neuro AE
  - but none within 30d infusion; none were deemed treatment-related

[Stephen Schuster…Martin Dreyling]
Dreyling et al., *Blood* (2024)

ELARA Study : Tisa-cel for 3L FL, extended follow-up

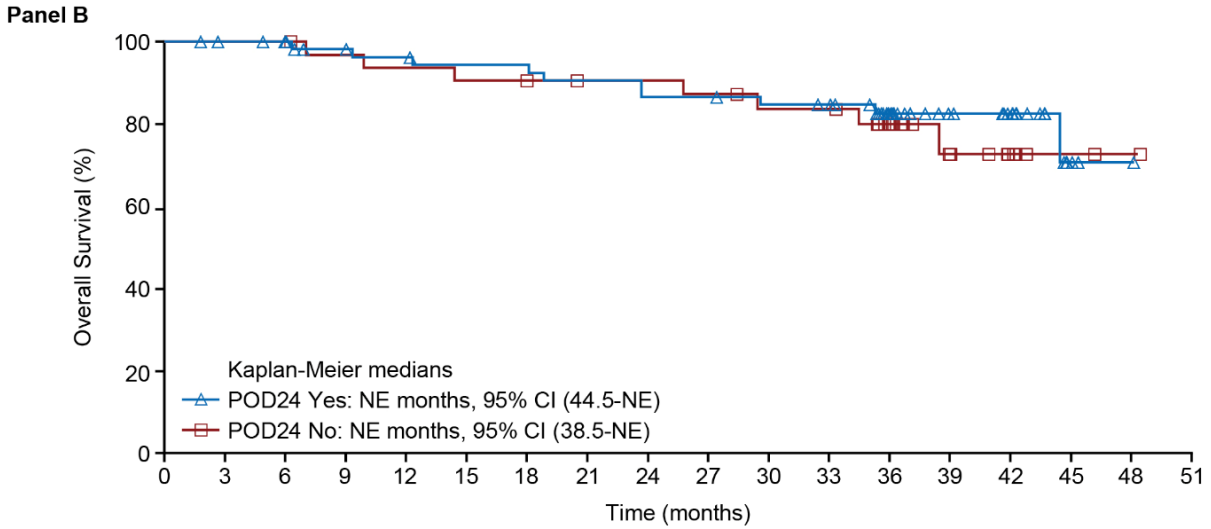
Progression-Free Survival



Number of patients still at risk

POD24 Yes	61	59	49	40	36	34	33	30	30	29	29	29	28	28	28	27	25	24	14	7	6	3	0
POD24 No	33	32	29	27	27	25	24	24	24	23	21	21	20	20	20	18	17	16	8	3	3	1	0

Overall Survival



Number of patients still at risk

POD24 Yes	61	59	58	53	51	49	49	47	45	45	43	42	30	19	15	3	1	0				
POD24 No	33	33	33	31	30	29	29	27	27	26	24	24	17	9	5	2	1	0				

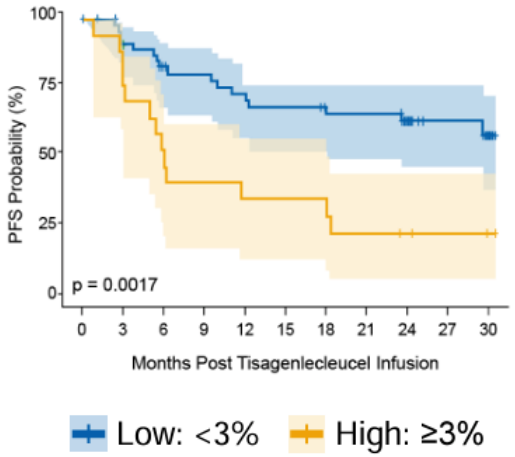
In **all** patients: mPFS 37m
mDOR NR
mOS NR
76% of CRs ongoing at 3y

[Stephen Schuster…Martin Dreyling]
Dreyling et al., *Blood* (2024)

ELARA Study : Tisa-cel for 3L FL, extended follow-up

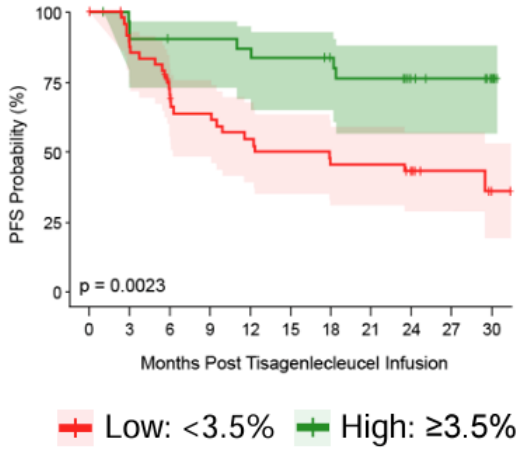
In TME

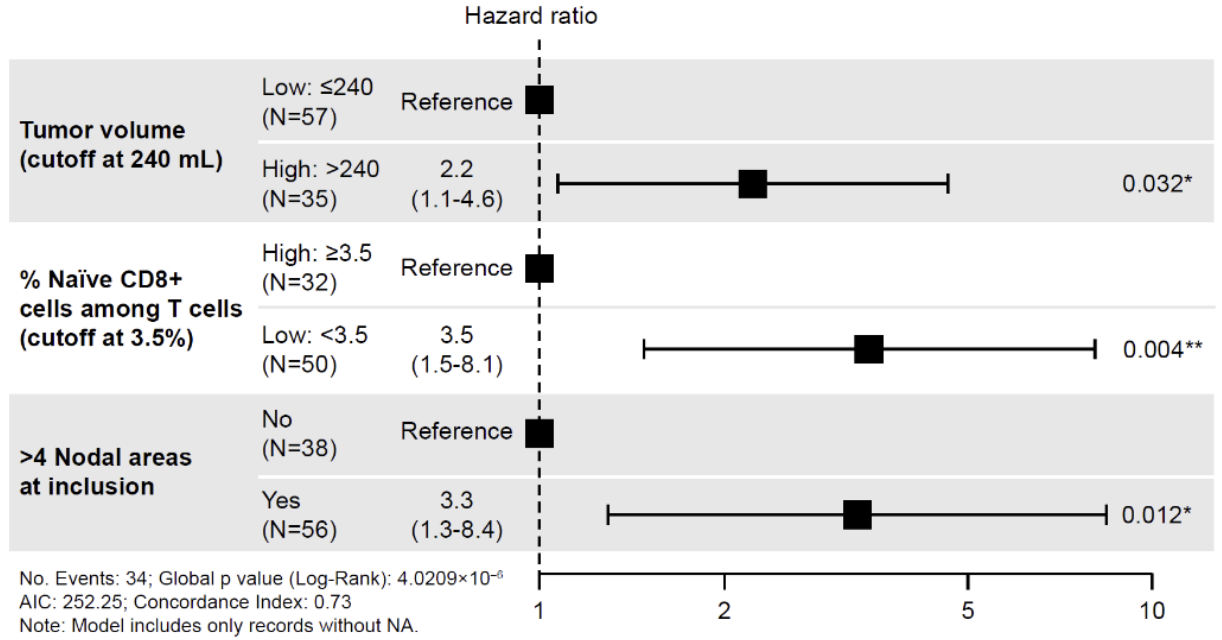
PFS by %LAG3+CD3+ Cells



In Peripheral Blood

PFS by %CD8+ Naïve T-Cells





Supplemental Figure 2. Multivariate analysis of clinical factors significantly associated with PFS.

AIC, Akaike information criteria; CD, cluster of differentiation; NA, not available; PFS, progression-free survival.

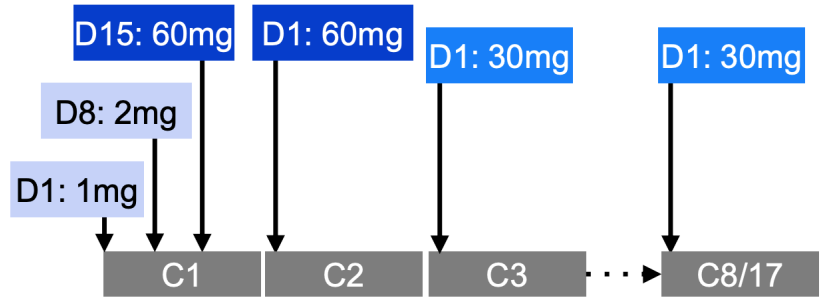
- POD24-negative patients had higher CAR expansion and longer persistence (?due to distance from chemotherapy or underlying disease factors?)
- High baseline CD8+ T cells associated with longer PFS and DOR
- High tumor burden (again) associated with poor PFS

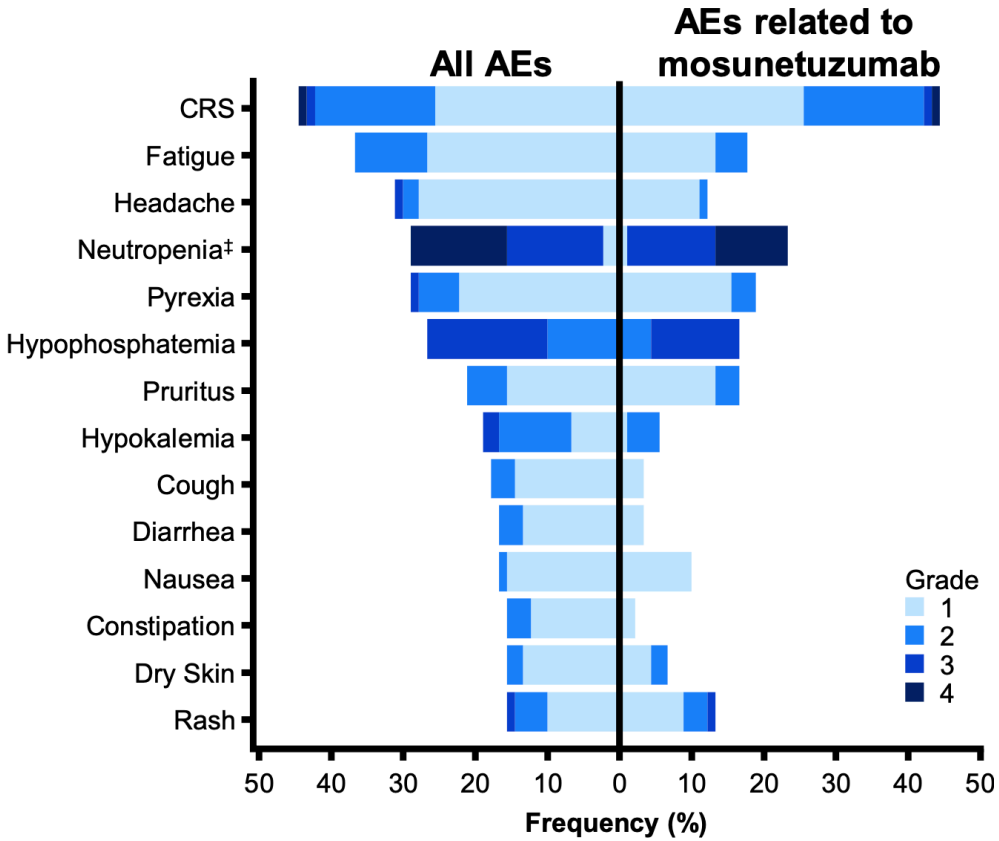
[Stephen Schuster…Martin Dreyling]
Dreyling et al., *Blood* (2024)

