THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

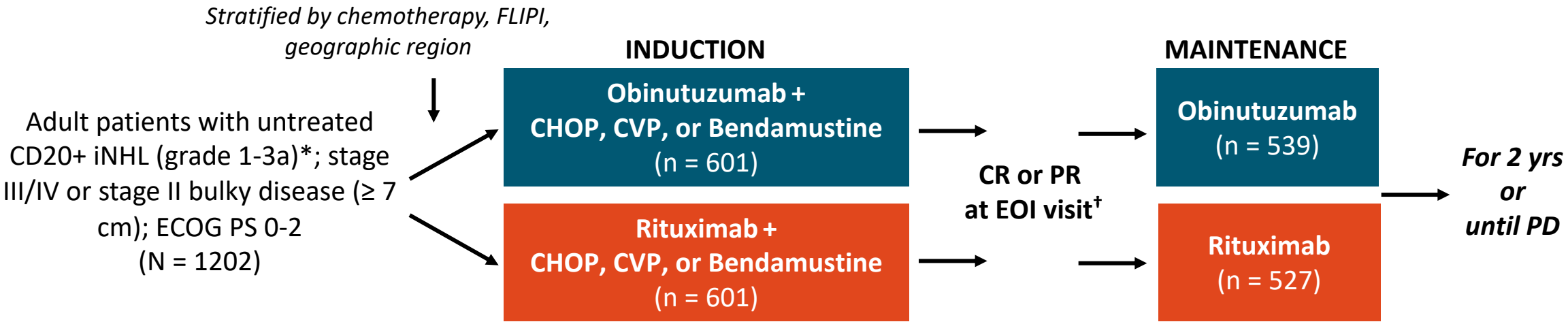
Making Cancer History®

Module 2: Follicular Lymphoma

Loretta J. Nastoupil, MD
UT MD Anderson Cancer Center
lnastoupil@mdanderson.org

GALLIUM: Frontline Obinutuzumab-Based vs Rituximab-Based Chemoimmunotherapy

- International randomized, open-label phase III study
  - Obinutuzumab was designed to achieve enhanced therapeutic activity compared with rituximab

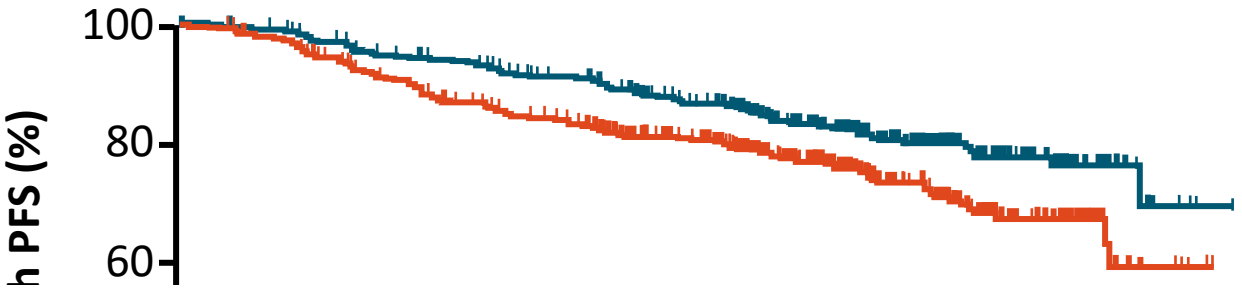


*All data presented for patients with FL, although study also enrolled patients with MZL (randomized separately).
†Patients with SD at EOI followed up to 2 yrs for PD.

- Primary endpoint: PFS by investigator in patients with FL
- Secondary endpoints: PFS by IRC, OS, DFS, DoR, TTNT, CR/ORR at EOI (± FDG-PET), safety

Marcus et al. *N Engl J Med*. 2017;377:1331.

GALLIUM: Investigator-Assessed PFS



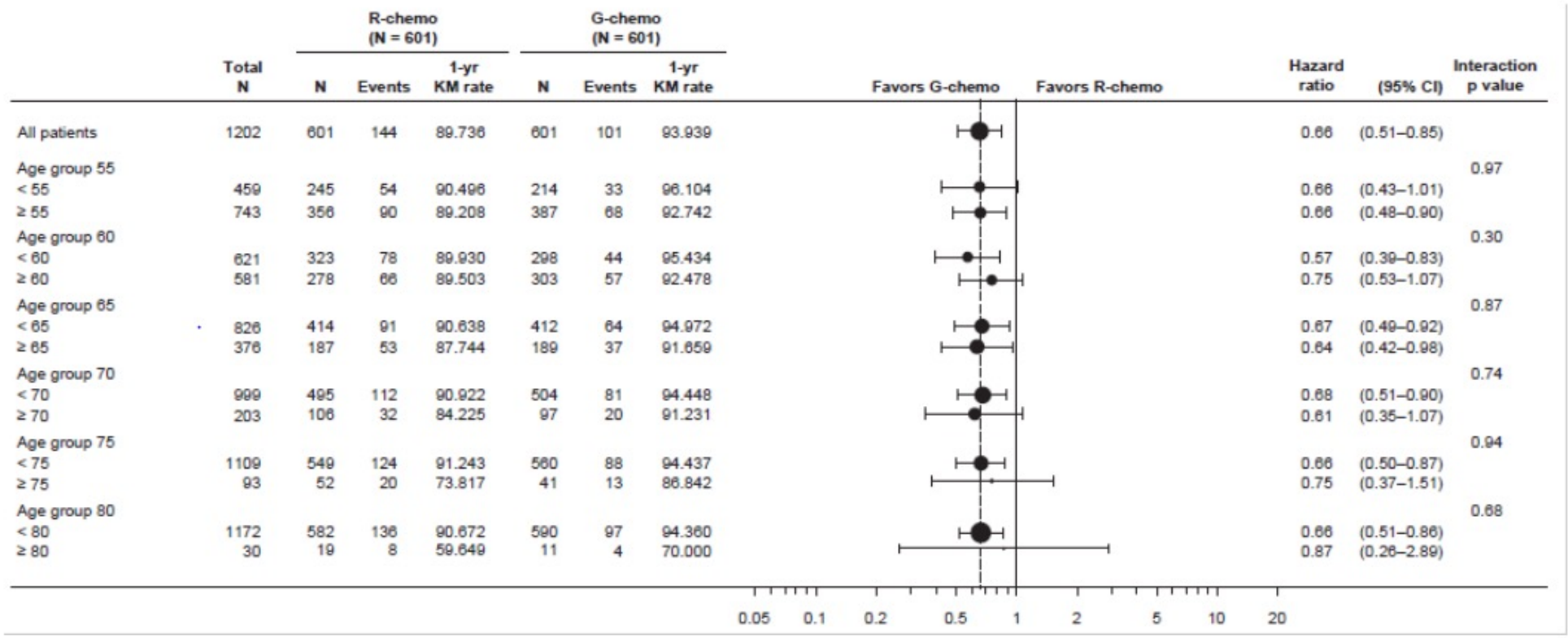
	Obinutuzumab + CT	Rituximab + CT
Patients, n	601	601
		24.0
		73.3 (68.8-77.2)

Patients at
Obinutuzu
Rituximab

- N
  G

: 0-54.5)

5;



Marcus et al. *N Engl J Med*. 2017;377:1331.

