How to treat early relapse in a patient with FL

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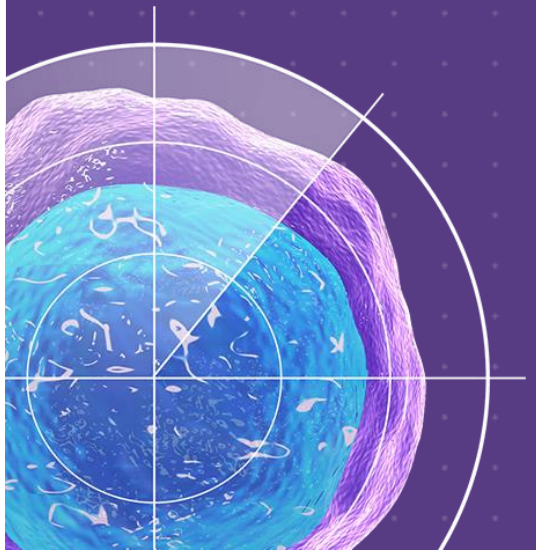
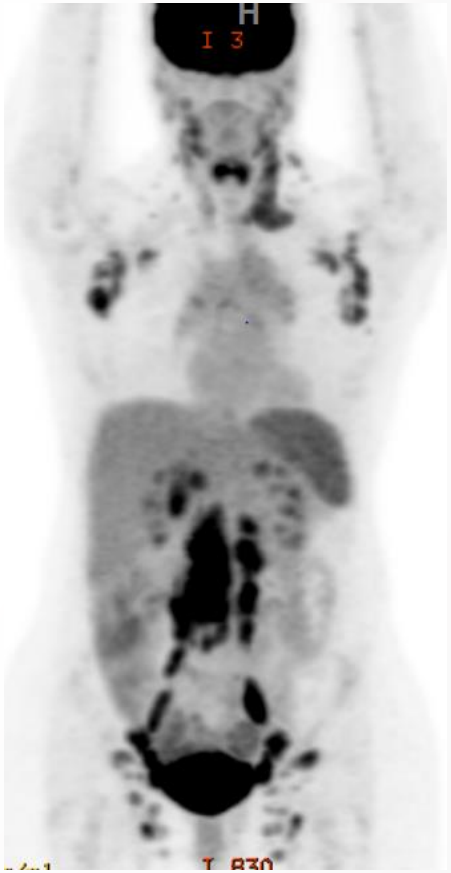


Disclosures

	Research funding	Consultancy
Celgene	√	√
Gilead	√	√
Roche	√	√
Janssen	√	√
Novartis	√	√
Takeda	√	√
TG Therapeutics	√	√

Clinical case: Early relapse follicular lymphoma

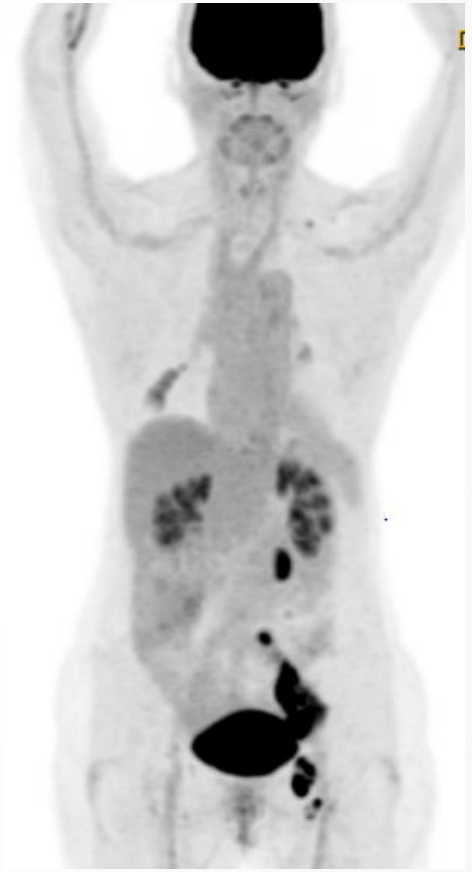
- 75 y/o female with a history of FL, Grade 3a
  - 2 years ago, she presented with widespread lymphadenopathy (>7cm)
  - Bone marrow was involved with FL (Stage IV)
  - ECOG PS 1
  - Labs notable for LDH > ULN, B2M > ULN
  - High-risk FLIPI (age, stage, LDH, # nodal sites)
  - Prior therapy: BR x 6 cycles resulting in a CR on PET/CT



B2M, beta-2 microglobulin; BR, bendamustine + rituximab; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; PET/CT, positron emission tomography and computed tomography; ULN, upper limit of normal.