3-year follow-up of Mosunetuzumab in r/r FL

i.v. Mosunetuzumab	
Patients	Relapsed/Refractory FL (≥ 2L of prior tx)
Phase	2
Sites	Multinational
Design	Open label, single tx arm
Arms	Mosunetuzumab i.v., up to 17 cycles
Endpoints	CR (1°)
Registration	NCT02500407

Median FU = 37.4 months

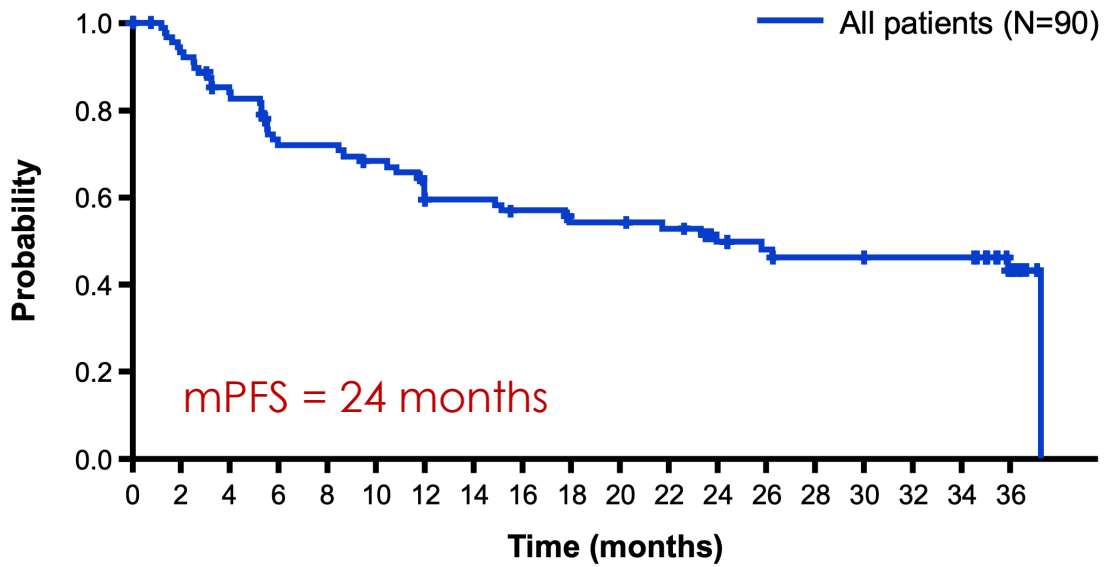




[Stephen Schuster…L. Elizabeth Budde]

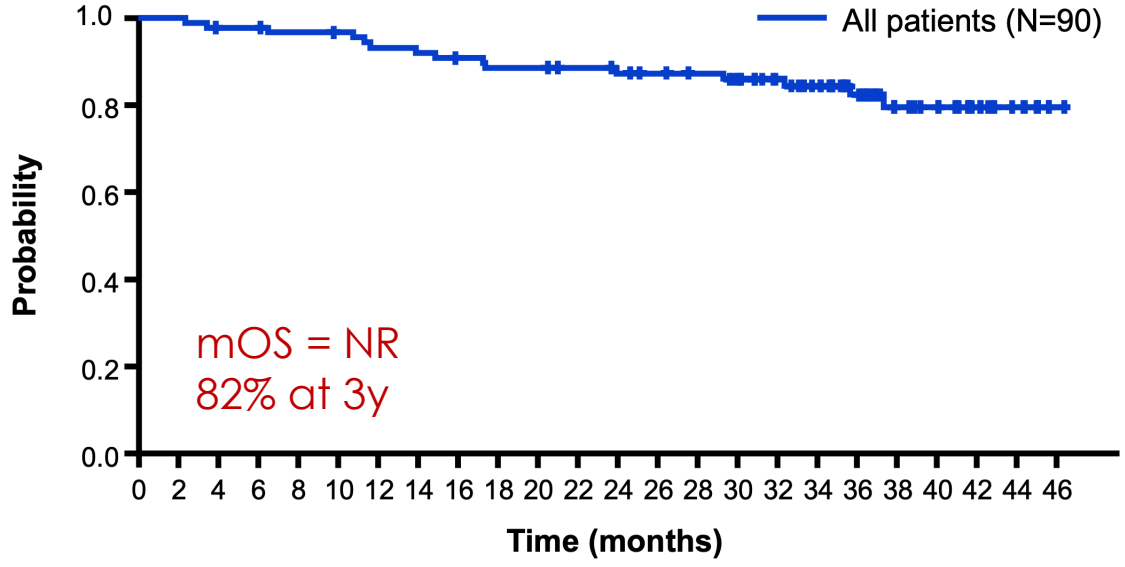
3-year follow-up of Mosunetuzumab in r/r FL