GALLIUM: Adverse Events

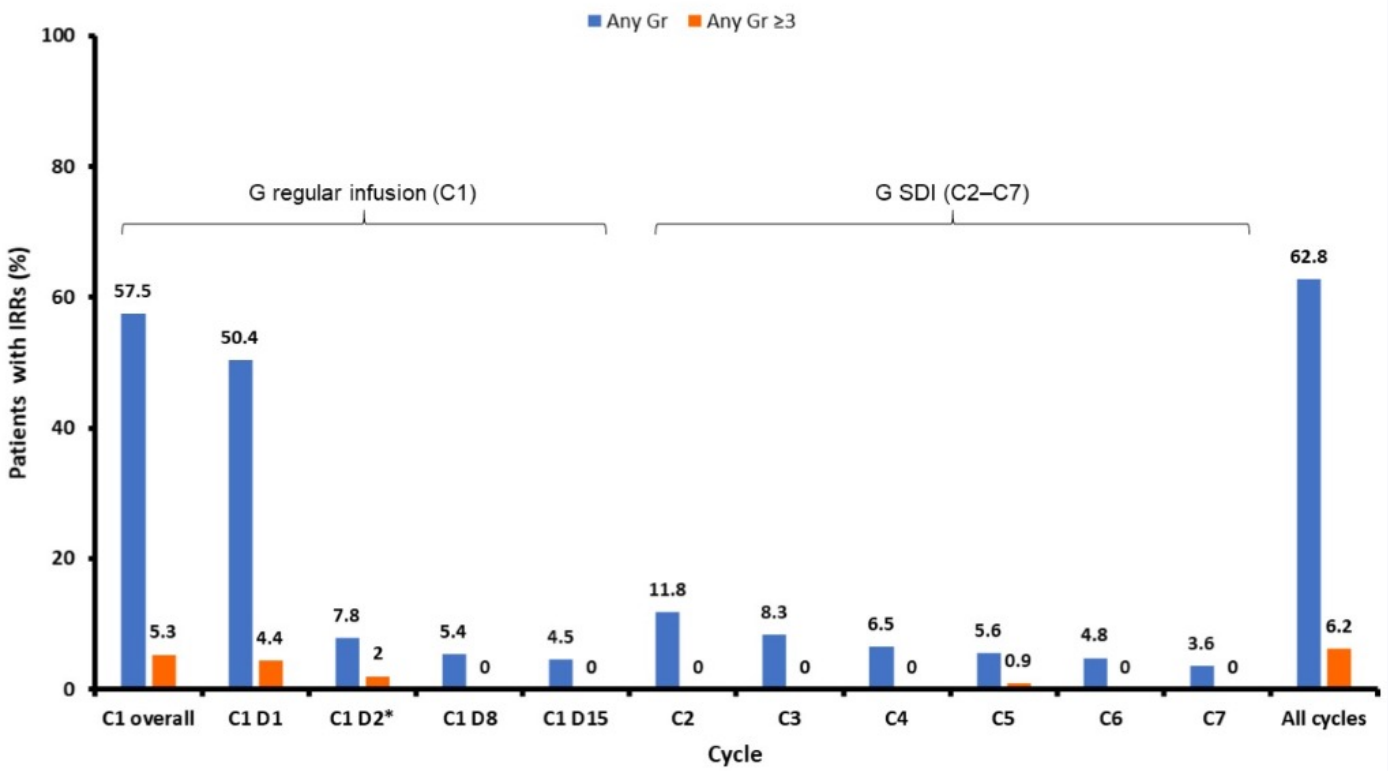
AE, %	All AEs		Grade 3-5 AEs		Serious AEs	
	Obinutuzumab (n = 595)	Rituximab (n = 597)	Obinutuzumab (n = 595)	Rituximab (n = 597)	Obinutuzumab (n = 595)	Rituximab (n = 597)
Infection	77.3	70.0	20.0	15.6	18.2	14.4
Neutropenia	50.6	45.1	45.9	39.5	8.4	7.4
Infusion related	68.2	58.5	12.4	6.7	5.5	2.3
▪ Antibody related	59.3	48.9	10.6	5.0	4.7	2.0
Tumor lysis syndrome	1.0	0.5	1.0	0.5	0.5	0.2
Cardiac event	13.1	9.7	3.7	2.8	4.4	2.0
Thrombocytopenia	11.4	7.5	6.1	2.7	0.7	0.2
Second neoplasm	7.2	5.0	4.7	2.7	5.2	2.8
▪ Nonmelanoma skin cancer	3.0	2.3	1.2	0.5	1.5	0.5
▪ Hematologic event	1.0	0	1.0	0	1.0	0
▪ Other	3.7	3.0	2.9	2.5	3.0	2.7
Myelodysplastic syndrome	0.3	0	0.3	0	0.3	0
GI perforation	0.7	0.5	0.5	0	0.5	0
Hemorrhagic event	9.6	10.4	0.8	1.2	1.0	0.8

Marcus. NEJM. 2017;377:1331.

Anti-CD20 antibodies were given as part of chemoimmunotherapy regimen.

Phase IV GAZELLE — Obinutuzumab short duration infusion in previously untreated advanced FL

Patients (%) with IRRs by Cycle and Grade



*time point applicable only to pts treated with bendamustine.

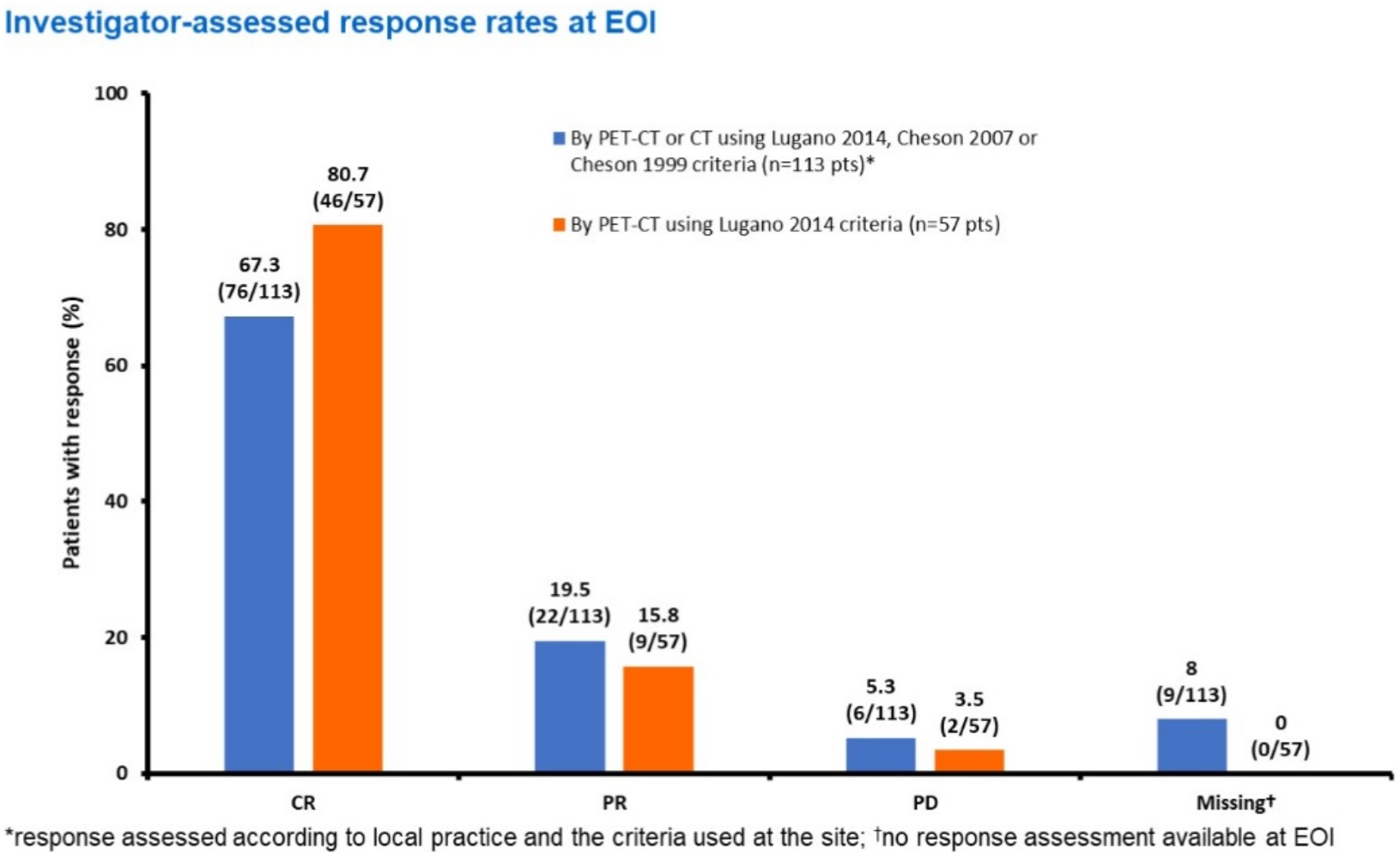
Safety summary during induction

N (%) unless indicated	Induction phase (N=113)
Any AE*	112 (99.1)
Neutropenia	69 (61.1)
IRR	69 (61.1)
Nausea	47 (41.6)
Constipation	40 (35.4)
Lymphopenia	22 (19.5)
Thrombocytopenia	21 (18.6)
Anemia	20 (17.7)
Leukopenia	20 (17.7)
Insomnia	19 (16.8)
Headache	19 (16.8)
Peripheral neuropathy	18 (15.9)
Fatigue	17 (15.0)
Any Gr 3–5 AE†	78 (69.0)
Neutropenia	56 (49.6)
Leukopenia	13 (11.5)
Lymphopenia	12 (10.6)
Thrombocytopenia	8 (7.1)
IRR	7 (6.2)
Febrile neutropenia	6 (5.3)
Any SAE	21 (18.6)
Any AE leading to treatment discontinuation	6 (5.3)

*listed preferred terms are those with ≥15% incidence during induction; †listed preferred terms are those with ≥5% incidence during induction

Canales et. al, ASCO 2021, Abstract 7545

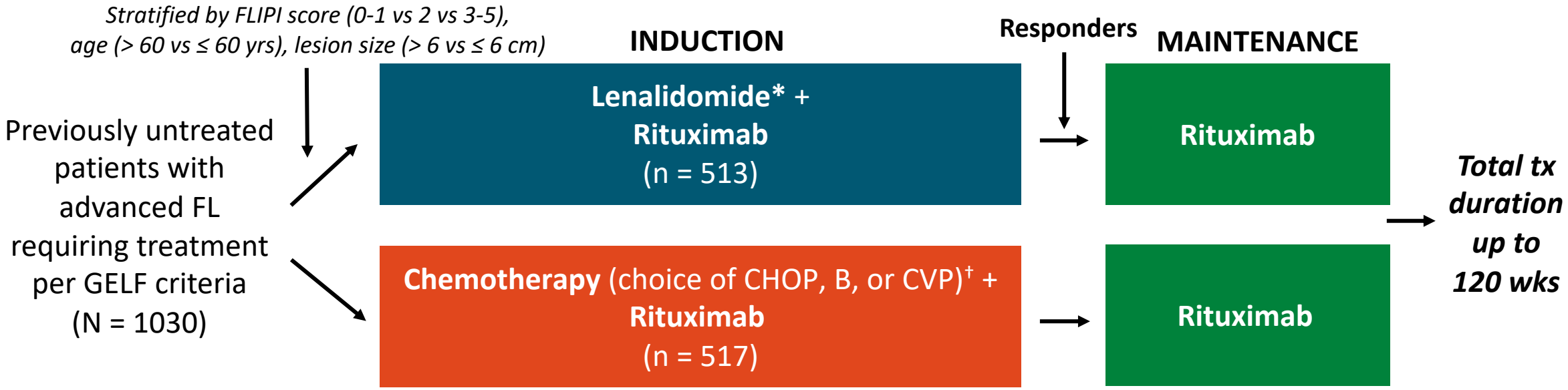
GAZELLE — Response rates at end of induction (EOI)