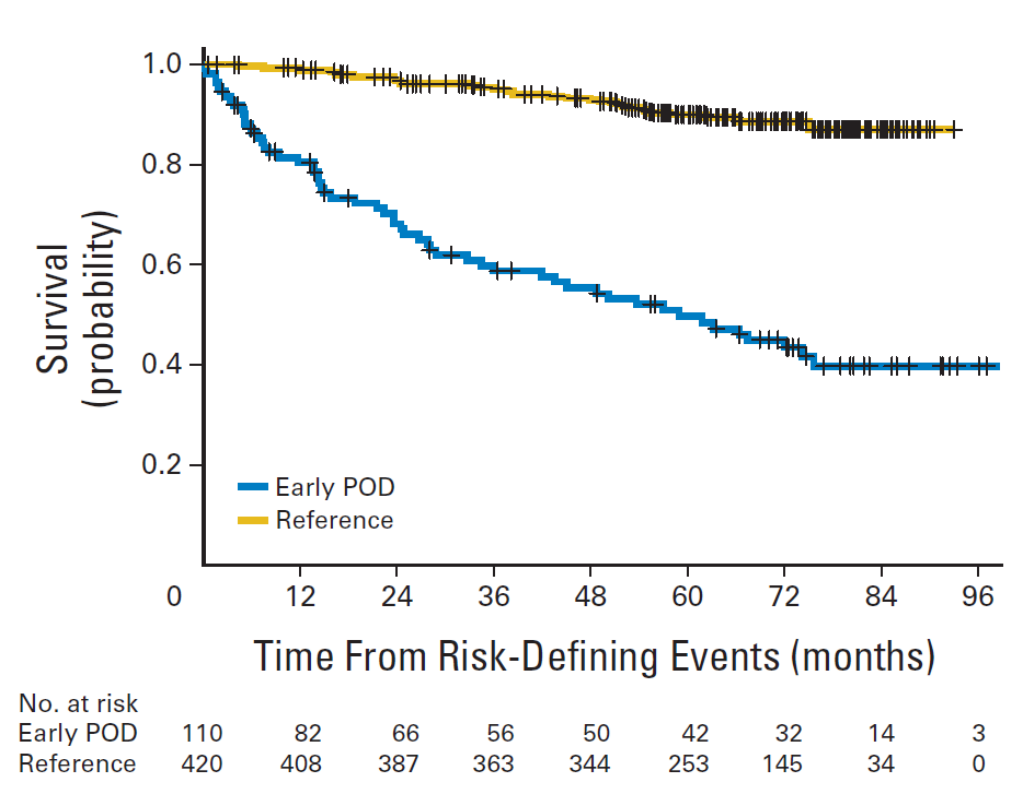
Clinical case continued

- 15 months later (21 months since diagnosis), she presents with palpable inguinal lymphadenopathy
- She reports fatigue and 15 lb weight loss
- Biopsy is pursued; confirms relapsed FL, Grade 3a
- **77 y/o F with recurrent FL (POD24); how would I treat this patient?**

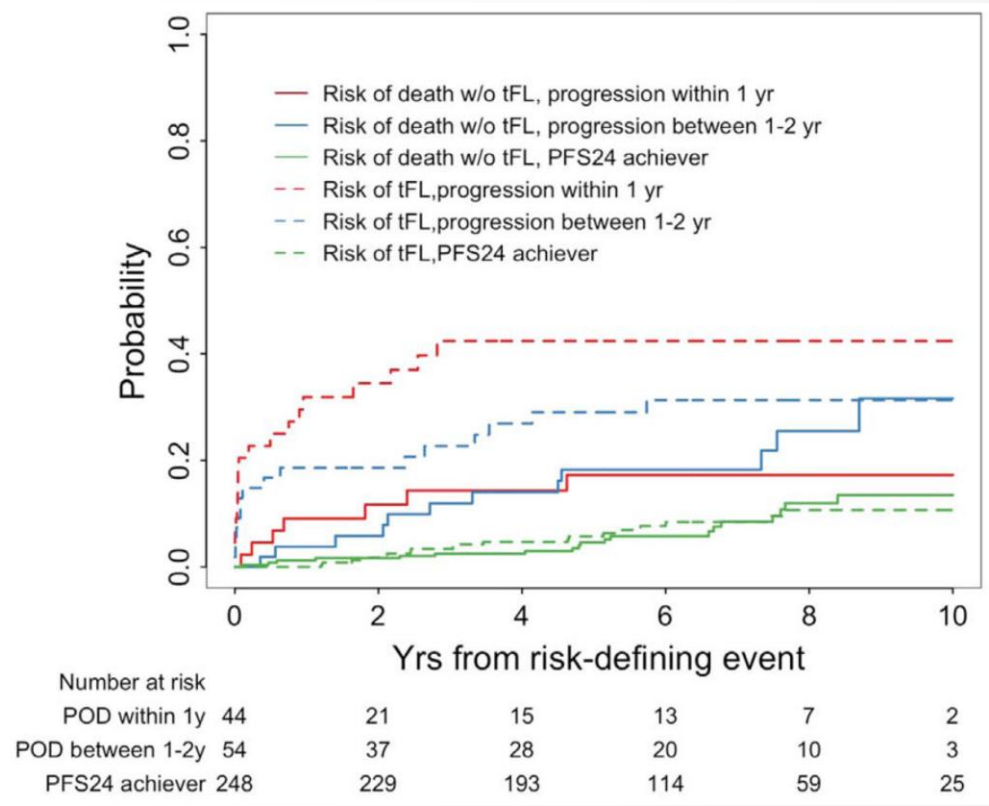


F, female; FL, follicular lymphoma; POD24, progression of disease within 24 months of diagnosis.