Progress-Free Survival



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

Overall Survival



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

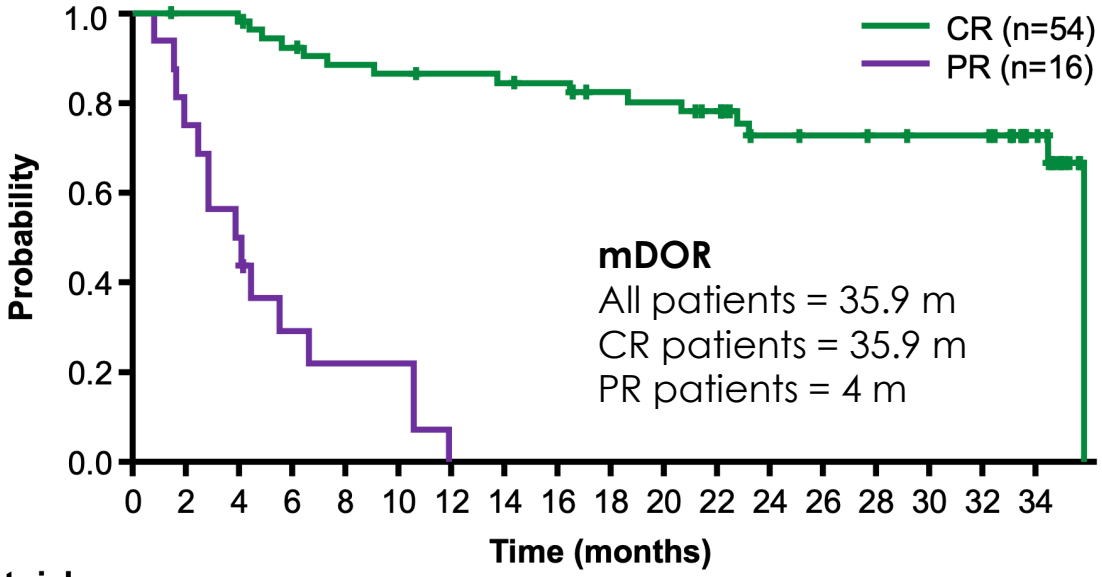
Full Cohort
ORR 80%
CR 60%

→ Retreatment allowed at progression →

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

3-year follow-up of Mosunetuzumab in r/r FL

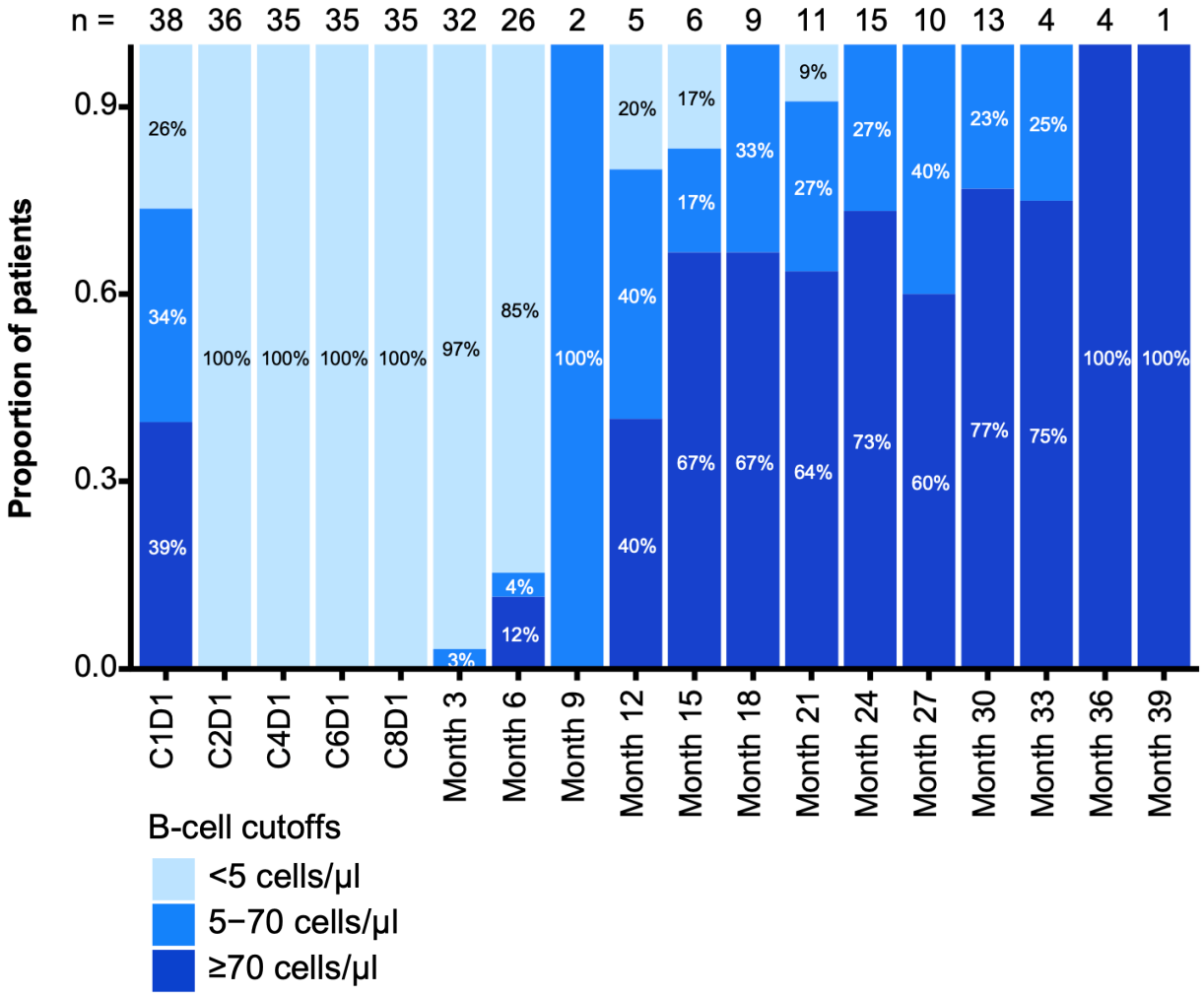
Duration of response



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

B cell recovery



s.c. Mosunetuzumab in 1L FL

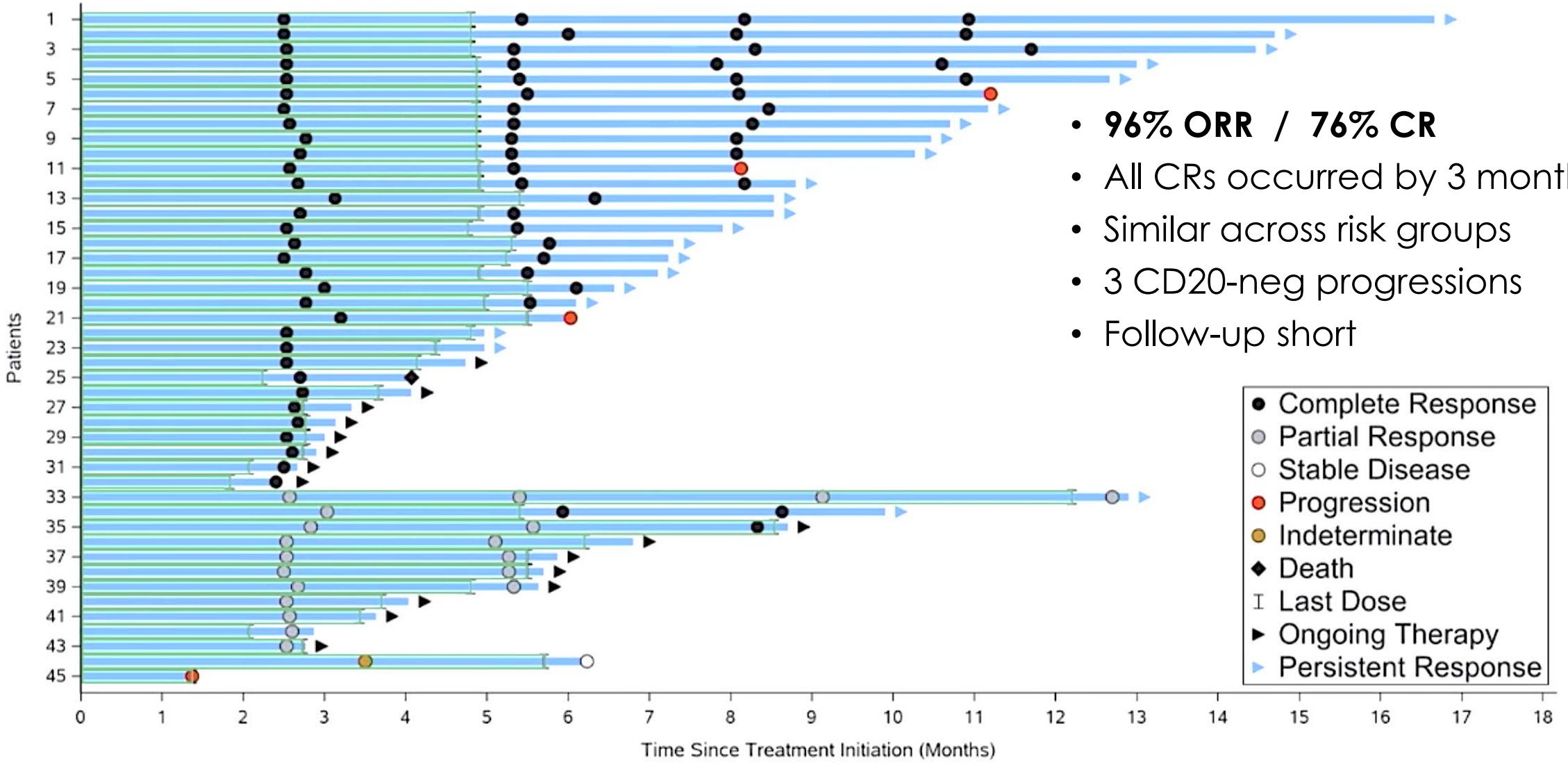
s.c. mosunetuzumab in 1L FL	
Patients	Untreated FL meeting GELF
Phase	2
Sites	NY/NJ
Design	Open label, single tx arm
Arms	Sc Mosunetuzumab 5mg (D1), 45 mg (D8, D15 and D1 of all subsequent cycles)

- 43 patients
  - 40% bulky
  - 39 safety-evaluable
  - 26 efficacy evaluable
- No mandated hospitalization

- Injection site reactions 72% (most G1)
- Grade ≥3 AEs
  - neutropenia 10%
  - infection 5%
- All CRS G1-2; no neurotoxicity
- 2 patients required hospitalization for G2 CRS to receive tocilizumab

[Lorenzo Falchi…Gilles Salles]

s.c. Mosunetuzumab in 1L FL

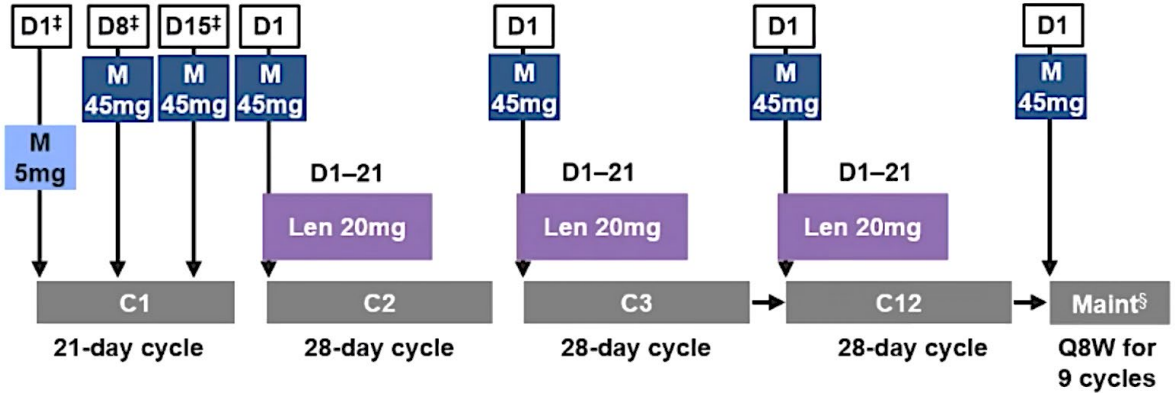


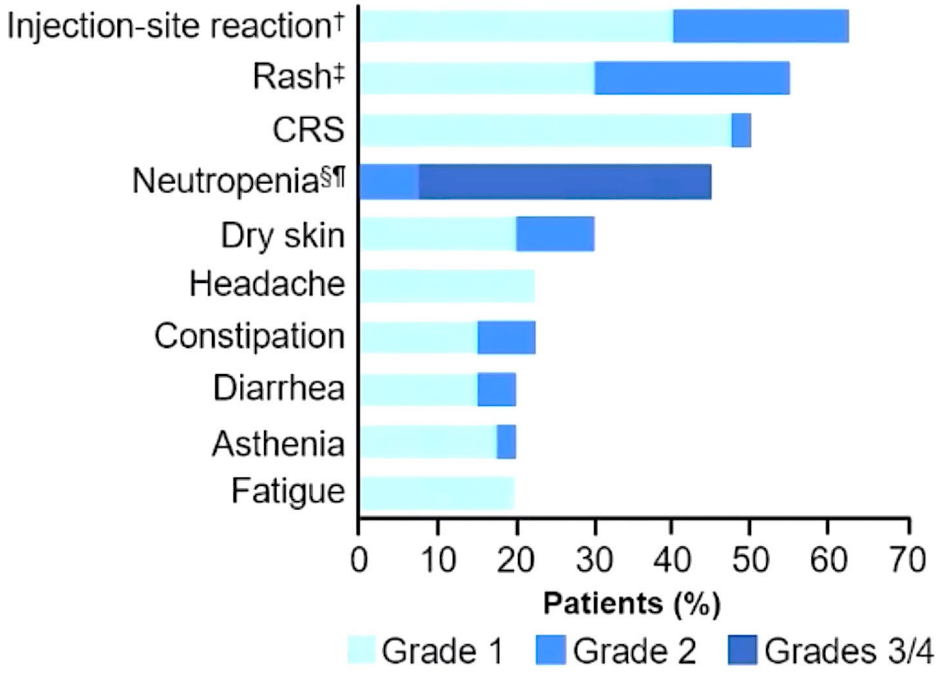
- **96% ORR / 76% CR**
- All CRs occurred by 3 months
- Similar across risk groups
- 3 CD20-neg progressions
- Follow-up short

[Lorenzo Falchi…Gilles Salles]

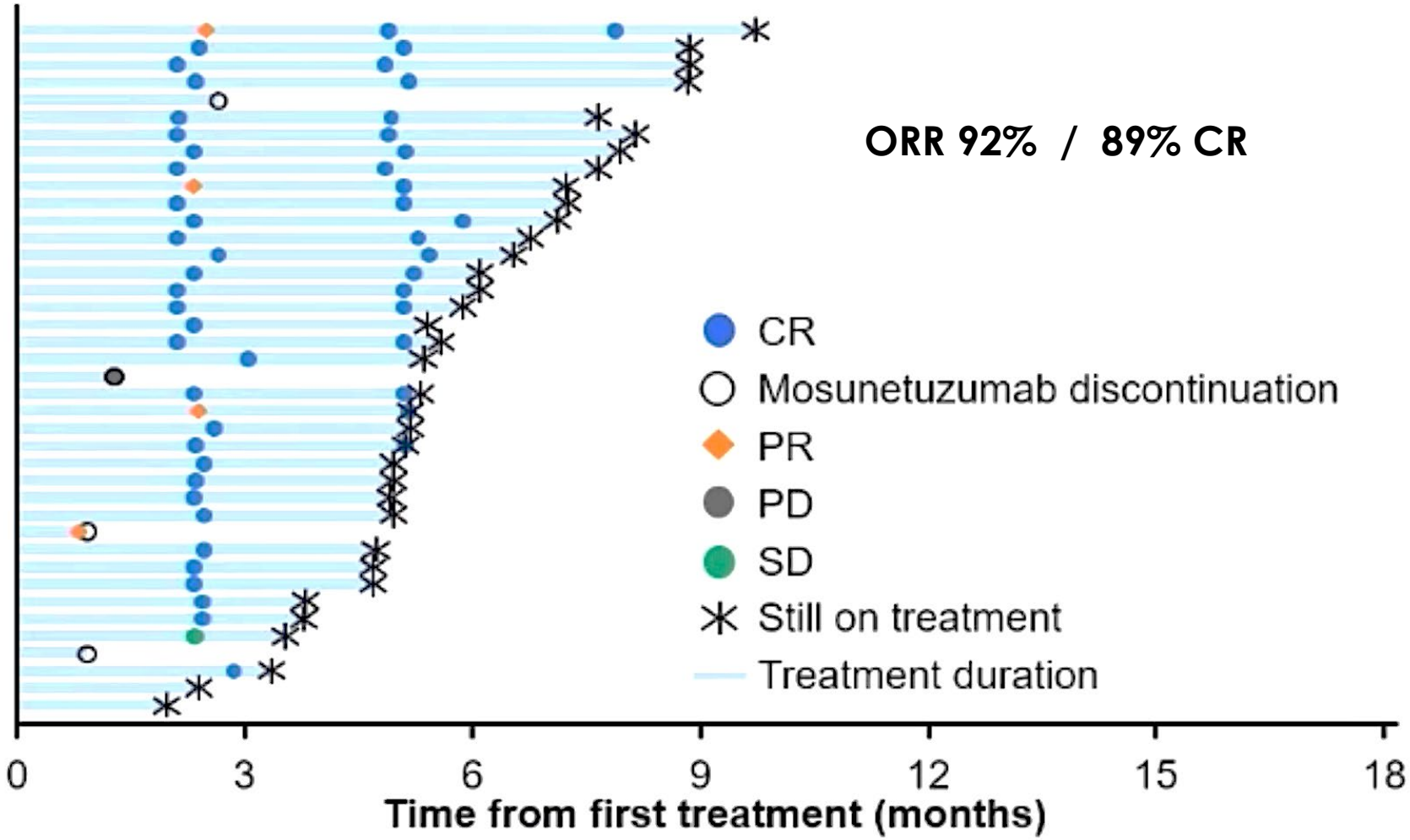
s.c. Mosunetuzumab + lenalidomide in 1L FL