Canales et. al, ASCO 2021, Abstract 7545

RELEVANCE: Study Design

- International, open-label, randomized phase III study
  - Lenalidomide: immunomodulatory agent with MoA complementary to rituximab

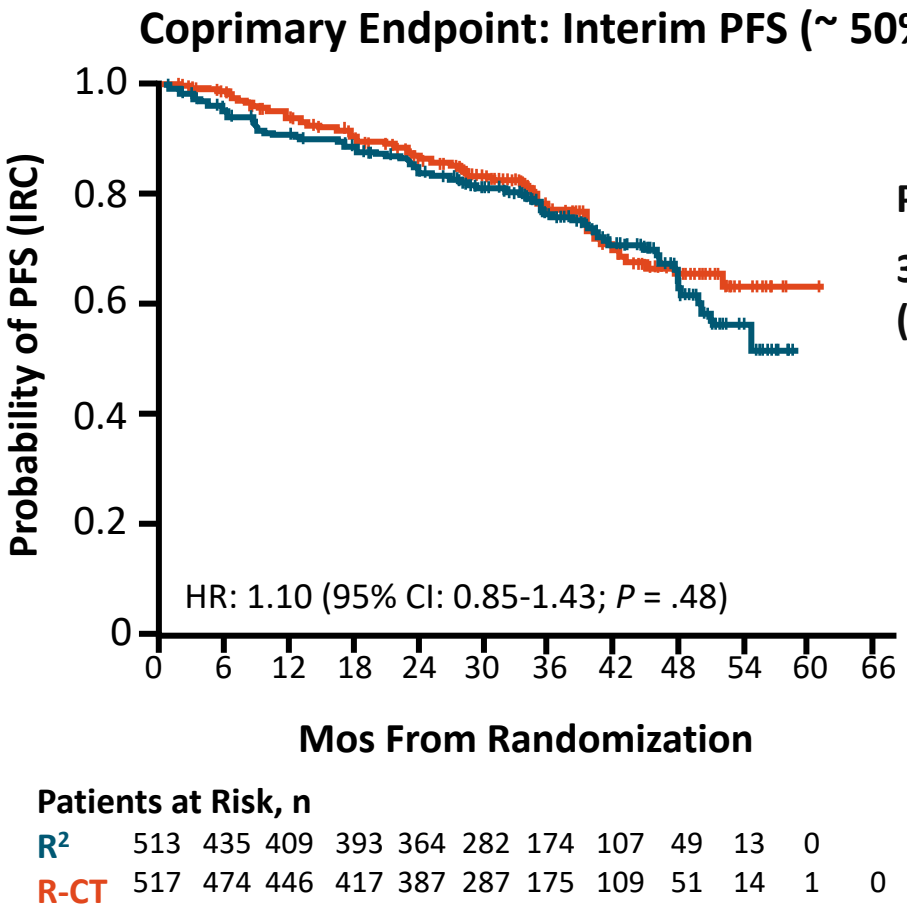


*20 mg PO QD on Days 2-22, 28-day cycles (18 cycles); dose reduced to 10 mg QD in patients who achieved CR/CRu at cycle 6, 9, or 12.

- Co-primary endpoints (superiority): CR/CRu at 120 wks, PFS

Morschhauser et al. *N Engl J Med*. 2018;379:934. Fowler et al. *Lancet Oncol*. 2014;15:1315.
Gribben et al. *J Clin Oncol*. 2015;33:2803.

RELEVANCE: PFS by IRC

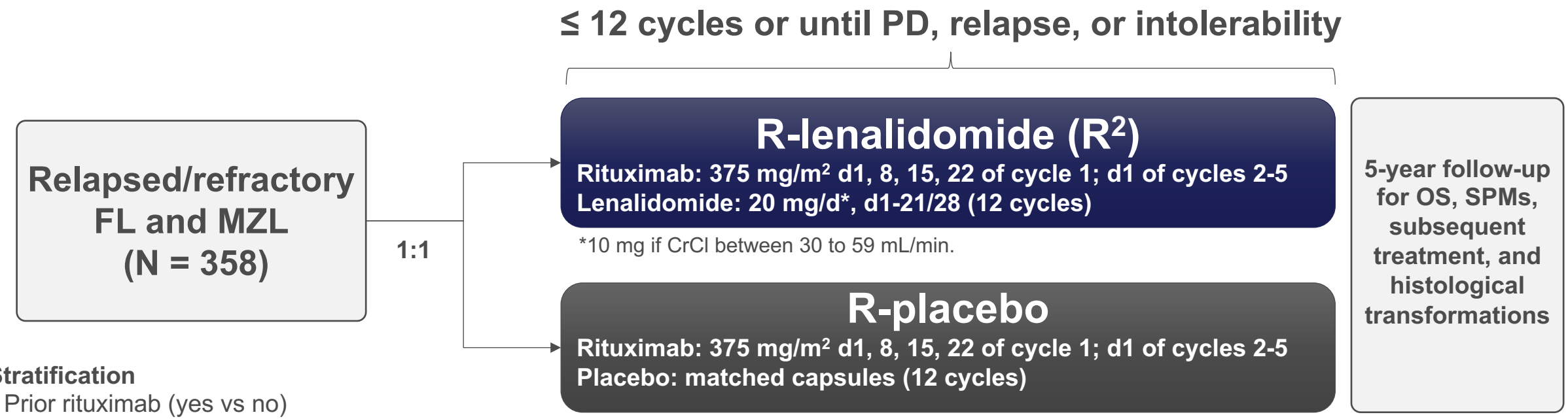


	R²	R-CT
Patients, n	513	517
3-Yr PFS, % (95% CI)	77 (72-80)	78 (74-82)

- Interim PFS at median follow-up of 37.9 mos was similar in both arms
- PFS benefit observed across prespecified subgroups

Morschhauser et al. *N Engl J Med*. 2018;379:934.

AUGMENT: RANDOMIZED DOUBLE BLIND PHASE III TRIAL



Stratification
- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

Key eligibility criteria
- MZL or FL (grades 1-3a) in need of treatment
- ≥ 1 prior chemotherapy, immunotherapy or chemoimmunotherapy
- Not rituximab refractory

- Prophylactic anticoagulation / antiplatelet Rx recommended for at risk patients
- Growth factor use was allowed per ASCO/ESMO guidelines[1,2]

- Primary endpoint: PFS by IRC (2007 IWG criteria w/o PET)

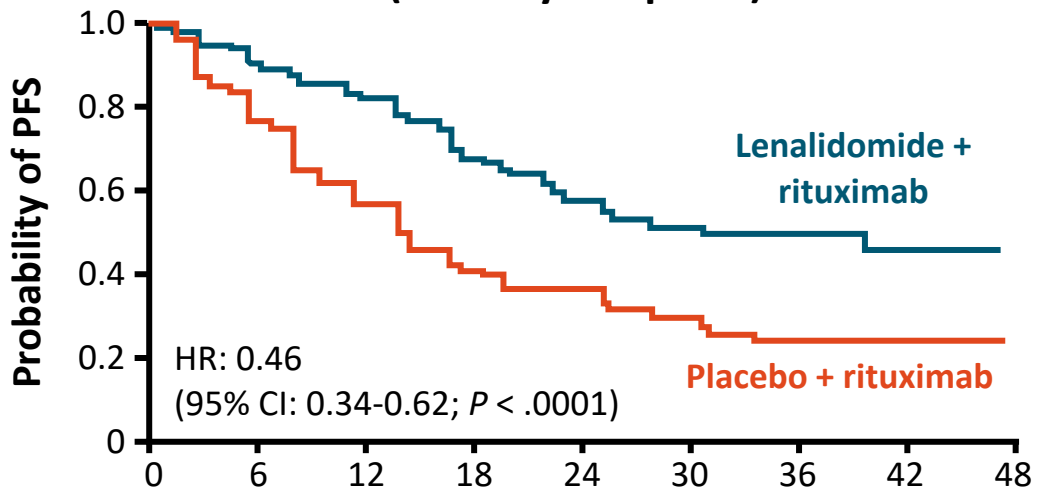
NCT01938001

1. Crawford et al. *Ann Oncol.* 2010;21 Suppl 5:248-251. 2. Smith et al. *J Clin Oncol.* 2015;33:3199-3212.

Leonard, ASH 2018

AUGMENT: Efficacy and Safety Outcomes

IRC-Assessed PFS in Intention-to-Treat Population (Primary Endpoint)



Patients at Risk, n									
Len + rituximab	178	148	124	91	59	39	20	7	0
Placebo + rituximab	180	132	92	58	40	26	10	4	0

