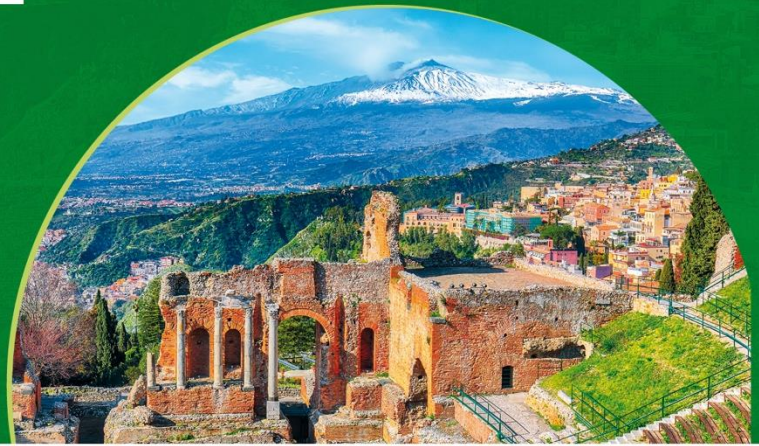
CORSO EDUCAZIONALE COMMISSIONE ANZIANI

XIII EDIZIONE

Giardini Naxos - Marriott Delta Hotels
17-18 aprile 2026



FONDAZIONE ITALIANA LINFOMI

Linfoma Follicolare nel pz anziano: come cambia il sequencing terapeutico

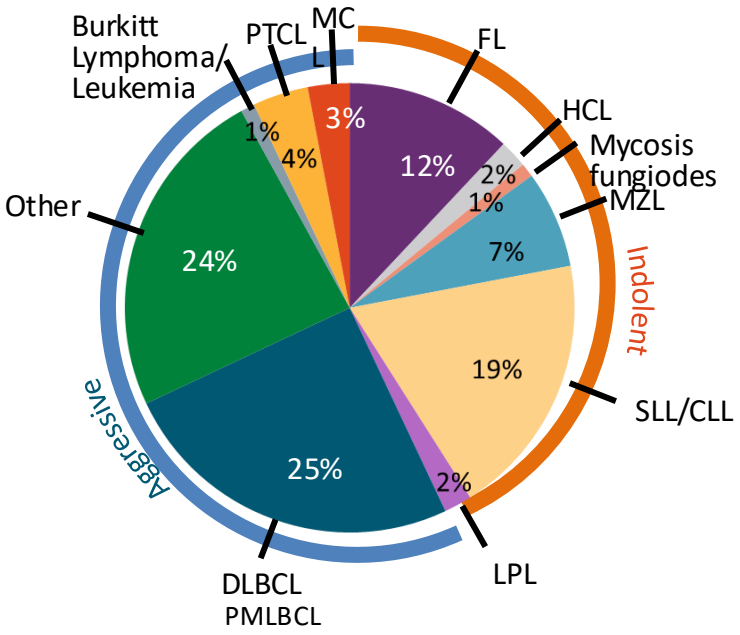
Annalisa Chiarenza
Divisione di Ematologia con Trapianto A.O.U. Policlinico G. Rodolico
Catania