s.c. mosunetuzumab + lenalidomide in 1L FL	
Patients	Untreated FL meeting GELF
Phase	1b/2
Sites	multinational
Design	Open label, single tx arm
Arms	s.c. Mosunetuzumab + p.o. lenalidomide





s.c. Mosunetuzumab + lenalidomide in 1L FL

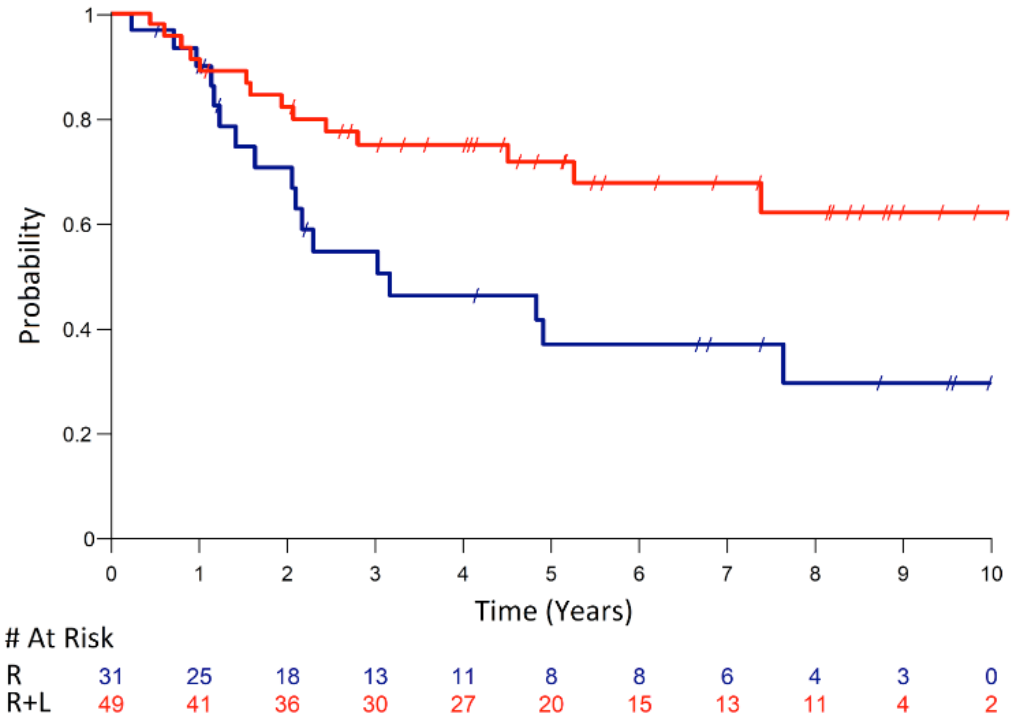


Short R vs R-lenalidomide – long-term follow-up

- 1L FL; 154 patients; randomized study
- Lenalidomide 15mg daily x 6 months

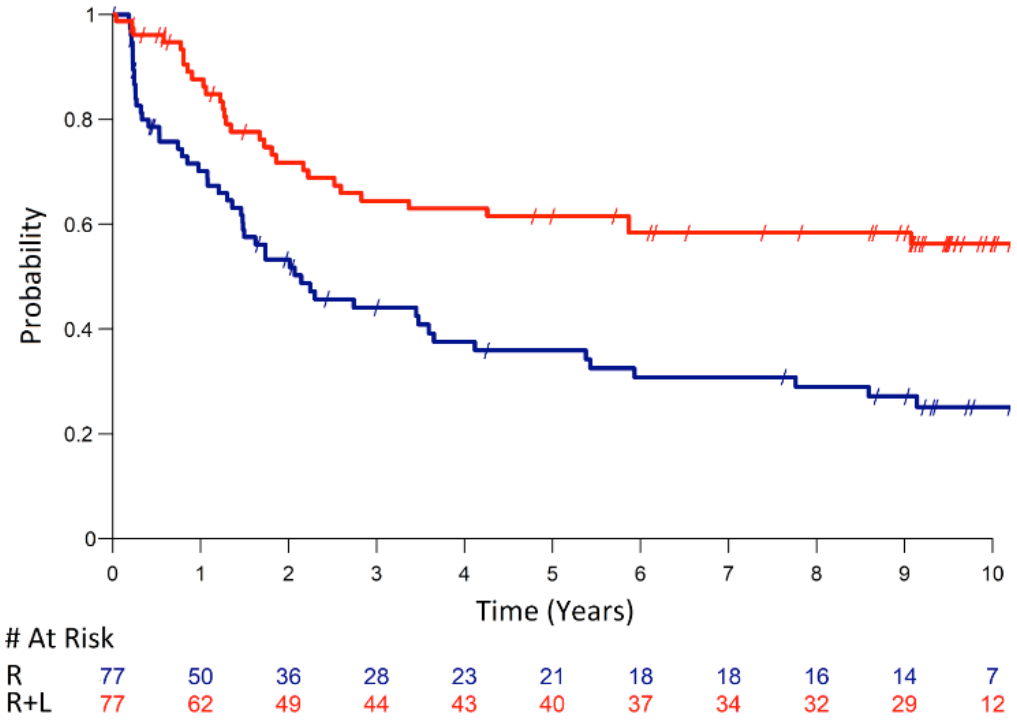
- 10y OS: 77% vs 78%
- mPFS 9.3 vs 2.3y [HR 0.58, p=0.013]

Duration of Complete Response



# At Risk											
R	31	25	18	13	11	8	8	6	4	3	0
R+L	49	41	36	30	27	20	15	13	11	4	2

Time to Next Treatment



# At Risk											
R	77	50	36	28	23	21	18	18	16	14	7
R+L	77	62	49	44	43	40	37	34	32	29	12

Long-Term Results of the SAKK 35/10 Randomized Trial of Rituximab Vs. Rituximab and Lenalidomide in Follicular Lymphoma in Need of First Therapy

[Emanuele Zucca…Eva Kimby]

MANTLE CELL LYMPHOMA

SYMPATICO study – late-breaking abstract

SYMPATICO Study	
Patients	Relapsed/Refractory MCL (≥ 1L of prior tx)
Phase	3
Sites	Multinational
Design	Randomized [1:1], double-blind, placebo-controlled
Arms	Ibrutinib + Venetoclax vs Ibrutinib + Placebo
Registration	NCT03112174

Ibrutinib = 560mg
Venetoclax = target dose 400mg

Treatment duration: 2 years, then ibrutinib alone

Stratification: ECOG PS, tx lines, TLS risk, CrCl

Endpoints: PFS (1°), CR, TTNT, OS, ORR

Prior data:
- Tam, NEJM 2018
- Wang J Hem Onc 2021
→ Promising initial signal

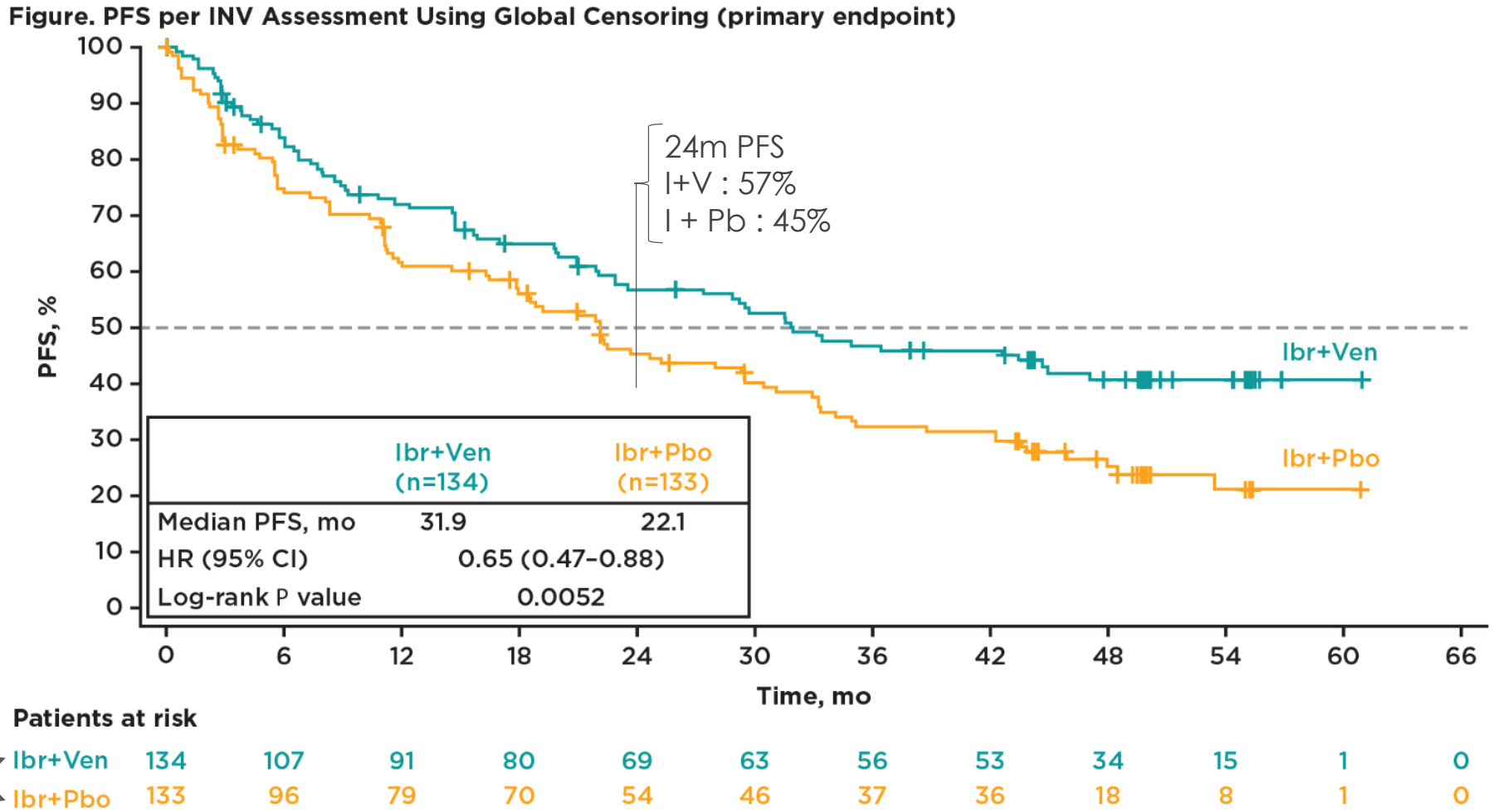
[Michael Wang…Constantine Tam]