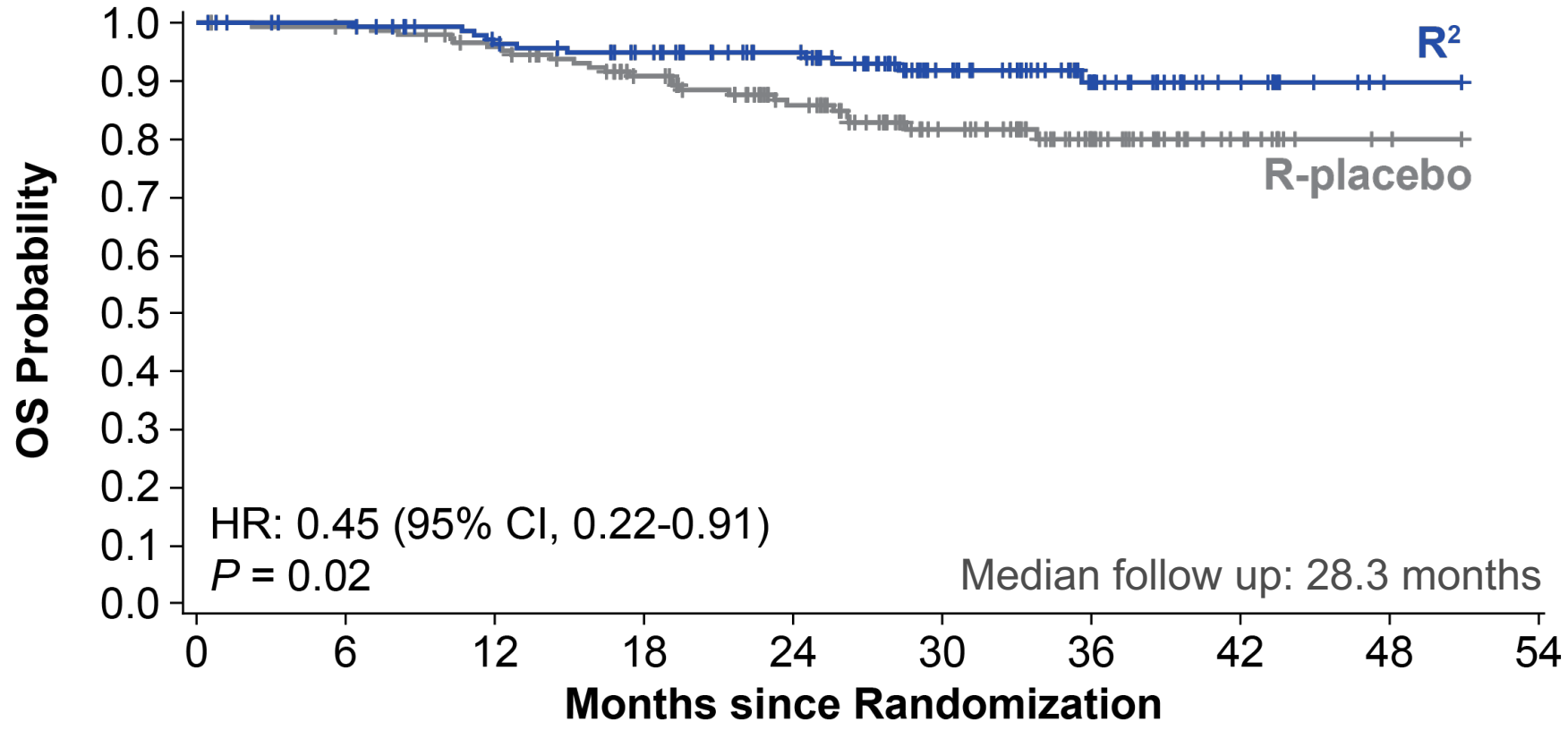
AEs of Interest, n (%)	R^2 (n = 176)	R-Placebo (n = 180)
Second primary malignancies	6 (3)*	10 (6)†
Venous TE	6 (3)	3 (2)
Arterial TE	1 (1)	4 (2)
Mixed TE	3 (2)	1 (1)

*n = 1 each, AML, carcinoid tumor of the GI tract, squamous cell carcinoma of the lung, basal cell carcinoma; n = 2, squamous cell carcinoma of the skin.
†n = 1 each, adenocarcinoma of colon, malignant melanoma, papillary thyroid cancer, transitional cell cancer of the renal pelvis and ureter localized, squamous cell carcinoma of the skin; n = 2 each, AML, invasive ductal breast carcinoma, basal cell carcinoma.

- OS improved with R^2 in patients with FL (HR: 0.45; 95% CI: 0.22-0.92; *P* = .02)
- Histologic transformation in 1% R^2 vs 6% R-placebo, with an incidence/100 PY of 0.5 vs 2.5, respectively

Leonard et al. *J Clin Oncol*. 2019;37:1188.
Lenalidomide Prescribing Information.

OVERALL SURVIVAL IN PATIENTS WITH FL (PRESPECIFIED SUBGROUP ANALYSIS)



No. at Risk										
R^2	147	142	130	121	105	70	39	13	1	0
R-placebo	148	145	137	117	94	64	35	12	2	0

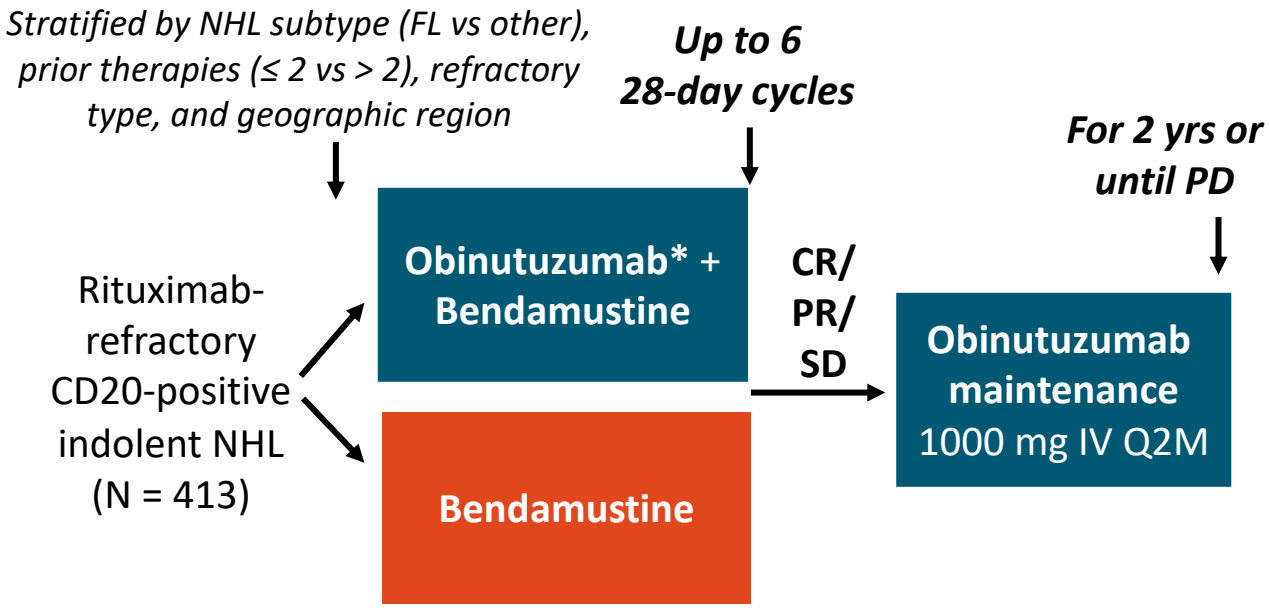
- 35 total deaths (11 R^2, 24 R-placebo)
- 2-year OS was 95% (95% CI, 90%-98%) for R^2 and 86% (95% CI, 79%-91%) for R-placebo

Data cutoff June 22, 2018.

Leonard, ASH 2018

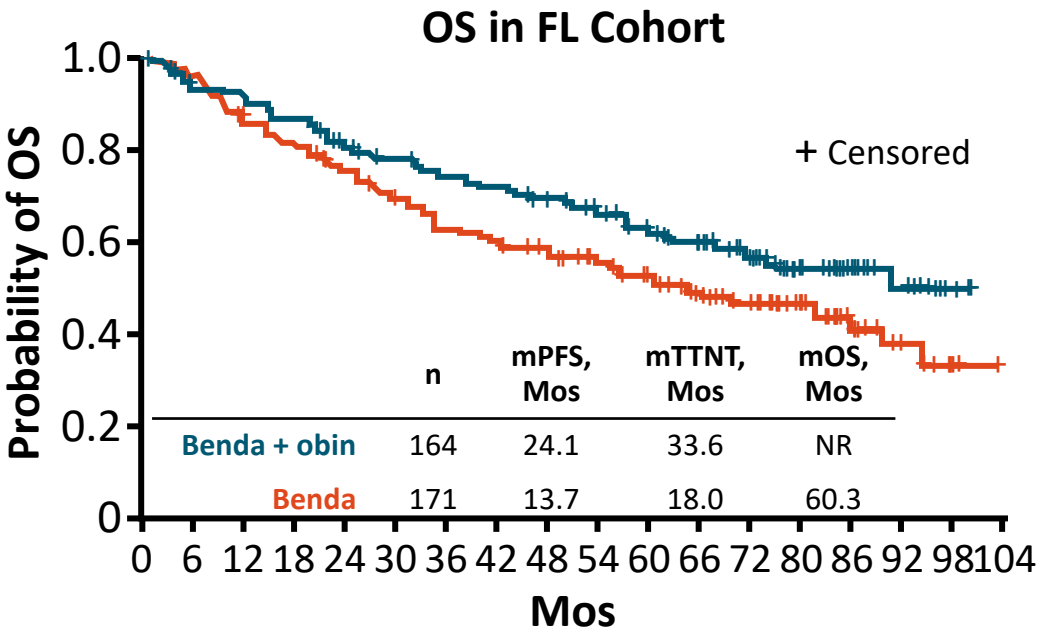
GADOLIN: Bendamustine + Obinutuzumab and Maintenance Obinutuzumab in Rituximab-Refractory NHL

- Randomized, open-label, international phase III trial



*1000 mg IV on Days 1, 8, 15 cycle 1; Day 1 cycles 2-6. Response monitored by CT scan post induction, then every 3 mos for 2 yrs, then every 6 mos (modified Cheson criteria 2007).