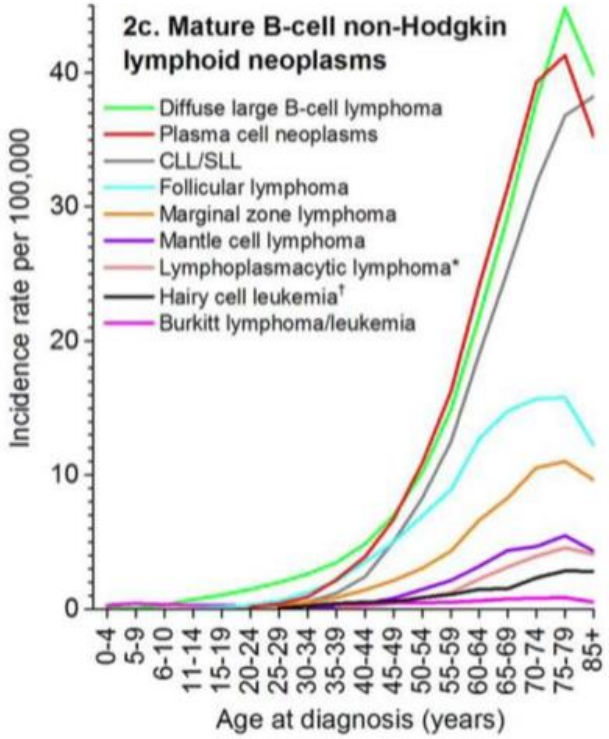
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche						X	X
Janssen					X	X	X
Abbvie					X	X	
Gilead						X	
AstraZeneca					X	X	
Takeda						X	
Lilly					X		X
Beigene					X		X

Outcomes in Indolent Lymphomas

Distribution of NHL Subtypes[2,4]





1. Freedman. Am J Hematol. 2020;95:316; 2. Teras. CA Cancer J Clin. 2016;66:443. 3,Howlander. SEER Cancer Statistics Review, 1975. 4. Armitage. JCO. 1998;16:2780. 5. Casulo. Blood. 2015;125:4

Follicular Lymphoma

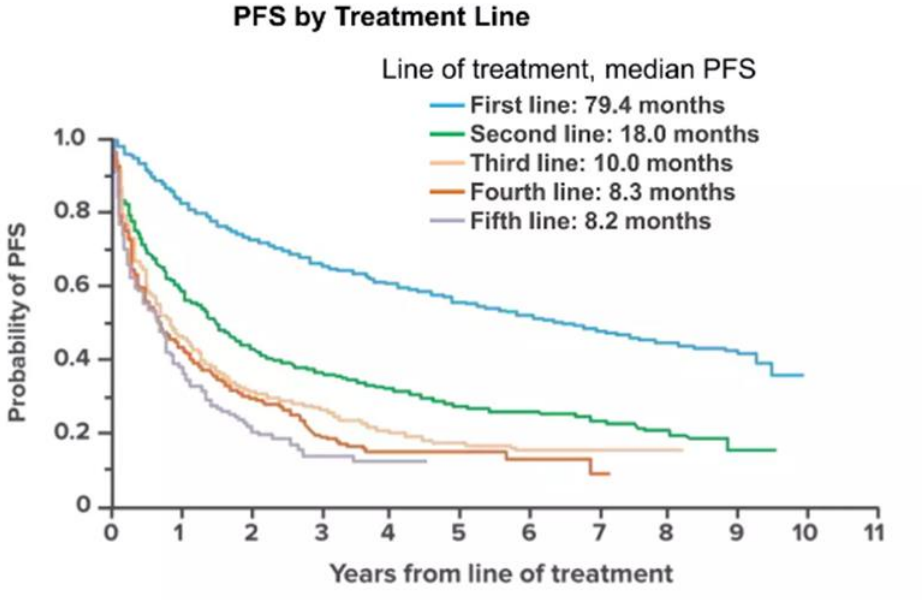
- FL typically good responses to initial therapy
- Outcomes improved substantially in the era of Rituximab-based strategies:

  - 10-yr survival rate: 64% to 92%[3]

  - Median survival is ~ 20 yrs, similar to age matched controls[5-8]
- Advances in the first-line treatment of FL continue to prolong PFS:

  -CD20 maintenance

  -Obinutuzumab plus chemo
- Relapsing remitting course
- Poor outcome for early progression
- Can transform into aggressive subtype