Early progression in the PET era



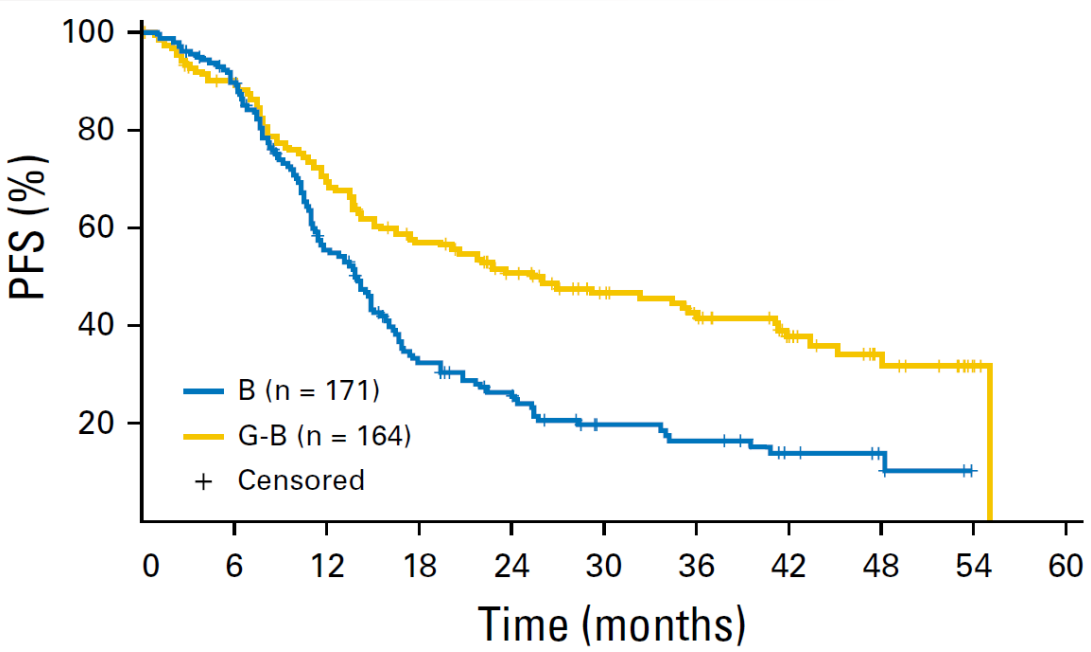
Casulo C, et al. *J Clin Oncol.* 2015;33(23):2516-2522.



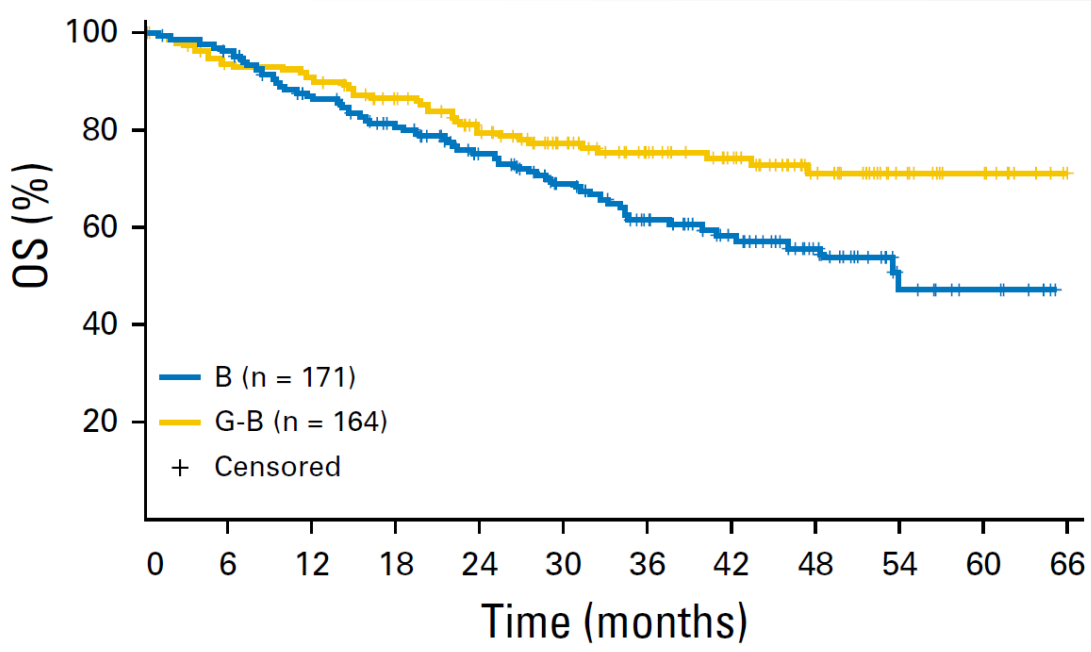
Batlevi CL, et al. *Eur J Cancer.* 2020;126:78-90.

PET, positron emission tomography; PFS24, progression-free survival at 24 months; POD, progression of disease; tFL, transformed follicular lymphoma; y, year.

Obinutuzumab plus bendamustine (GADOLIN) in R/R FL



No. at risk:										
B	171	141	84	45	32	18	15	9	4	
G-B	164	138	107	86	67	49	40	26	15	4