- Primary endpoint: PFS assessed independently



- Obinutuzumab + bendamustine followed by obinutuzumab is FDA approved for patients with FL who have relapsed after, or are refractory to, a rituximab-containing regimen

Sehn. Lancet Oncol. 2016;17:1081. Cheson. JCO. 2018;36:2259.

When to use obinutuzumab?

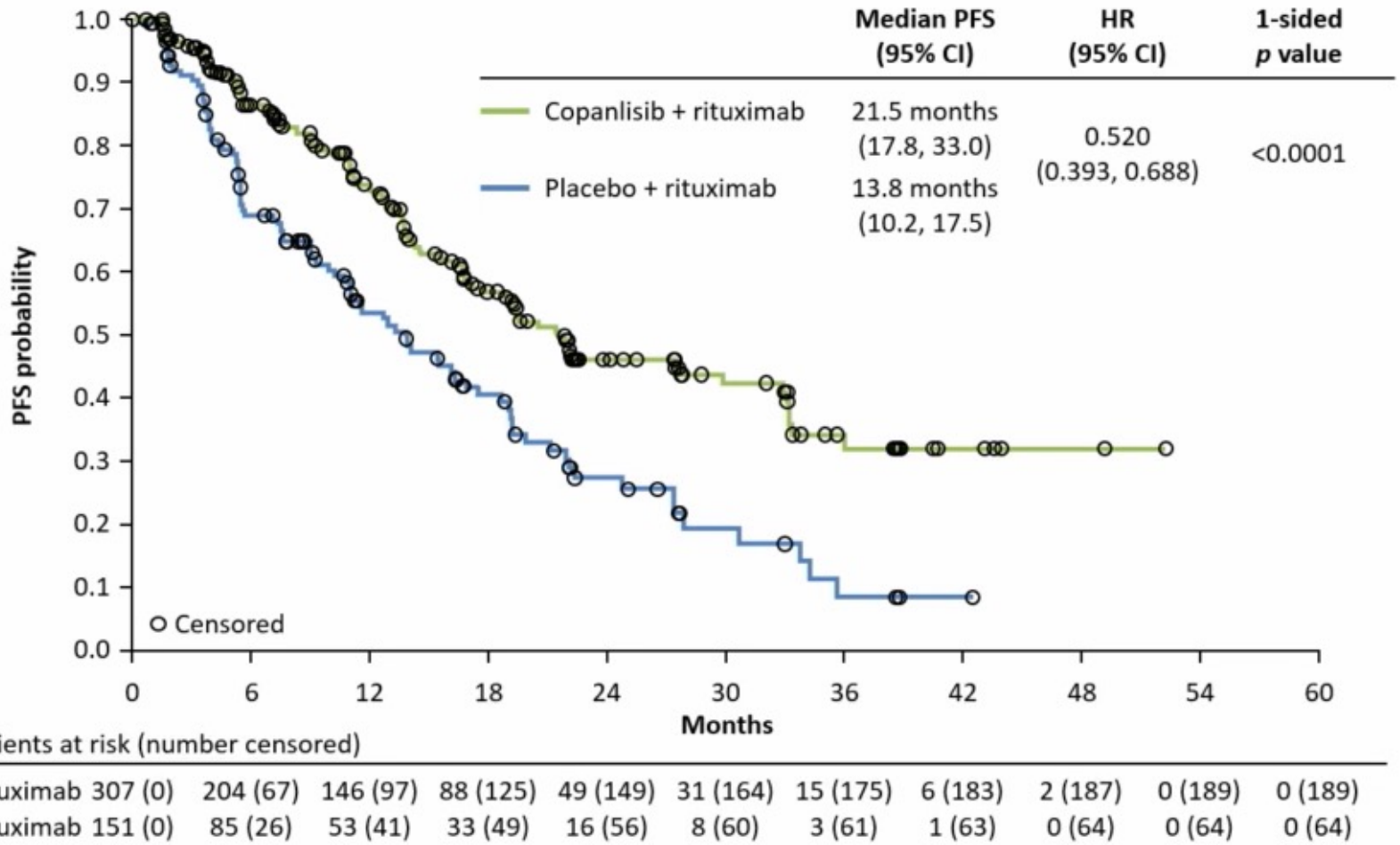
- Frontline FL
  - Patients < 60 years of age (GALLIUM)
  - Short duration infusion (90 minute cycle 2 and beyond, GAZELLE)
- Relapsed/Refractory FL
  - Rituximab refractory
  - Combination with bendamustine (GADOLIN)
  - Combination with lenalidomide (GALEN)
  - POD24 (SWOG 1608)

PI3K Inhibitors Approved for R/R FL

	Idelalisib[a]	Copanlisib[b]	Duvelisib[c]	Umbralisib[g]
Isoform targeted	δ	α, δ	δ,γ	δ,CK1ε
ORR in FL patients	54%	59%	42%	45%
mPFS	11 months	12.5 months	9.5 months	10.6 months
mOS	20.3 months	42.6 months	28.9 months	N/A
Serious AEs of interest	Black box warnings[d] Hepatotoxicity Diarrhea/colitis Pneumonitis Infection Intestinal perforation	Most common grade 3/4 AEs[e] Hyperglycemia Hypertension Neutropenia Pneumonia	Black box warnings[f] Diarrhea/colitis Infection Pneumonitis Skin reaction	Most common grade 3/4 AEs [g] Neutropenia Diarrhea ALT/AST elevation

a. Gopal AK, et al. *N Engl J Med*. 2014;370:1008-1018; b. Dreyling M, et al. *Am J Hematol*. 2020;95:362-371; c. Flinn IW, et al. *J Clin Oncol*. 2019;37:912-922; d. ZYDELIG® (idelalisib) [PI]. 2020; e. Dreyling M, et al. *J Clin Oncol*. 2017;35:3898-3905; f. COPIKTRA® (duvelisib) [PI]. 2019. g. Fowler et. al. *J Clin Oncol*. 2021;39:1609-1618.

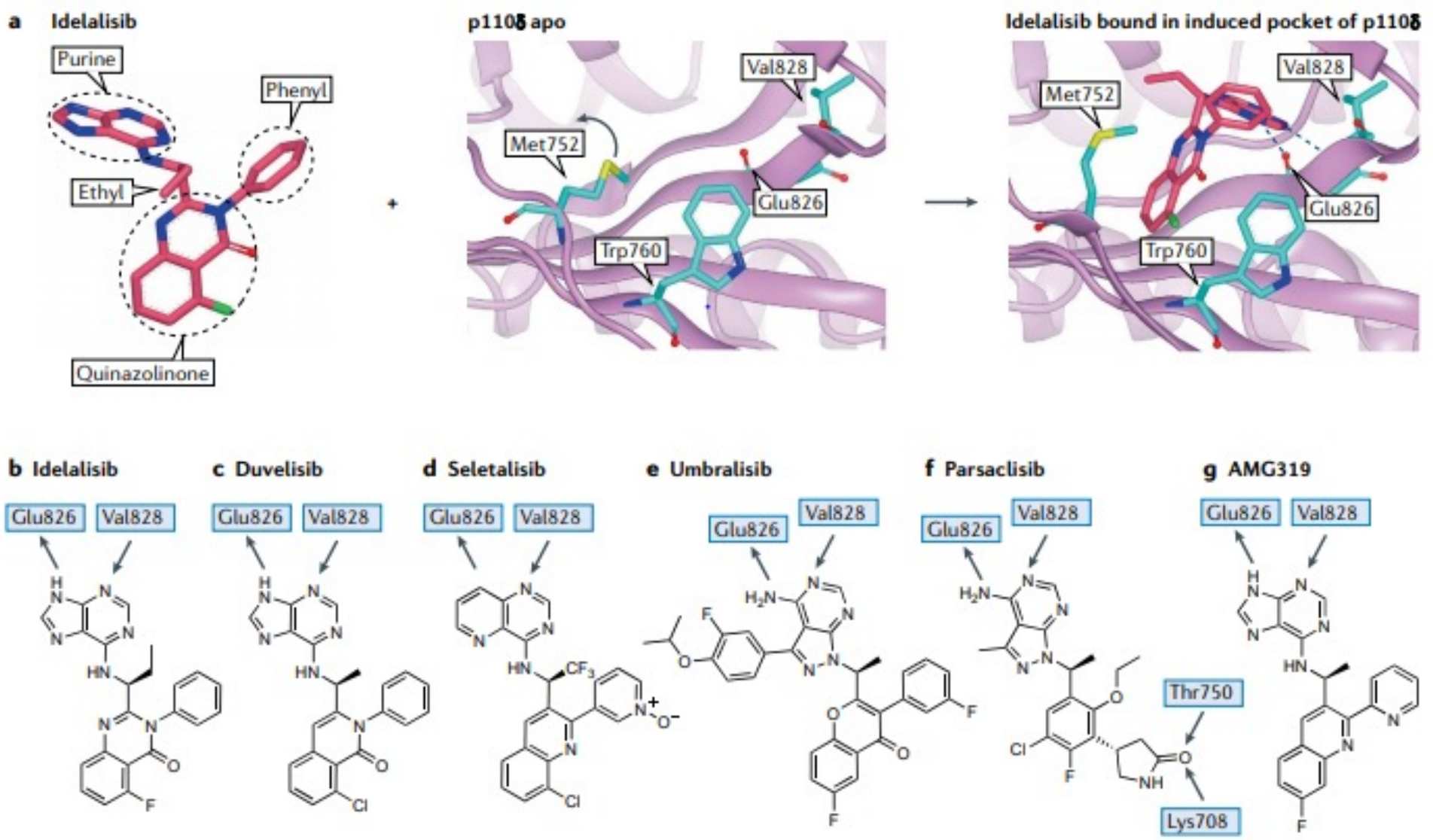
CHRONOS-3: Copanlisib + Rituximab Results in Superior PFS



- Median follow-up of 19.2 months

- Zinzani PL. et al. EHA 2021, abstract S211.