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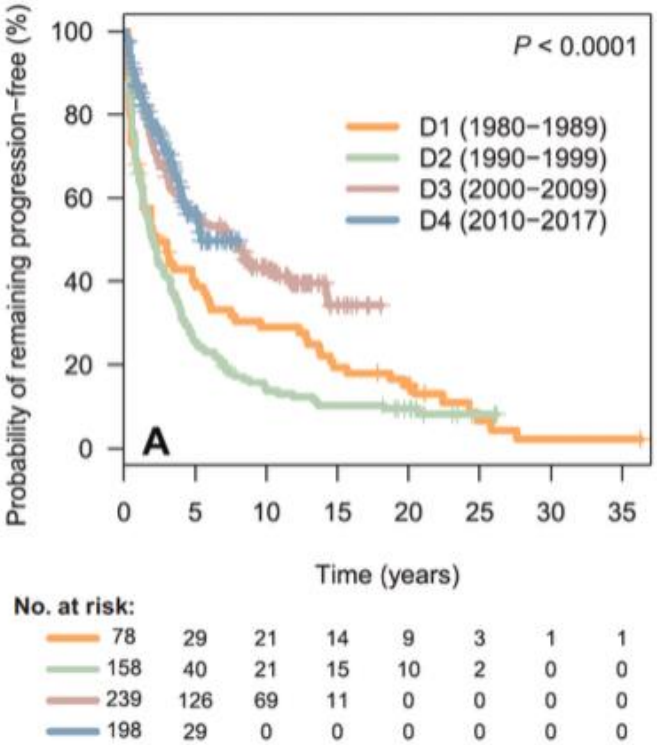
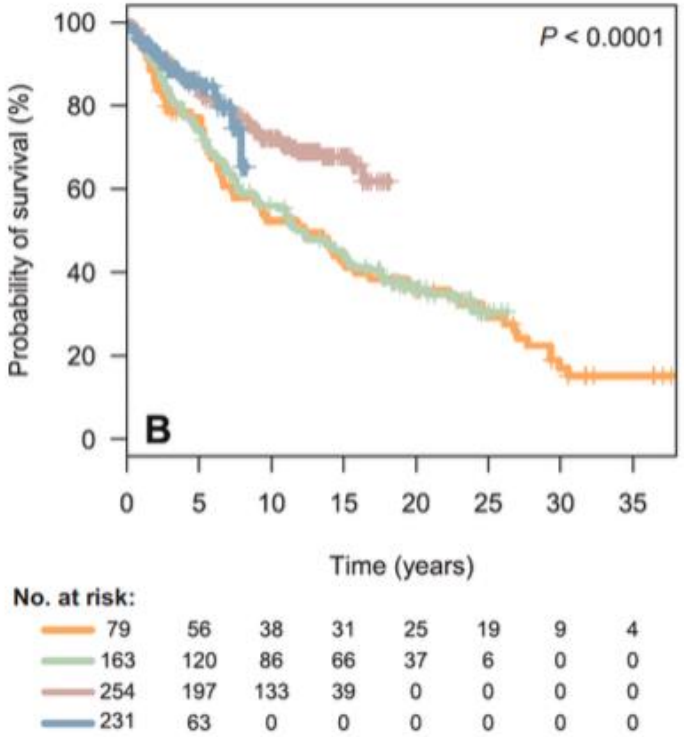