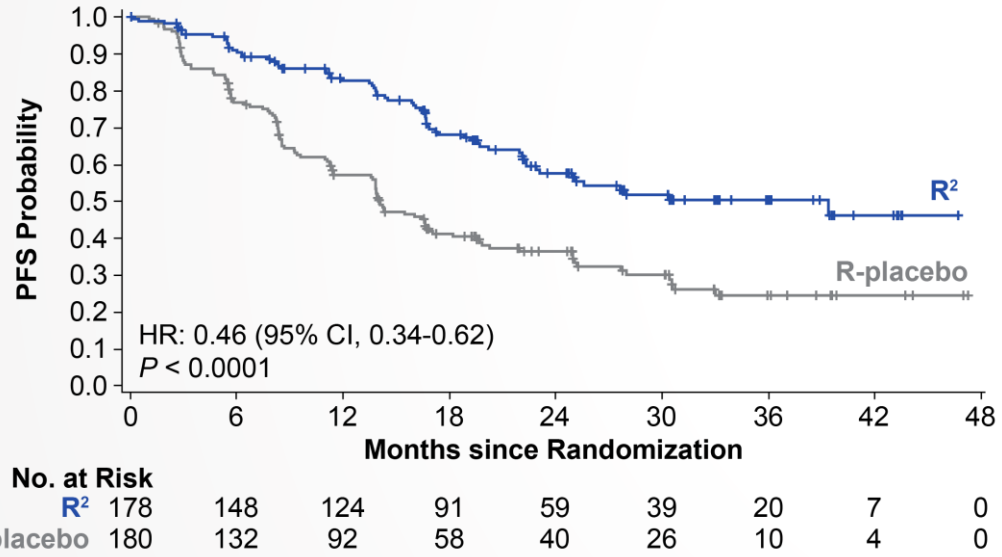


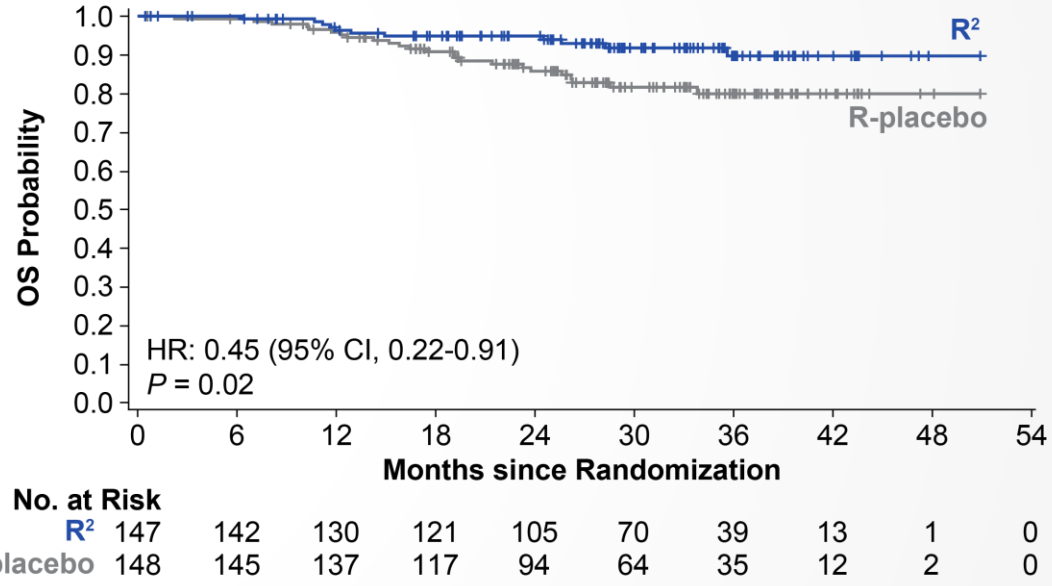
No. at risk:											
B	171	159	137	122	103	84	65	49	32	13	7
G-B	164	147	141	129	111	90	71	56	38	20	12

B, bendamustine; FL, follicular lymphoma; G-B, obinutuzumab + bendamustine; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

Cheson BD, et al. *J Clin Oncol.* 2018;36(22):2259-2266.

Lenalidomide plus rituximab (AUGMENT) in R/R FL



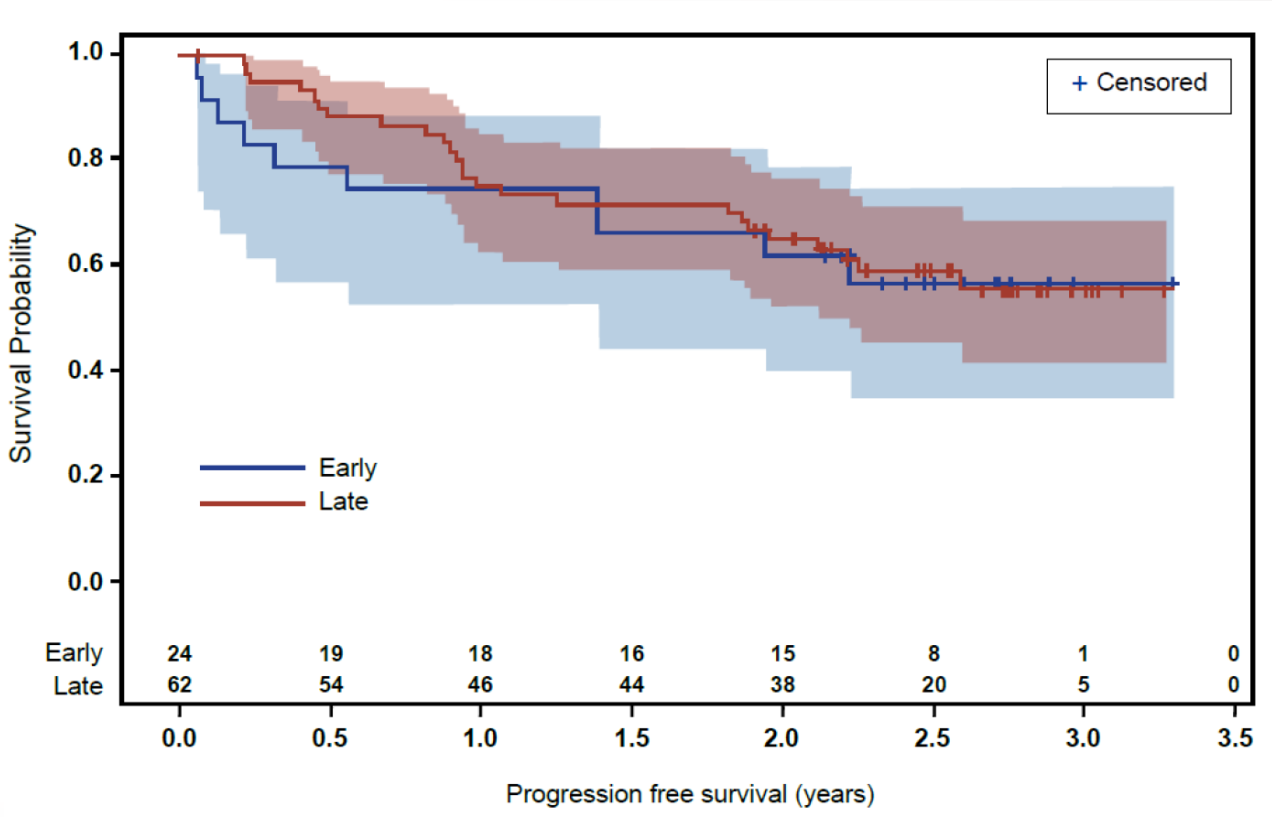


FL, follicular lymphoma; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; R-placebo, rituximab + placebo; R^2, lenalidomide + rituximab; R/R, relapsed/refractory.