SYMPATICO study – late-breaking abstract

Adverse Events, Grade ≥3	I + V	I + placebo
Any Grade ≥3	84%	76%
Neutropenia	31%	11
Pneumonia	13%	11%
Thrombocytopenia	13%	8%
Anemia	10%	3%
Diarrhea	8%	2%
Leukopenia	7%	0%
Atrial fibrillation	5%	5%
COVID-19	5%	1%
Hypertension	4%	9%

[Michael Wang…Constantine Tam]

SYMPATICO study – late-breaking abstract



267 patients

96% with PS 0-1
38% vs 31% high risk MIPI
30% vs 28% TP53 mutated

[Michael Wang…Constantine Tam]

SYMPATICO study – late-breaking abstract

	Ibr+Ven (n=134)	Ibr+Pbo (n=133)	HR (or rate ratio) (95% CI)[a]	*P* value[b]
Median PFS by INV, mo				
Global censoring[c]	31.9	22.1	0.65 (0.47–0.88)	0.0052
US FDA censoring[d]	42.6	22.1	0.60 (0.44–0.83)	0.0021
Median PFS by IRC, mo				
Global censoring[c]	31.8	20.9	0.67 (0.49–0.91)	0.0108
US FDA censoring[d]	43.5	22.1	0.63 (0.45–0.87)	0.0057
Median TTNT, mo	NR	35.4	0.60 (0.40–0.89)	0.0096
ORR, %	82	74	1.10 (0.97–1.25)	0.1279
CR rate, %	54	32	1.66 (1.24–2.22)	0.0004
Median duration of response, mo	42.1	27.6		
Median duration of CR, mo	NR	40.8		
Median OS, mo (interim analysis)	44.9	38.6	0.85 (0.62–1.19)	0.3465

Data from ~76% of full cohort

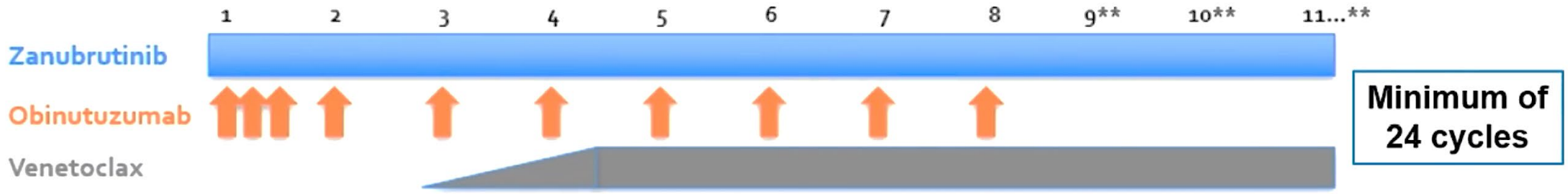
Summary

- Significant AEs in both arms (driven by ibrutinib treatment)
- Adding venetoclax to ibrutinib improves PFS in r/r MCL
- Combination generates deeper responses that are longer lasting
- As expected, TP53-mutated cases benefit similarly
- OS data not mature

- Question of I+V versus I→V remains, but prior data suggests I→V not very beneficial
- Unclear if venetoclax addition beneficial if using acalabrutinib or zanubrutinib

[Michael Wang…Constantine Tam]

BOVen Study in 1L TP53-mutated MCL



Dosing:

Zanubrutinib 160 mg oral twice daily

Obinutuzumab 1000 mg IVPB
Cycle 1: day 1, 8, 15
Cycle 2-8: day 1

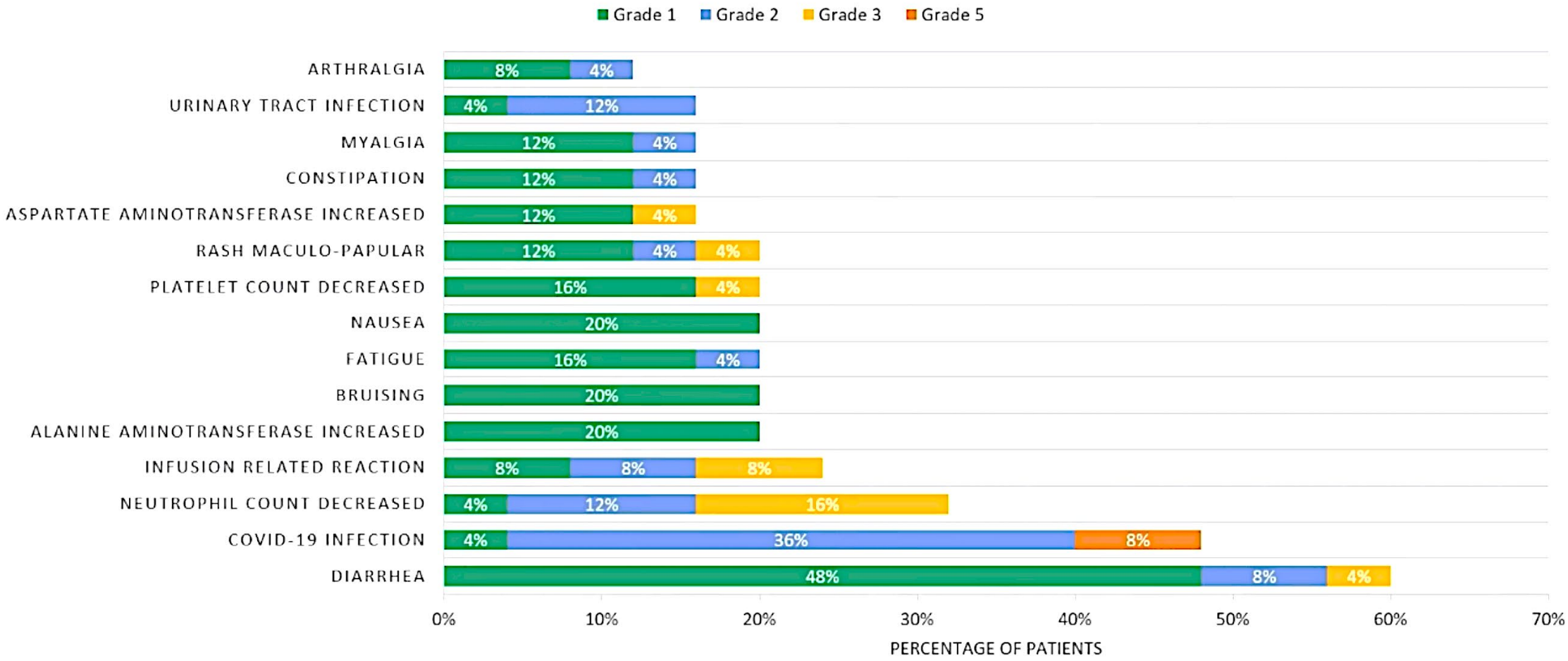
Venetoclax 400mg oral daily
5-week ramp-up: 1 week each of 20mg; 50mg; 100mg; 200mg; 400 mg oral daily

After 24 cycles, MRD-driven approach to limit treatment duration in selected patients:

CR and uMRD	→	Stop treatment
<CR and/or dMRD	→	Continue ZANU and VEN

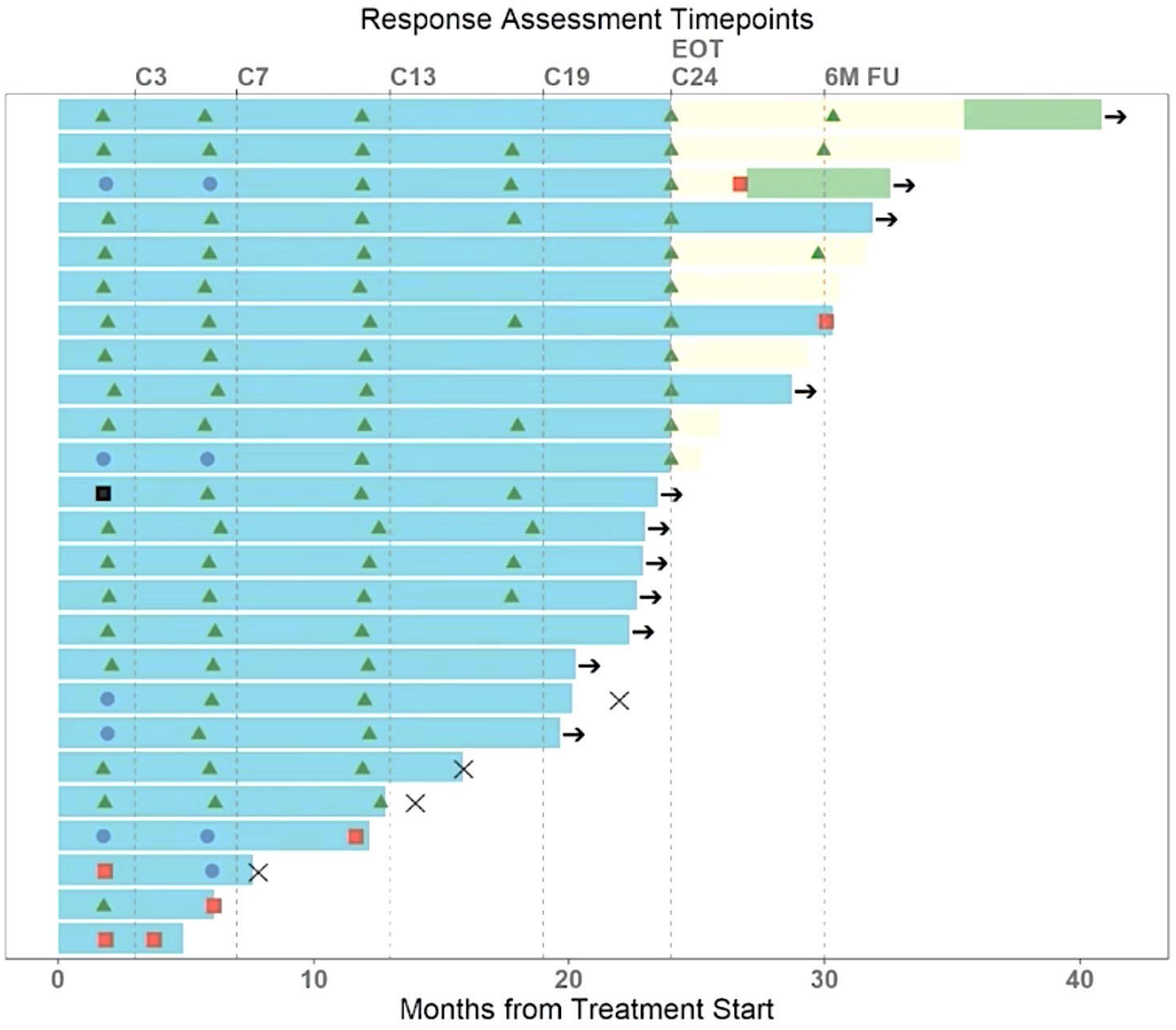
[Anita Kumar…Andrew Zelenetz]