Parsaclisib in R/R FL: CITADEL-203

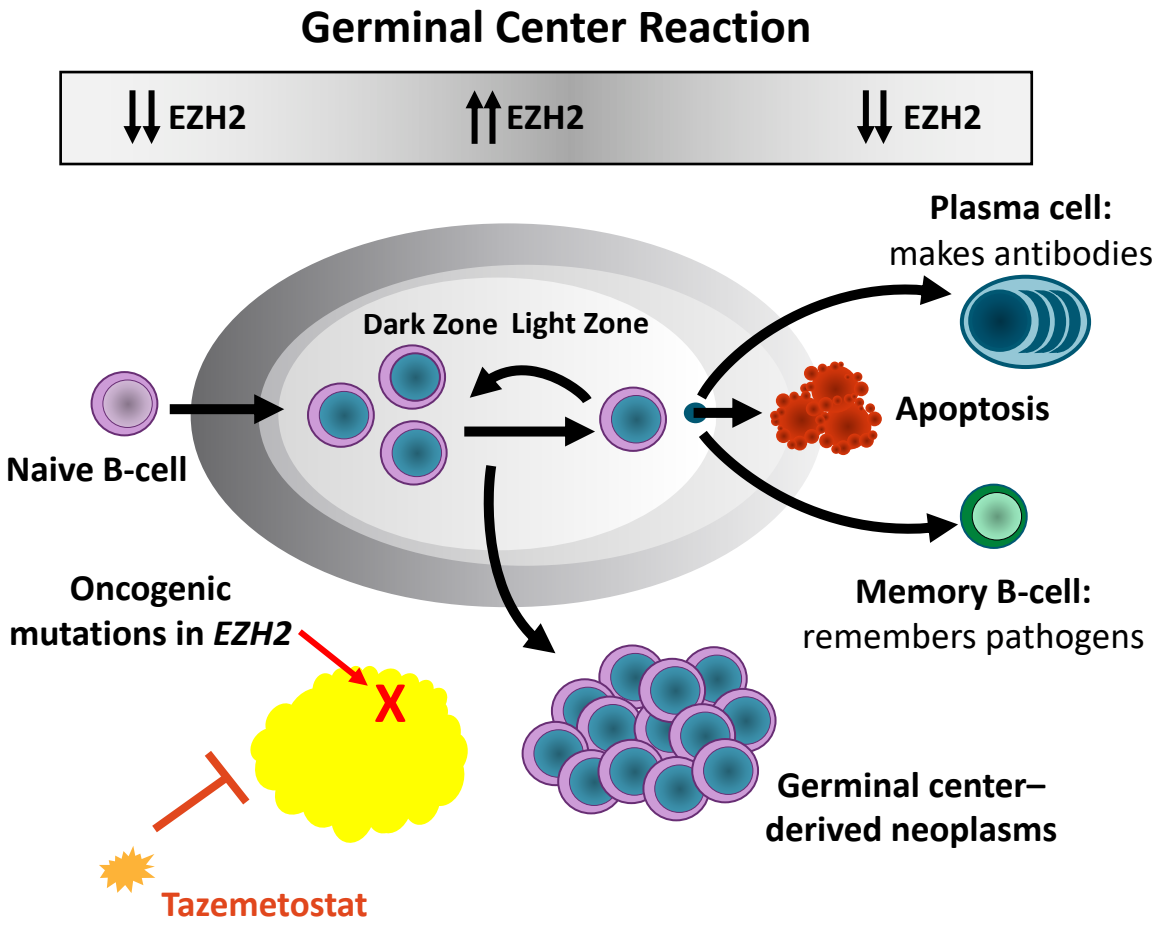


- Vanhaesebroeck et al. Nature Reviews 10/2021

Lynch et al. ASH 2021 abstract 813 12/13/21 5pm

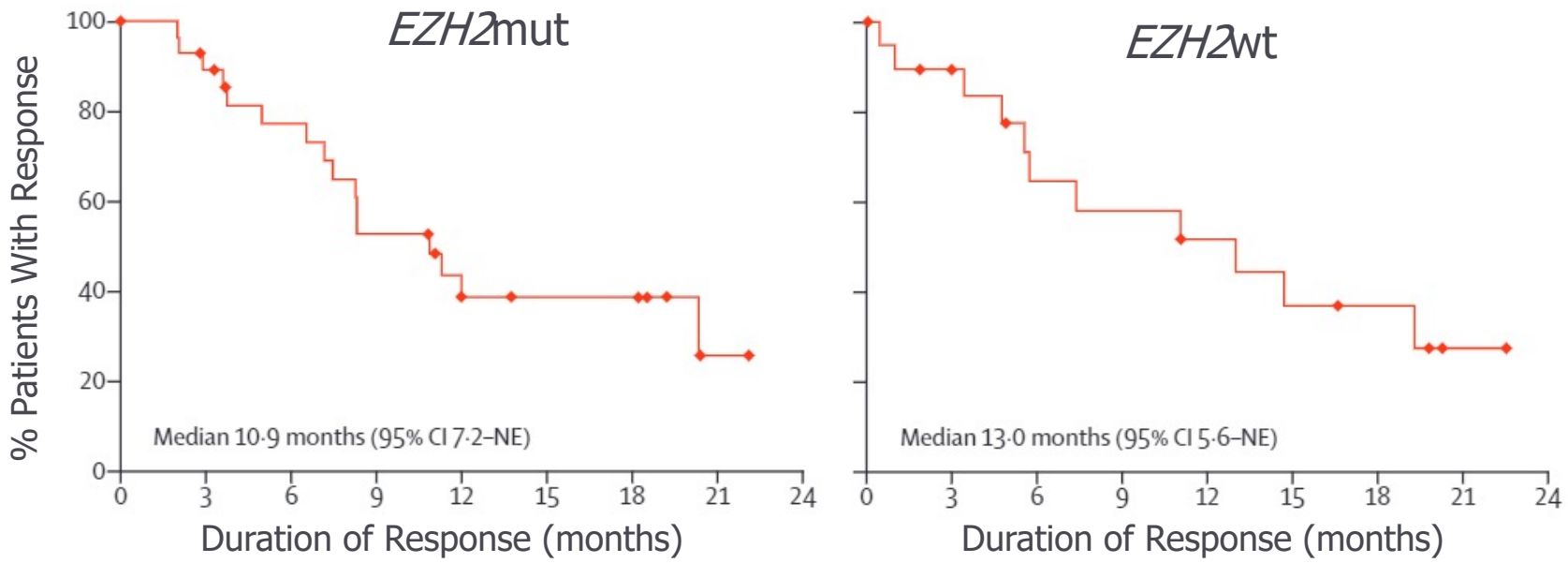
EZH2, a Histone Methyltransferase, in FL

- In normal B-cell biology, EZH2 regulates germinal center formation
- *EZH2* mutations can lead to oncogenic transformation by locking B-cells in germinal state and preventing terminal differentiation
- *EZH2*-activating mutations found in ~ 20% of patients with FL
- **Tazemetostat**: selective, oral, first-in-class EZH2 inhibitor
- Whether WT or mutant, *EZH2* biology relevant to FL



Tazemetostat: Efficacy

Durability of Response in Both EZH2mut and EZH2wt Cohorts



	*EZH2*mut	*EZH2*wt
Response ≥ 6 months	61%	53%
Response ≥ 12 months	23%	37%
Response ≥ 18 months	19%	21%

Morschhauser et al. *Lancet Oncol*. 2020;21:1433-1442.