Leonard JP, et al. *J Clin Oncol.* 2019;37(14):1188-1199.

Obinutuzumab plus lenalidomide (GALEN) in R/R FL

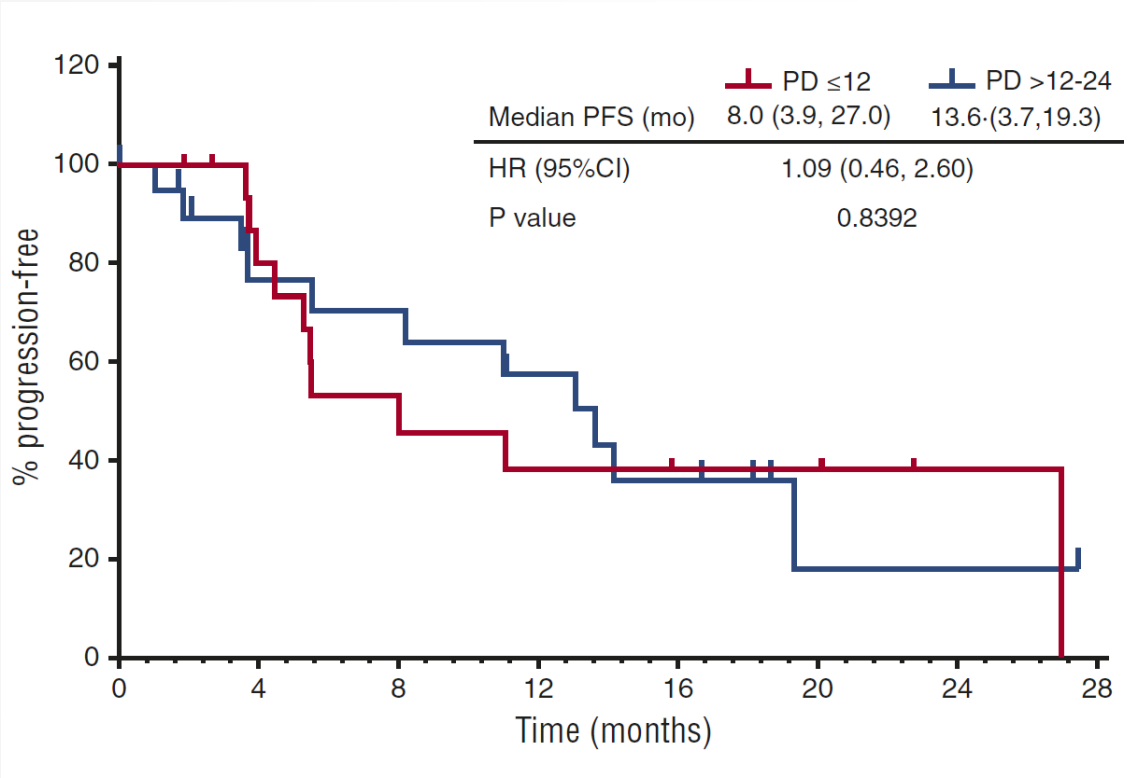
Response/survival % (95% CI)	Early relapse (≤2 y; POD24) n = 24	Late relapse (>2 y) n = 62
ORR IWG 1999	75.0 (53.3–90.2)	87.1 (76.2–94.3)
ORR IWG 2007	70.8 (48.9–87.4)	85.5 (74.2–93.1)
2-year PFS	62.5 (40.3–78.4)	65.5 (52.1–76.0)
2-year OS	82.8 (60.3–93.2)	88.5 (77.4–94.4)



CI, confidence interval; FL, follicular lymphoma; IWG, International Working Group; ORR, overall response rate; PFS, progression-free survival; POD24 progression of disease within 24 months of diagnosis; R/R, relapsed/refractory; y, years.

Morschhauser F, et al. *Lancet Haematol.* 2019;6(8):e427-e437.