BOVen Study in 1L TP53-mutated MCL



[Anita Kumar…Andrew Zelenetz]

BOVen Study in 1L TP53-mutated MCL



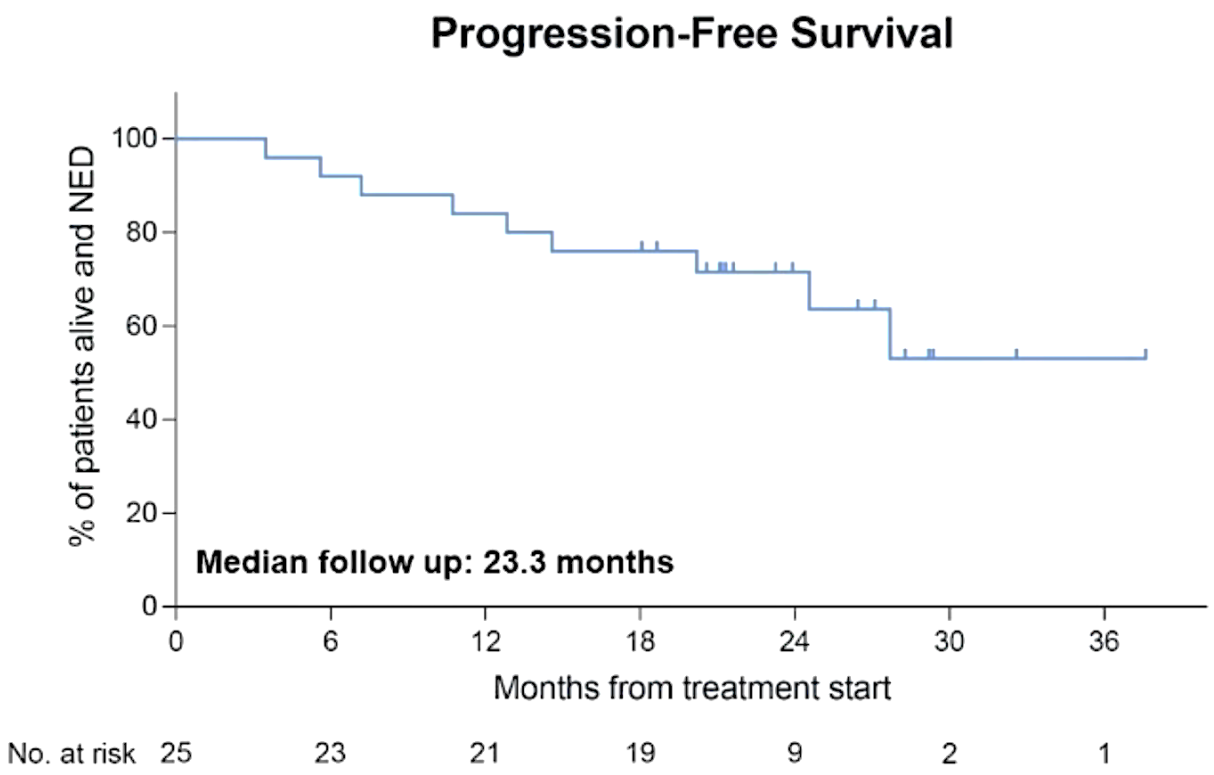
- **96% ORR / 88% CR**
- mFU = 23.3 m
- 4 deaths (of 25) – all in response
  - 2 COVID
  - 1 Pneumonia
  - 1 unknown

High rate of uMRD by C13

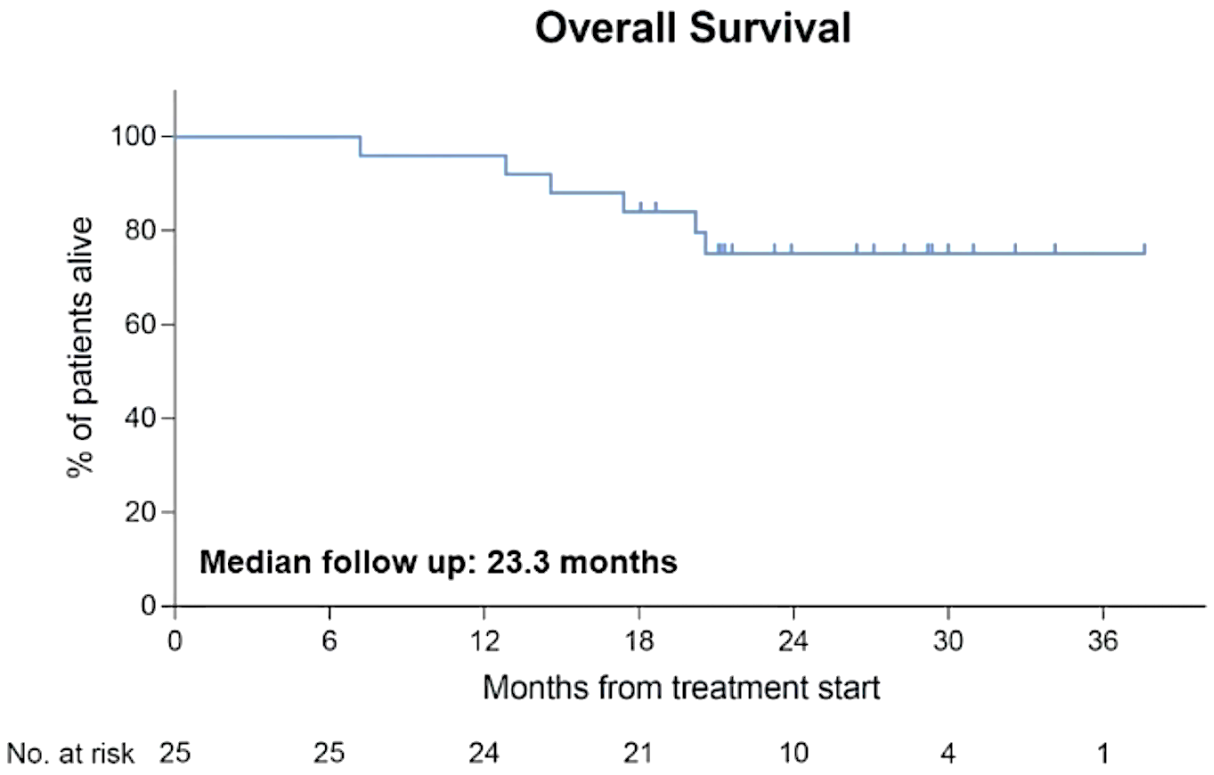
	Baseline	Cycle 3	Cycle 13	EOT / Cycle 24
uMRD in PB (10^{-6})	0 % (0/24)	32% (7/22)	95% (18/19)	60% (6/10)

[Anita Kumar…Andrew Zelenetz]

BOVen Study in 1L TP53-mutated MCL



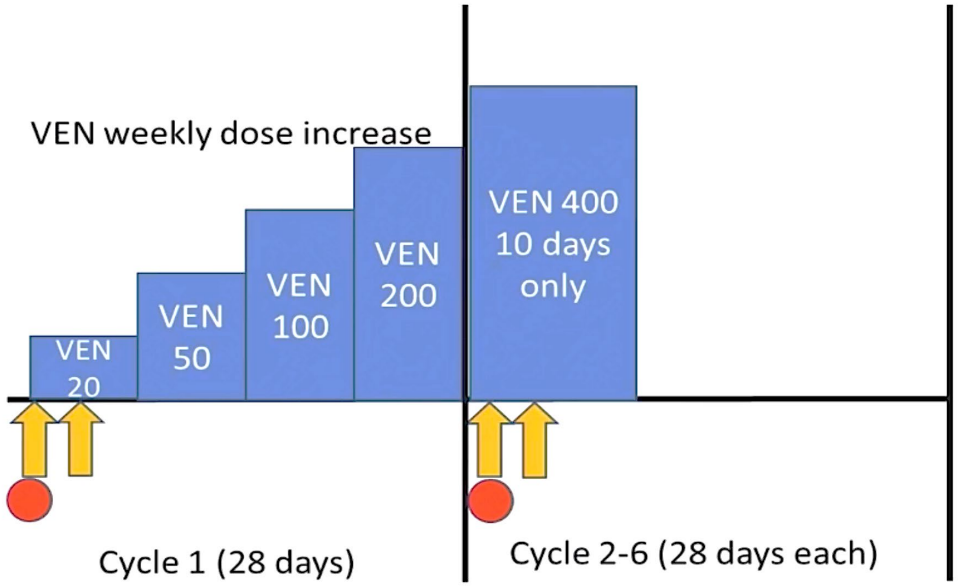
2-year PFS: 72% [95% CI: 56, 92]
Median PFS: not reached



2-year OS: 75% [95% CI: 58, 93]
Median OS: not reached

[Anita Kumar…Andrew Zelenetz]

RB + venetoclax induction for elderly MCL



→ 61% received maintenance rituximab (was at investigator discretion)

→8 deaths – 4 due to COVID-19; all 4 were in remission at the time of death

N=33: All treated patients		
Event	**All Grades**	**Grade ≥ 3**
GI events		
Nausea	19	1
Diarrhea	11	0
Constipation	6	0
Decreased Appetite	4	0
Infectious Toxicity		
COVID Pneumonia	4	3
Other events		
Fatigue	17	1
Infusion Reaction	8	0
Blood Creatinine Decreased	5	0
Headache	4	0