Tazemetostat: Safety Profile

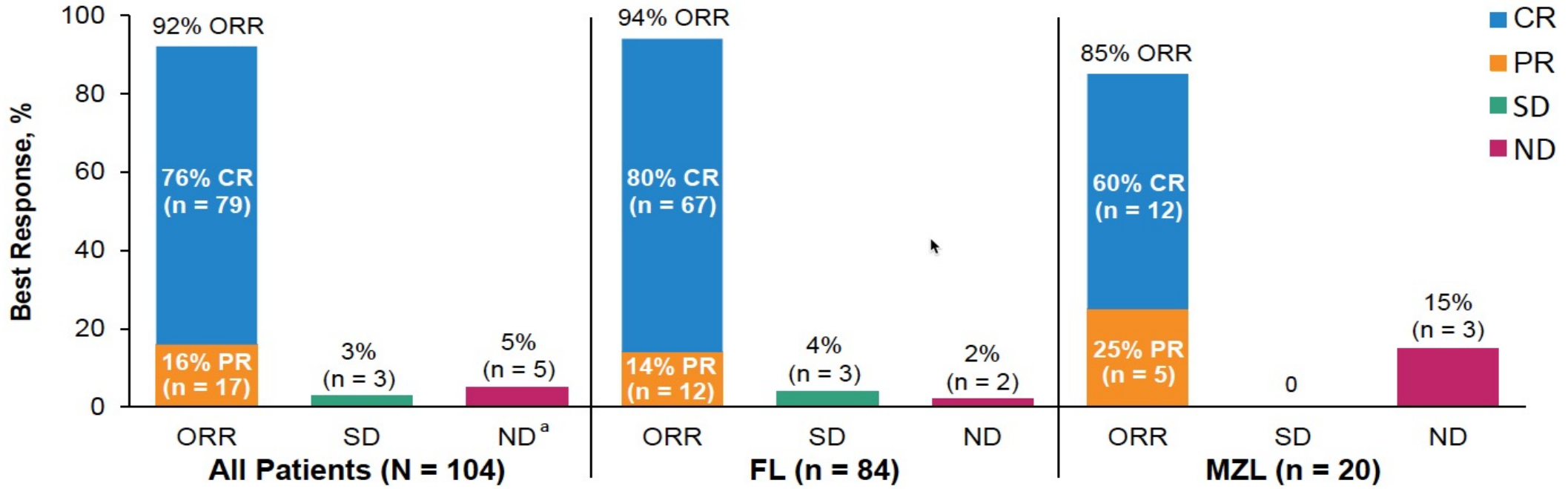
	Treatment-emergent adverse events			Treatment-related adverse events		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Nausea	23 (23%)	0	0	19 (19%)	0	0
Diarrhoea	18 (18%)	0	0	12 (12%)	0	0
Alopecia	17 (17%)	0	0	14 (14%)	0	0
Cough	16 (16%)	0	0	2 (2%)	0	0
Asthenia	15 (15%)	3 (3%)	0	13 (13%)	1 (1%)	0
Fatigue	15 (15%)	2 (2%)	0	11 (11%)	1 (1%)	0
Upper respiratory tract infection	15 (15%)	0	0	1 (1%)	0	0
Bronchitis	15 (15%)	0	0	3 (3%)	0	0
Abdominal pain	12 (12%)	1 (1%)	0	2 (2%)	0	0
Headache	12 (12%)	0	0	5 (5%)	0	0
Vomiting	11 (11%)	1 (1%)	0	6 (6%)	0	0
Back pain	11 (11%)	0	0	0	0	0
Pyrexia	10 (10%)	0	0	2 (2%)	0	0

- 5% of all patients discontinued treatment
- 9% had dose reductions due to treatment-related AEs

Morschhauser et al. *Lancet Oncol*. 2020;21:1433-1442.

ZUMA-5: Axi-cel in R/R iNHL

ORR by IRRC Assessment Was 92% (95% CI, 85 – 97); CR Rate Was 76% (95% CI, 67 – 84)

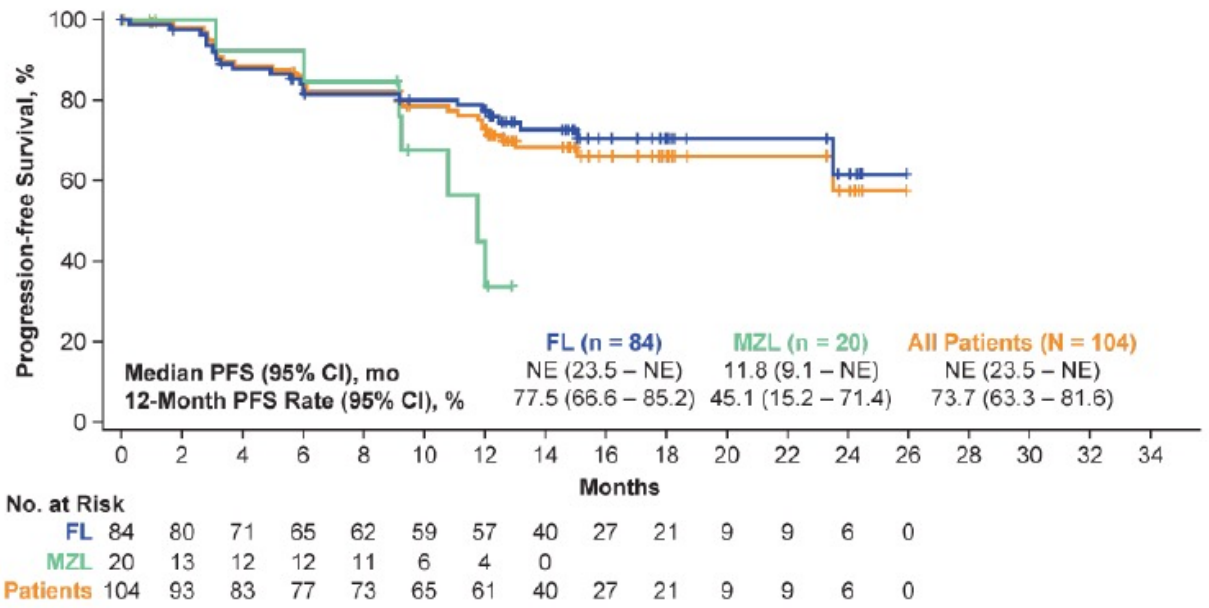


- The median time to first response was 1 month (range, 0.8 – 3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9 – 11.2)

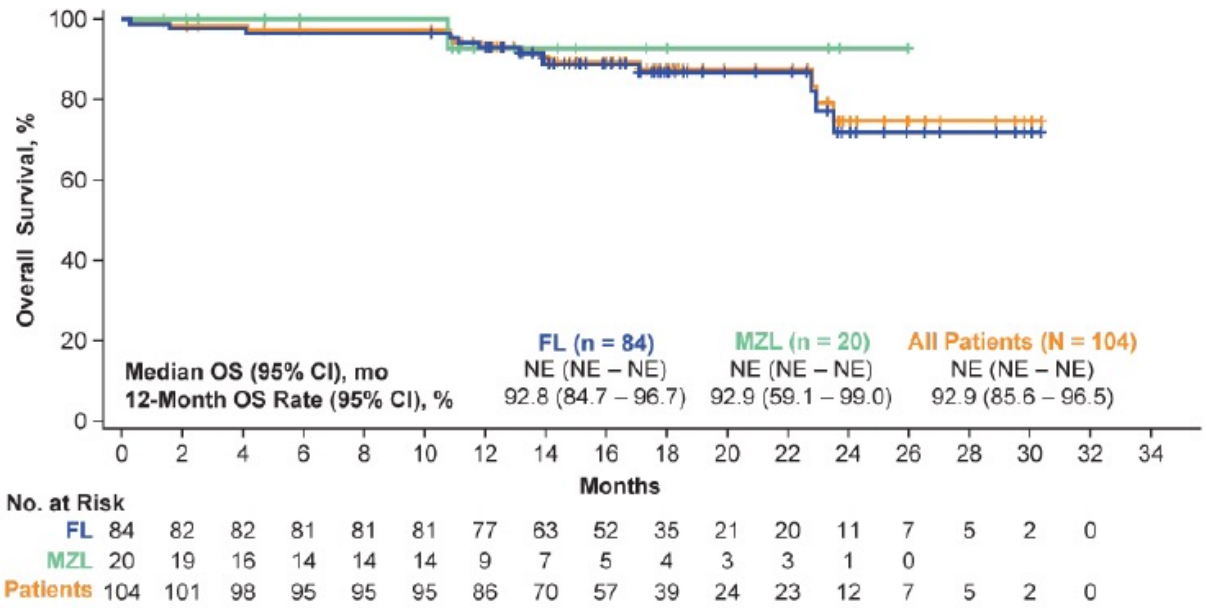
The investigator-assessed ORR (N = 104) was 95%, with a CR rate of 77%. Concordance between investigator-assessed and IRRC-assessed ORR was 91%. [a] For the 5 patients reported as ND, 4 (1 FL; 3 MZL) had no disease at baseline and postbaseline per IRRC but were considered with disease by the investigator; 1 patient with FL died before the first disease assessment.
CR, complete response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, undefined/not done; ORR, overall response rate; PR, partial response; SD, stable disease.