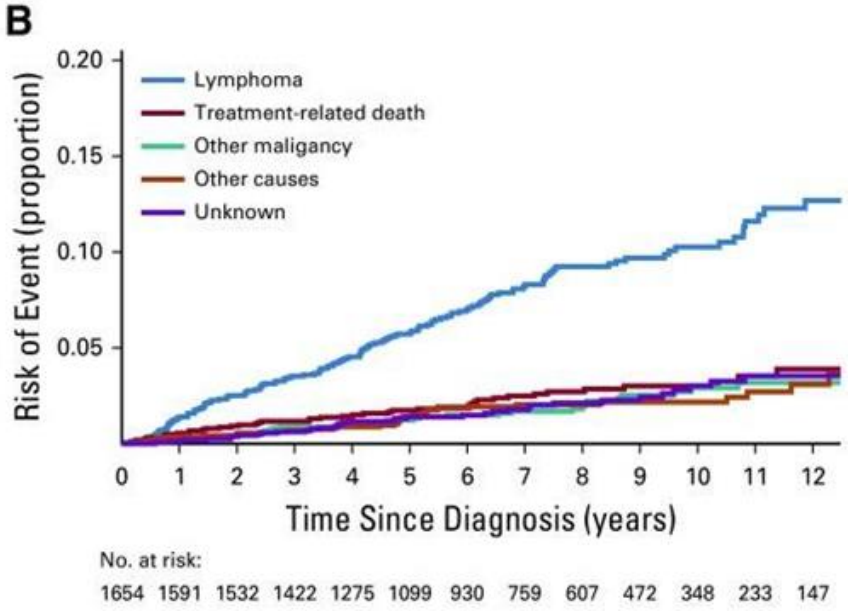
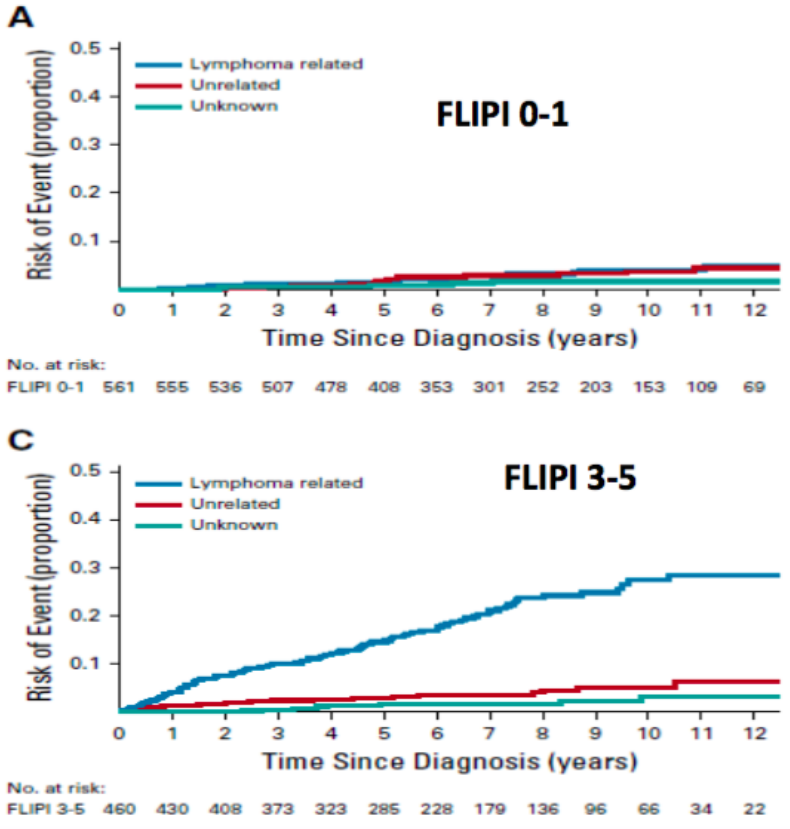
Outcomes in Follicular Lymphomas Over Time