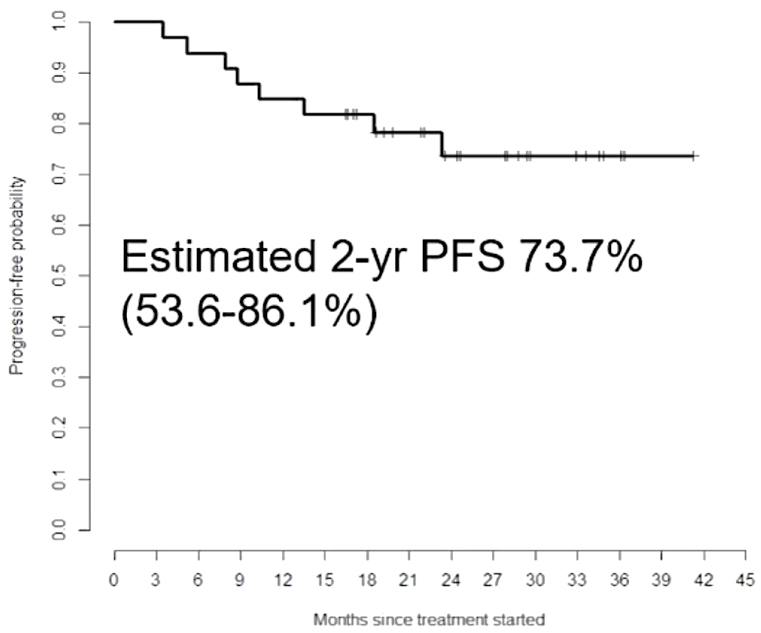
N=33: All treated patients		
Event	**All Grades**	**Grade ≥ 3**
Neutropenia	10	8
Thrombocytopenia	9	5
Anemia	8	2
Lymphopenia	9	9
Leukopenia	7	4
	Grade 3-5	**Grade 5**
Overall Heme TRAE Gr ≥ 3	28	0
Overall non-Heme TRAE Gr ≥ 3	15	2

[Craig Portell…Brad Kahl]

RB + venetoclax induction for elderly MCL

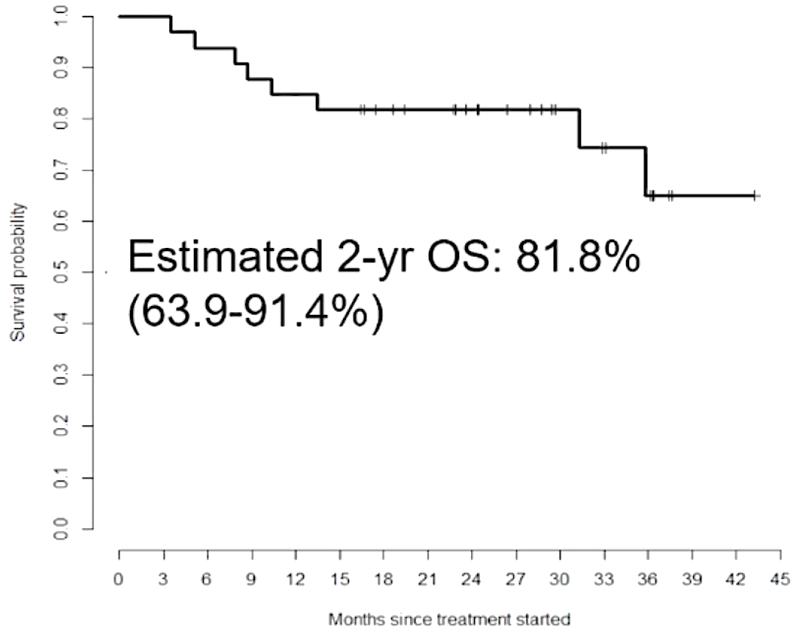
End of Induction Response*		
Overall Response	97%	32/33
PET and BM confirmed CR EOT*	85%	28/33
MRD by NGS at EOT	Under analysis	
*Met primary endpoint (≥ 23 with CR)		

Progression-Free Survival



Estimated 2-yr PFS 73.7%
(53.6-86.1%)

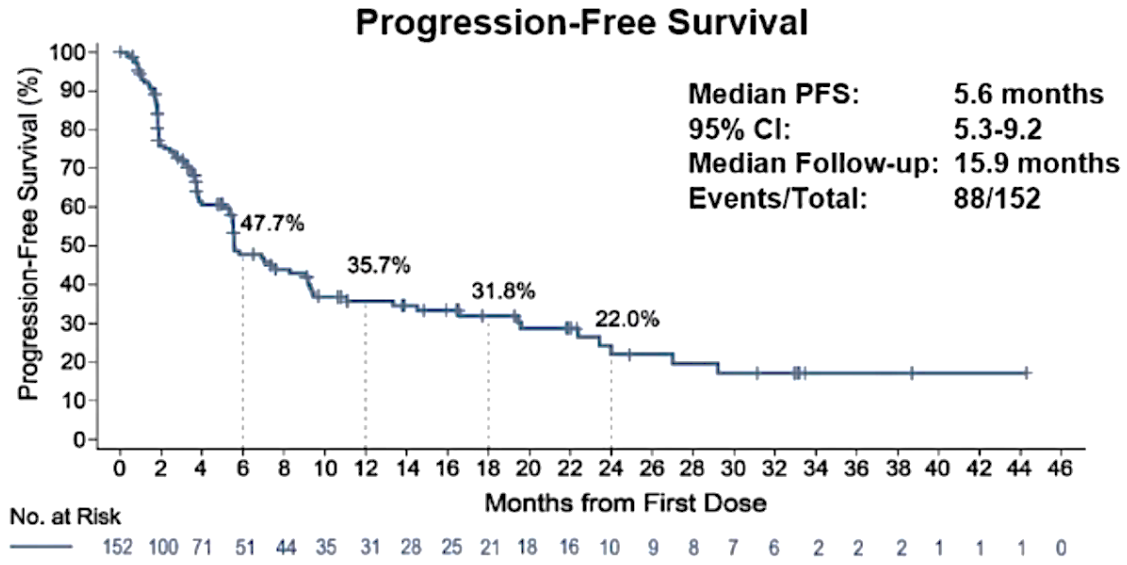
Overall Survival

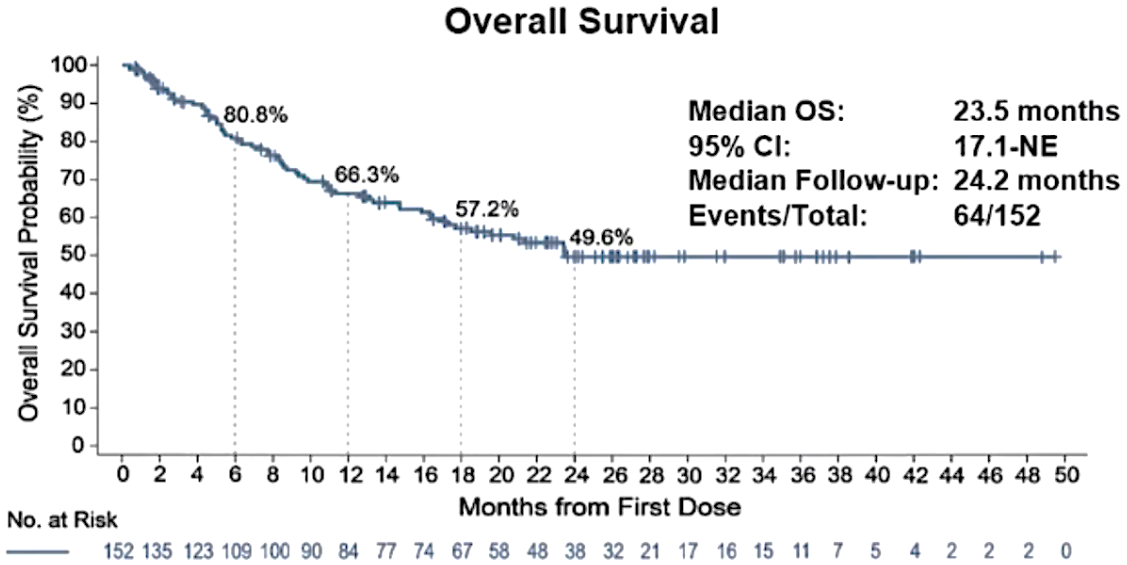


Estimated 2-yr OS: 81.8%
(63.9-91.4%)

* Median (Q1, Q3) follow up of 28.7 (22.8, 36.1)

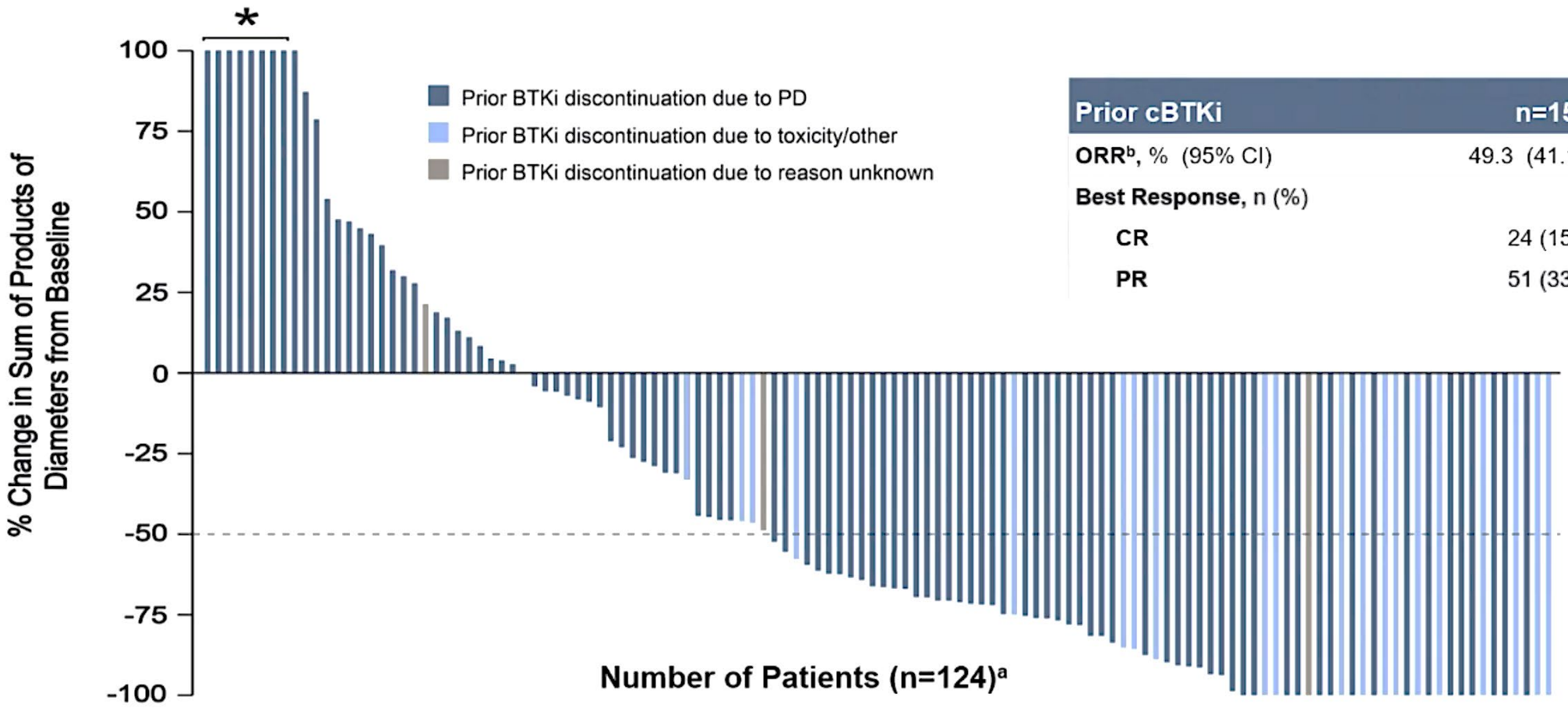
Pirtobrutinib in rr MCL





- 166 patients
  - 91.6% had prior BTKi
    - 84% had progressed on prior BTKi
  - 9% prior CAR-T
  - 22% prior transplant