Progression-Free Survival and Overall Survival

Progression-Free Survival



Overall Survival



- With a median follow-up of 17.5 months, median PFS and median OS were not reached
  - The 12-month PFS rate was 73.7% (95% CI, 63.3 – 81.6) for all patients
  - The 12-month OS rate was 92.9% (95% CI, 85.6 – 96.5) for all patients

FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

ELARA (Tisa-Cel) in R/R FL Efficacy

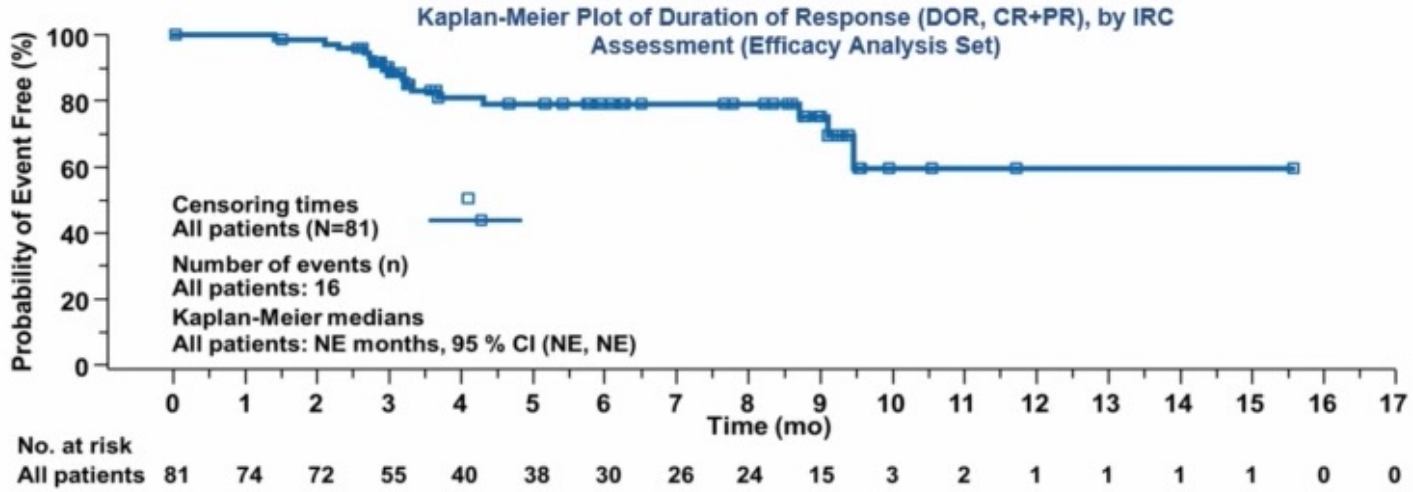
- Primary endpoint was met, CRR by IRC was 66%, ORR 86%

Best Overall Response Rate

Response Rate, %	Patients Evaluable for Efficacy[b] (n=94)
CR	66.0[b]
PR	20.2
ORR (CR+PR)	86.2

- Investigator-assessed CRR was 69.1%[c] (ORR 90.4%)
- CRRs/ORRs were comparable among key high-risk subgroups

Median DOR Was Not Reached at 11 Months Median Follow-Up



- Median follow-up for efficacy (n=94): 11 (4.3-19.7) months
- Probability for a responding patient to remain in response ≥6 months was 79% (95% CI, 66-87)
- 12 of 18 PRs (66.6%) converted to CRs; all but 1 occurred between Month 3 and Month 6
- Median time to next antilymphoma treatment was not reached

First efficacy assessment conducted at Month 3 (all but 1 responded at Month 3 assessment); probability of remaining in CR > Month 6.
[a]The primary end point was met at interim analysis. [b]$P<0.0001$; indicates statistical significance (1-sided) at the 0.0025 level so that the null hypothesis CRR ≤0.15 is rejected. [c]95% CI, 58.8-78.3
CI, confidence interval; CR, complete response; CRR, complete response rate; DOR, duration of response; IRC, Independent Review Committee; NE, not estimable; PR, partial response; ORR, overall response rate.

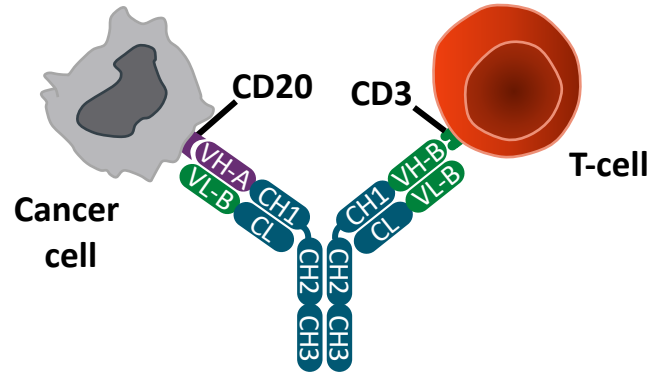
- Dreyling M, et al. EHA 2021, abstract S210

Investigational Anti-CD20xCD3 Bispecific Antibodies Being Explored in FL

Agent	Mosunetuzumab[1]	Odronextamab (REGN1979)[2]	Epcoritamab (GEN3013)[3]
Phase	I/II (NCT02500407)	II (NCT02290951)	I/II (NCT03625037)
Population	R/R indolent NHL after ≥ 2 prior regimens	R/R B-NHL after 2 prior regimens	R/R B-NHL after prior anti-CD20 mAbs
N (efficacy/safety)	90 (FL cohort)	30/136	16/68 (5 at ≥12 mg level)
Efficacy (with FL/iNHL), %	▪ ORR: 80 ▪ CR: 60	▪ ORR: 90 ▪ CR: 70	▪ ORR: 80 ▪ CR: 60
Safety (all patients), %	▪ CRS: All grade: 44 Grade ≥ 3: 2 ▪ Neurotoxicity[a]: – All grade: 4 – Grade ≥ 3: 0	▪ CRS: – All grade: 61 – Grade ≥ 3: 7.4 ▪ Neurotoxicity: – All grade: NR – Grade 3: 1.5	▪ CRS: – All grade: 59 – Grade ≥ 3: 0 ▪ Neurotoxicity: – All grade: 5.9 – Grade 3: 2.9

[a]Data from abstract

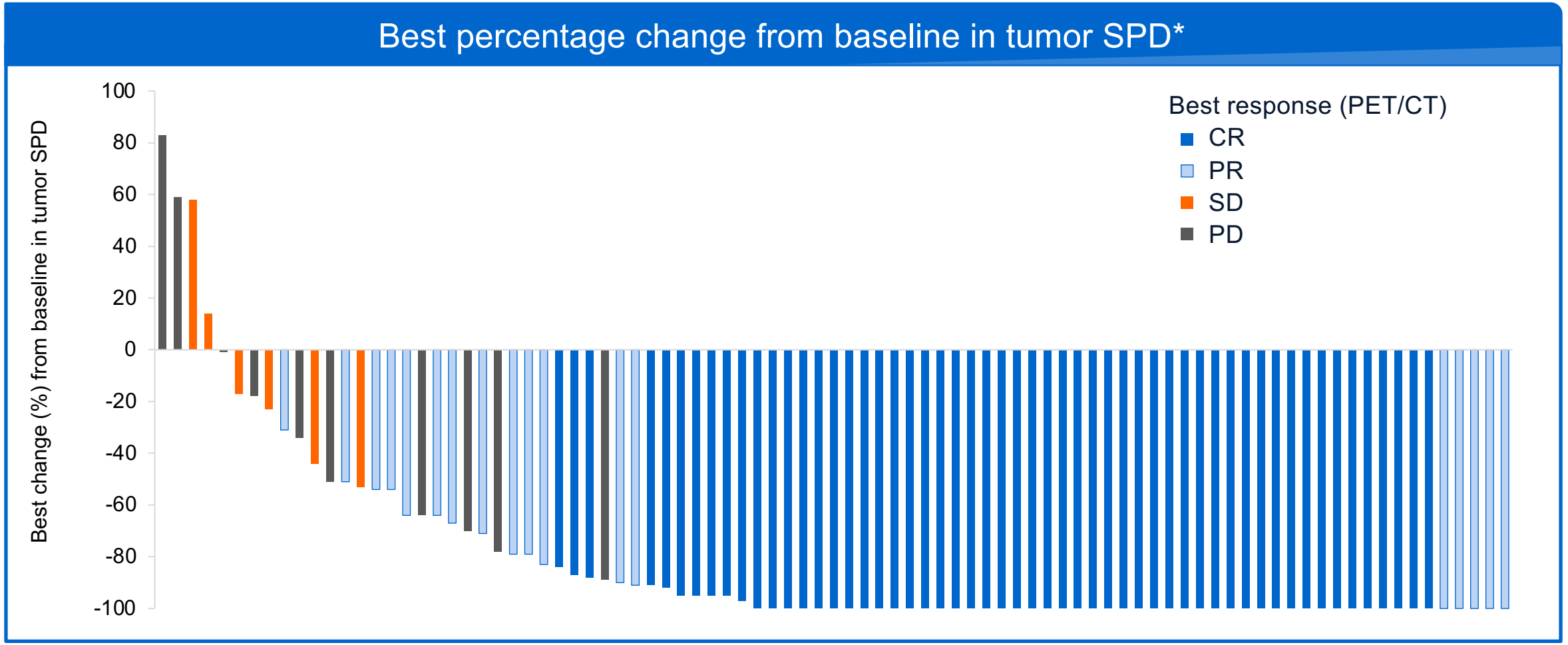
Anti-CD20/CD3 Bispecific Antibody



Simultaneous binding of CD20 on malignant B-cells and CD3 on cytotoxic T-cells results in crosslinking of CD3, activation of T-cells, and cancer cell killing

1. Budde et al. ASH 2021. Abstract 127
2. Bannerji et al. ASH 2020. Abstract 400.
3. Hutchings et al. ASH 2020. Abstract 402.

Mosunetuzumab Anti-tumor efficacy



*in all patients with a baseline and ≥1 post-baseline SPD available; PD, progressive disease; SPD, sum of product diameters

Budde. ASH 2021 Abstract 127, Saturday 12:00pm

Conclusions

- Outcomes for FL continue to improve, likely the result of novel therapies in the R/R setting.

- The ever expanding treatment landscape creates new challenges-
  How do we sequence therapy?
  Can we identify predictive biomarkers?
  Is the MOA or toxicity profile distinguishable enough to inform treatment selection?

- The paucity of randomized studies creates a need for RWD/RWE for comparative effectiveness analyses.

- OS is favorable, PFS is far less robust beyond frontline, are we satisfied with this being a chronic disease or should we continue to strive for cure?