Idelalisib in early relapse R/R FL



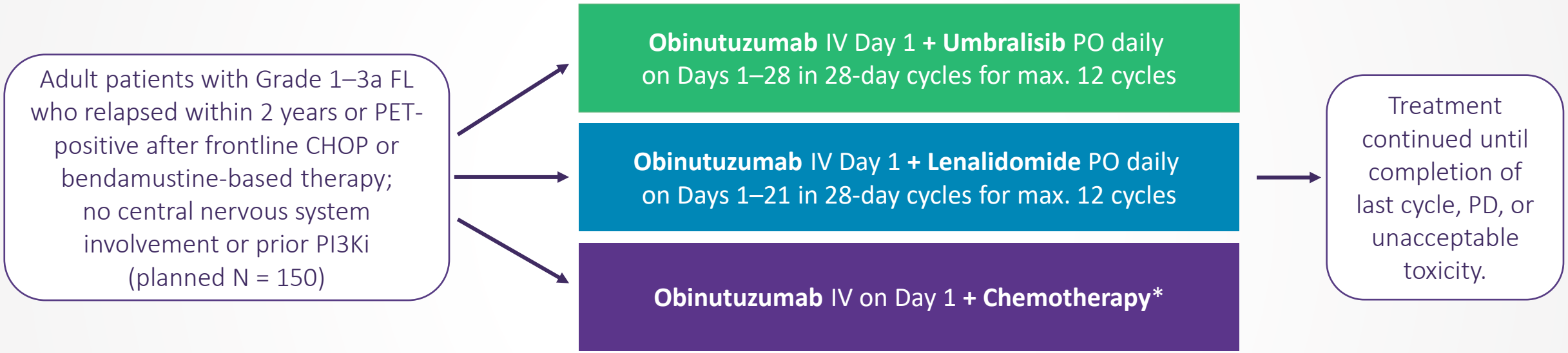
- 72 patients with FL
- N = 37 with early relapse (defined as PD within 24 months from the start of treatment)
- ORR was 56.8% (CR = 13.5%)
- The median PFS was 11.1 mos
  - mPFS PD ≤12 mos: 8 mos
  - mPFS PD 12–24 mos: 13.6 mos

CI, confidence interval; CR, complete response; FL, follicular lymphoma; HR, hazard ratio; mos, months; mPFS, median PFS; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory.

Gopal AK, et al. *Blood.* 2017;129(22):3037-3039.

SWOG 1608: Randomized trial of obinutuzumab-based therapy in early progressing/refractory FL

- Prospective, multicenter, randomized, open-label phase II trial



- Primary endpoint: CR by PET/CT
- Secondary endpoints: CR30, PFS, DOR, OS, AEs, m7-FLIPI model validation†

AE, adverse event; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisolone; CR30, complete response at 30 months; DOR, duration of response; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; IV, intravenous; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PI3K, phosphoinositide 3 kinase inhibitor; PO, oral.

*For patients who received prior bendamustine-based chemotherapy: cyclophosphamide IV, doxorubicin hydrochloride IV, and vincristine sulfate IV on Day 1, and prednisone PO on Days 1–5; obinutuzumab dosed every 21 or 28 days for a maximum of 12 cycles; and chemotherapy repeated every 21 days for a maximum of 6 cycles. For patients who received prior CHOP: bendamustine IV on Days 1 and 2; treatment dosed in 28-day cycles for a maximum of 6 (bendamustine) or 12 (obinutuzumab) cycles.

†m7-FLIPI prognostic model includes the mutation status of 7 genes (EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, and CARD11)

https://www.clinicaltrials.gov/ct2/show/NCT03269669.

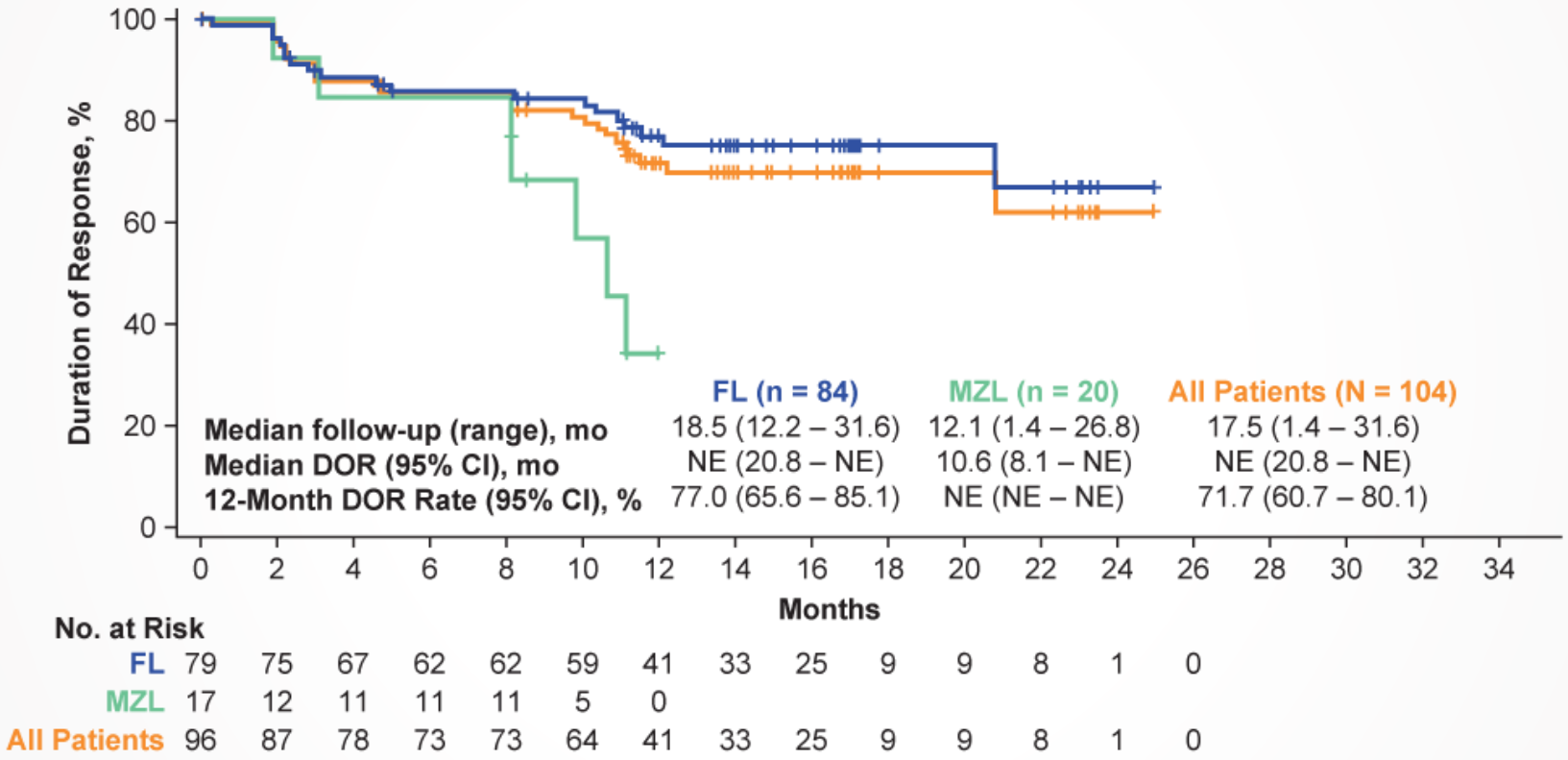
Treatment with tazemetostat demonstrated clinical activity in high-risk subgroups