Pirtobrutinib in rr MCL



Prior cBTKi	n=152
ORR[b], % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)

Median Time to First Response was 1.8 months (range: 0.8-13.8)

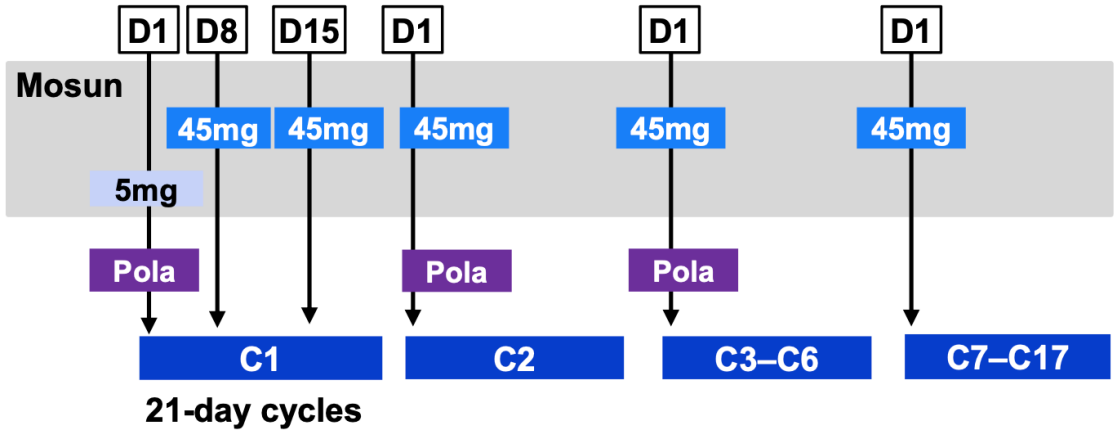
Clinical Research Frontiers

- Allogeneic CAR-T cells
- CAR-NK
  - AFM13 + CAR-NK for refractory CD30+ lymphomas
- Degraders: BTK, EZH2, STAT3
- MRD, ctDNA for disease monitoring during treatment

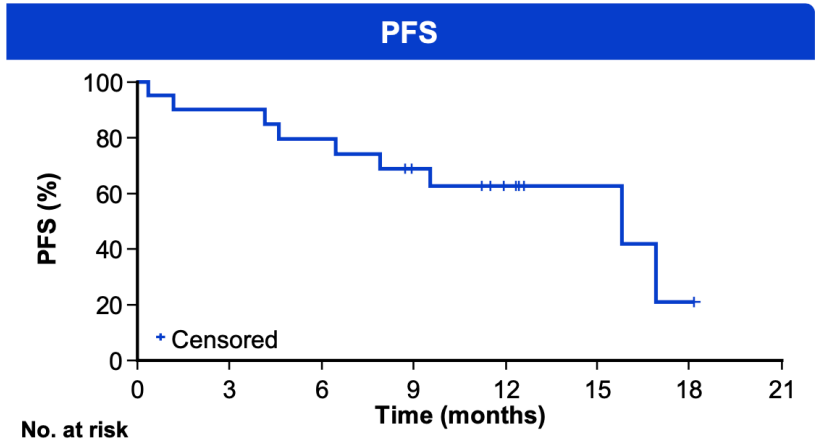
THANK YOU!

EXTRA SLIDES

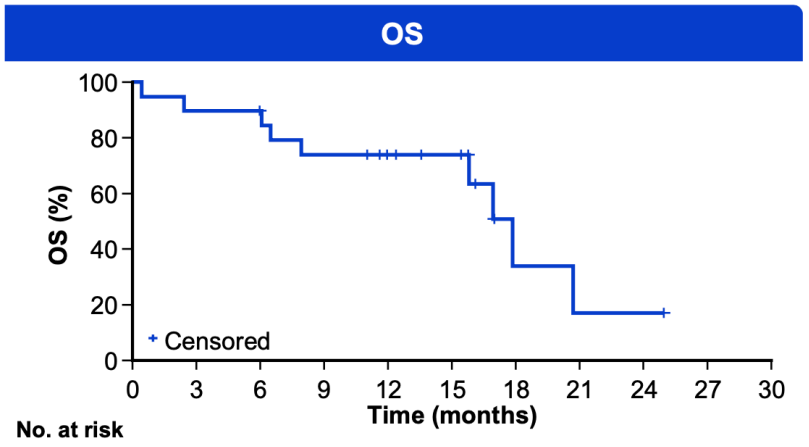
Mosunetuzumab + Polatuzumab-vedotin in MCL



ORR 75% / CR 70%



	N=20
Median PFS, months (95% CI)	15.8 (8.0–NE)
9-month event-free rate, % (95% CI)	68.8% (48.1–89.6)



	N=20
Median OS, months (95% CI)	17.9 (15.8–20.7)
9-month event-free rate, % (95% CI)	74.1% (54.5–93.7)

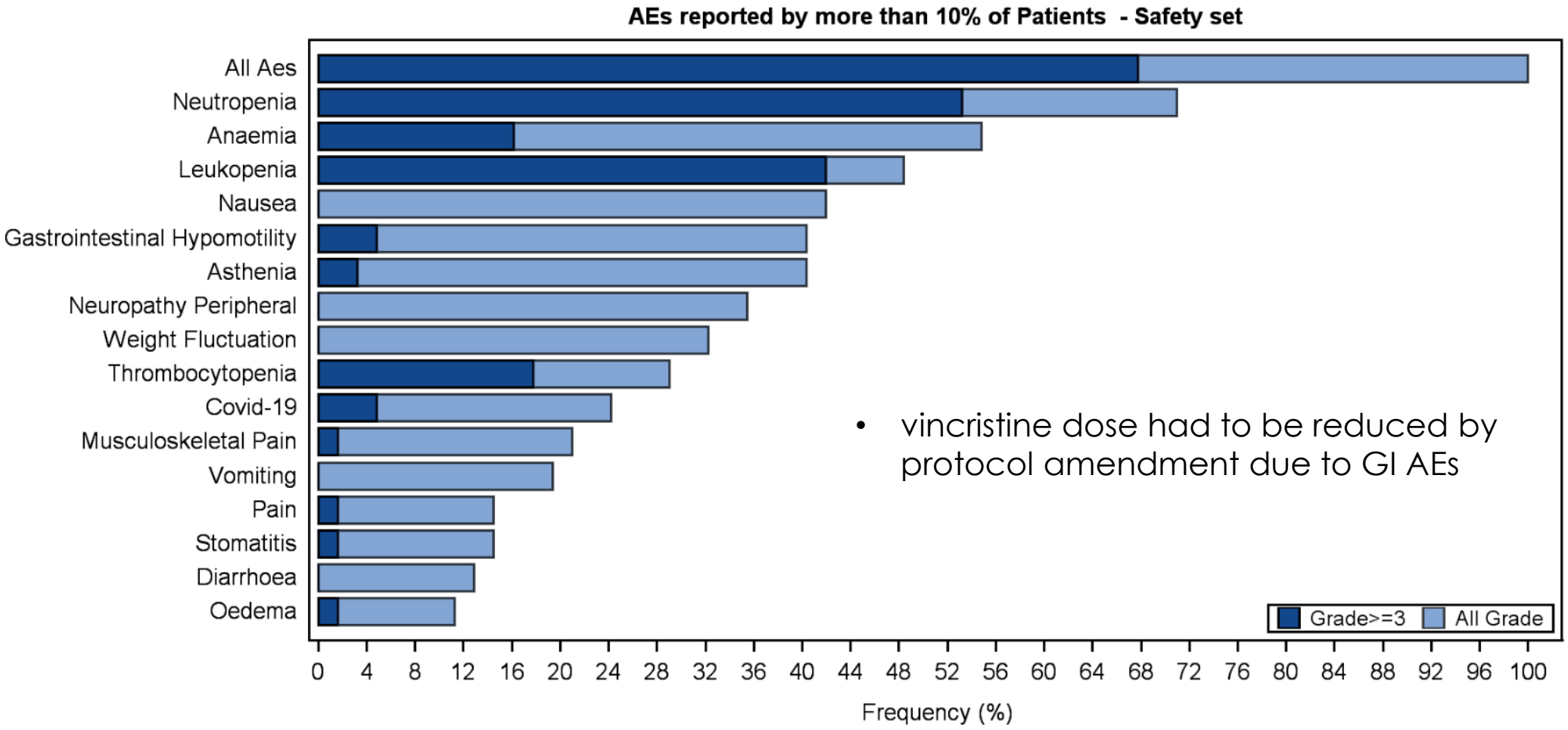
Epi-RCHOP in 1L high-risk FL

	Epi-RCHOP
Patients	Untreated FL with FLIPI 3-5 and meeting GELF criteria
Phase	2
Sites	France, Belgium (LYSA study)
Design	Open label, single tx arm; multiple cohorts
Arms	Tazemetostat 800mg BID + RCHOP x 6 → R + Taz x 2 → **EOI** → R + Taz x 6m → R x 18m
Endpoints	PET-CR (1°)

- Fixed duration tazemetostat (~12 mo)
- Study required BM Bx and reverted CRs to PRs when not done
- 62 patients
  - 17% EHZ2 mutated

[Loic Ysebaert…Franck Morschhauser]

Epi-RCHOP in 1L high-risk FL



- vincristine dose had to be reduced by protocol amendment due to GI AEs

[Loic Ysebaert…Franck Morschhauser]

Epi-RCHOP in 1L high-risk FL

- At end of induction
  - 79% CMR, 16% PMR = **95% ORR by PET**
  - Since BM Bx not done in 16 CMR patients, per protocol: 53% CR, 42% PR = **85% ORR**
  - In EZH2 mutated: **CMR 89%** (vs 46% in WT)

- mFU = 19 months
- 18-month PFS = 89.3%
- 18-month OS = 98.3%

- → Not clearly different from RCHOP in 1L FL
- RCHOP not used frequently in 1L FL at many centers, even in 'high risk' → relevance?

[Loic Ysebaert…Franck Morschhauser]