IRC assessment*

Parameter	MT *EZH2*			WT *EZH2*		
	Refractory to rituximab (n = 22)	POD24 (n = 19)	Refractory to prior treatment (n = 33)	Refractory to rituximab (n = 32)	POD24 (n = 32)	Refractory to prior treatment (n = 42)
Objective response rate, n (%)†	**13 (59)**	**12 (63)**	**21 (64)**	**10 (31)**	**8 (25)**	**12 (29)**
95% CI‡	36.4–79.3	38.4–83.7	45.1–79.6	16.1–50.0	11.5–43.4	15.7–44.6
Complete response, n (%)	2 (9)	2 (11)	5 (15)	1 (3)	1 (3)	1 (2)
Partial response, n (%)	11 (50)	10 (53)	16 (49)	9 (28)	7 (22)	11 (26)
Stable disease, n (%)	8 (36)	7 (37)	11 (33)	8 (25)	11 (34)	13 (31)
Progressive disease, n (%)	1 (5)	0	1 (3)	10 (31)	9 (28)	12 (29)
NE, missing, or unknown, n (%)	0	0	0	4 (13)	4 (13)	5 (12)
Median DOR (95% CI), months	7.3 (2.9–12.0)	6.6 (2.1–NE)	8.3 (3.7–NE)	7.4 (1.0–NE)	13.0 (0.5–NE)	7.4 (3.4–19.3)

CI, confidence interval; DOR, duration of response; IRC, independent review committee; MT, mutant; NE, non-evaluable; POD24, progression of disease within 24 months of prior therapy; WT, wild-type.
*Data from Morschhauser F, et al. Oral abstract #123. 61st ASH Annual Meeting and Exposition. Dec 7, 2019; Virtual.
†Best overall response based on Cheson (2007) criteria for lymphomas.
‡By Brookmeyer and Crowley method.

Axi-cel (ZUMA-5) in R/R FL

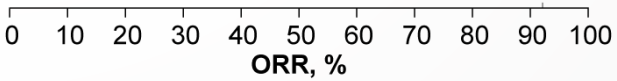


CI, confidence interval; DOR, duration of response; FL, follicular lymphoma; mo, months; MZL, marginal zone lymphoma; NE, not evaluable; R/R, relapsed/refractory.

Jacobson C, et al. Oral abstract #700. 62nd ASH Annual Meeting and Exposition. Dec 7, 2020; Virtual.

Axi-cel (ZUMA-5) in R/R FL

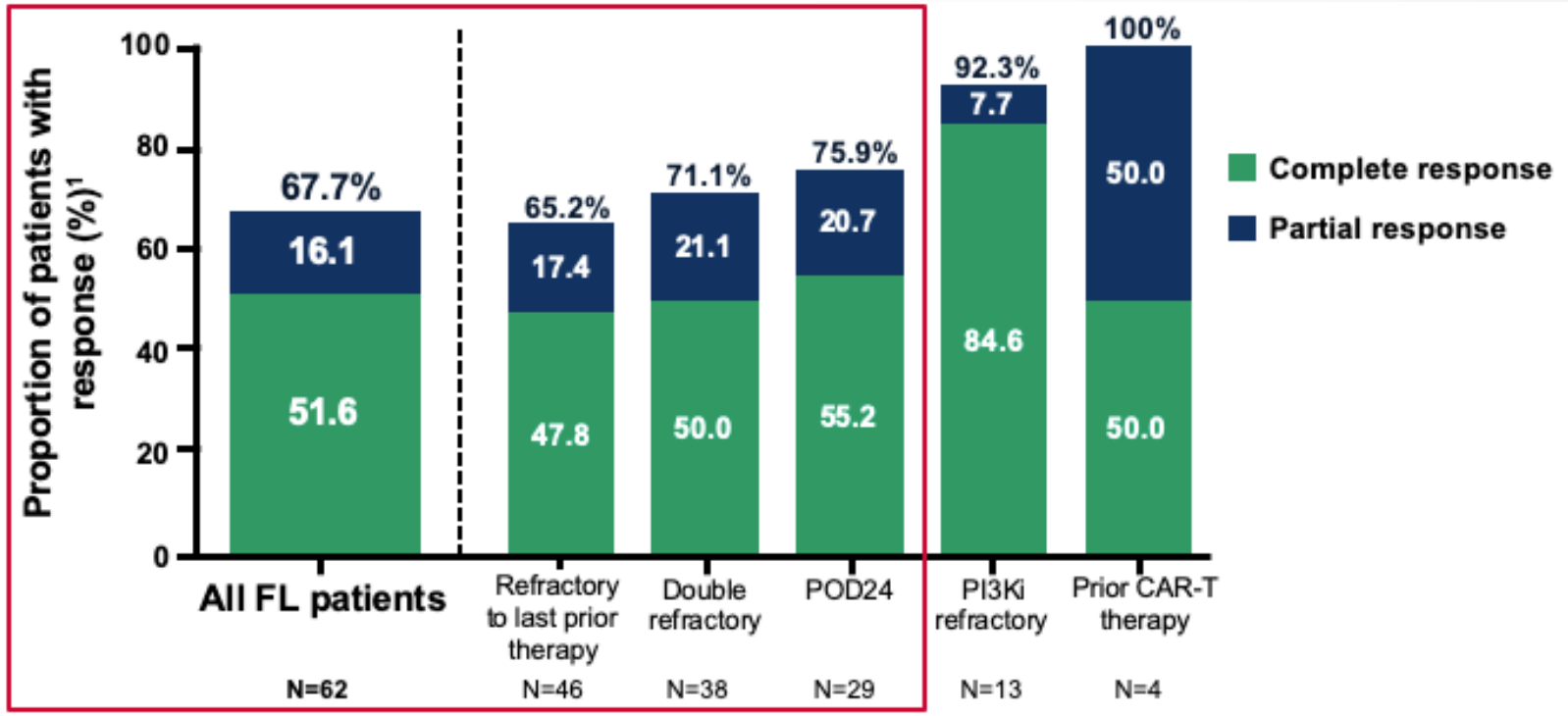
		Evaluable Patients	Responding Patients	ORR (95% CI)
Overall		104	96	92 (85 – 97)
Age	< 65	62	58	94 (84 – 98)
	≥ 65	42	38	90 (77 – 97)
Sex	Male	54	51	94 (85 – 99)
	Female	50	45	90 (78 – 97)
ECOG performance status	0	63	58	92 (82 – 97)
	1	41	38	93 (80 – 98)
FLIPI score	0 – 1	15	14	93 (68 – 100)
	2	36	32	89 (74 – 97)
	≥ 3	53	50	94 (84 – 99)
High tumor burden (GELF criteria)	Yes	49	47	96 (86 – 100)
	No	55	49	89 (78 – 96)
Number of prior therapies	2	32	28	88 (71 – 96)
	3	26	25	96 (80 – 100)
	≥ 4	46	43	93 (82 – 99)
Prior PI3K inhibitor	Yes	35	33	94 (81 – 99)
	No	69	63	91 (82 – 97)
Prior autologous SCT	Yes	23	21	91 (72 – 99)
	No	81	75	93 (85 – 97)
Relapsed/refractory subgroup	Relapsed	28	25	89 (72 – 98)
	Refractory	76	71	93 (85 – 98)
POD24 from initiating first anti-CD20 mAb–containing therapy	Yes	57	53	93 (83 – 98)
	No	36	33	92 (78 – 98)
CD19 status	Positive	83	76	92 (83 – 97)
	Negative	9	9	100 (66 – 100)
Corticosteroid and/or tocilizumab use	Yes	63	57	90 (80 – 96)
	No	41	39	95 (83 – 99)



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; mAb, monoclonal antibody; ORR, overall response rate; PI3K, phosphoinositide 3 kinase; POD24, progression of disease within 24 months; R/R, relapsed/refractory; SCT, stem cell transplant.
Jacobson C, et al. Oral abstract #700. 62nd ASH Annual Meeting and Exposition. Dec 7, 2020; Virtual.

Therapies on the horizon

- Bispecific antibodies
  - Mosunetuzumab
- High and consistent CR rates were observed in high-risk populations, including those with double-refractory disease, POD24, PI3Ki refractory, and those who received prior CAR T-cell therapy.



CAR, chimeric antigen receptor; CR, compete response; FL, follicular lymphoma; PI3Ki, phosphoinositide 3 kinase inhibitor; POD24, progression of disease within 24 months after treatment.
Assouline SE, et al. Oral abstract #702. 62nd ASH Annual Meeting and Exposition. Dec 7, 2020; Virtual.

How I approach early relapse FL

- Would pursue a PET/CT and biopsy to eval for transformed lymphoma
- Would consider a clinical trial as the first choice – access to novel therapy
  - CAR T-cell therapy
  - Lenalidomide + bispecific antibody
  - Lenalidomide + rituximab + tazemetostat
  - Lenalidomide + rituximab + tafasitamab
- Standard-of-care options include:
  - Chemoimmunotherapy
  - Lenalidomide + rituximab
  - For elderly, frail patients, can consider tazemetostat

CAR, chimeric antigen receptor; PET/CT, positron emission tomography and computed tomography.

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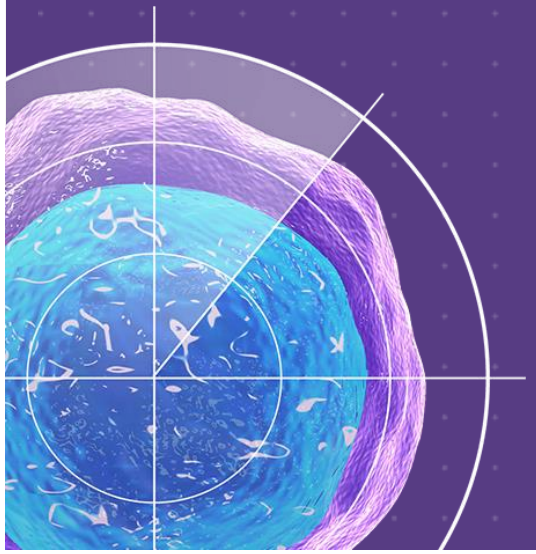
Thank you



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