Cause of Death in the first Decade of the Rituximab Era

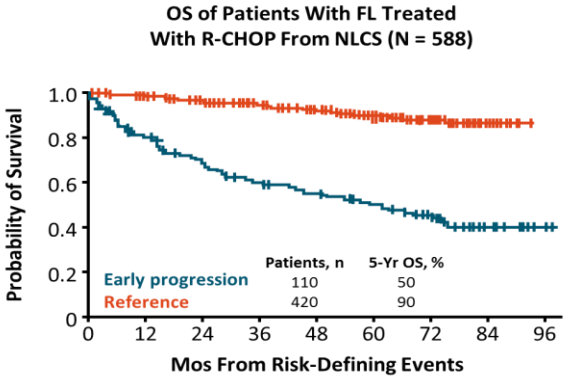


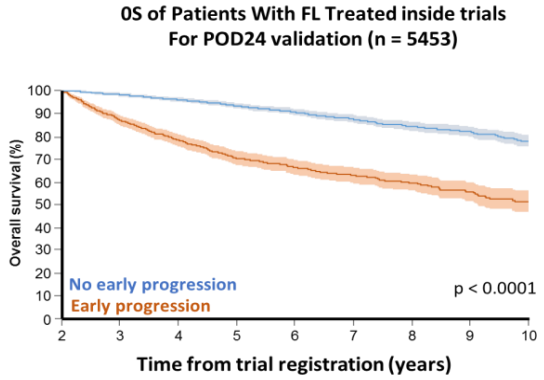


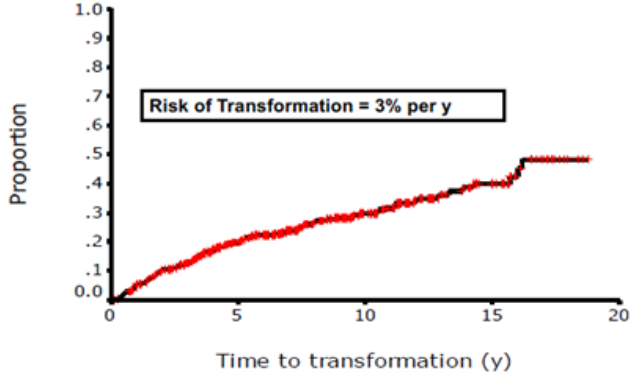
Sarkozy C. et al, J Clin Oncol. 2019;37:144-52.

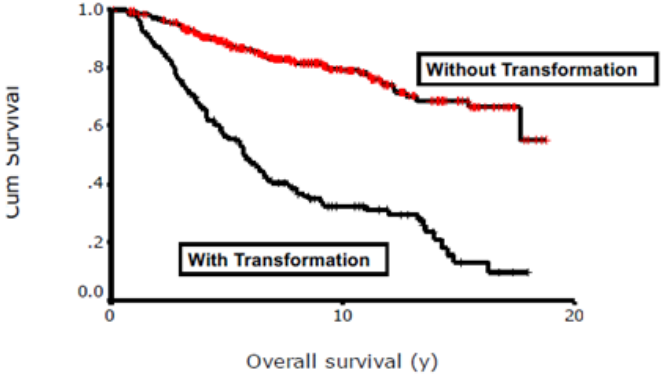
Early Progression and Transformation Predict Poor Prognosis

Survival With POD24





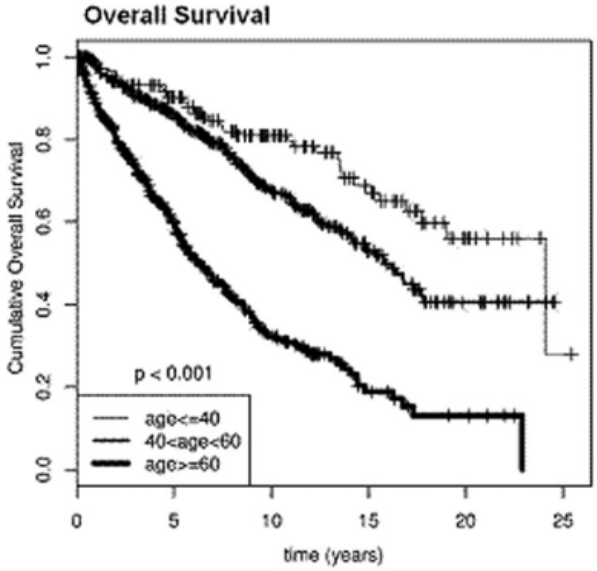


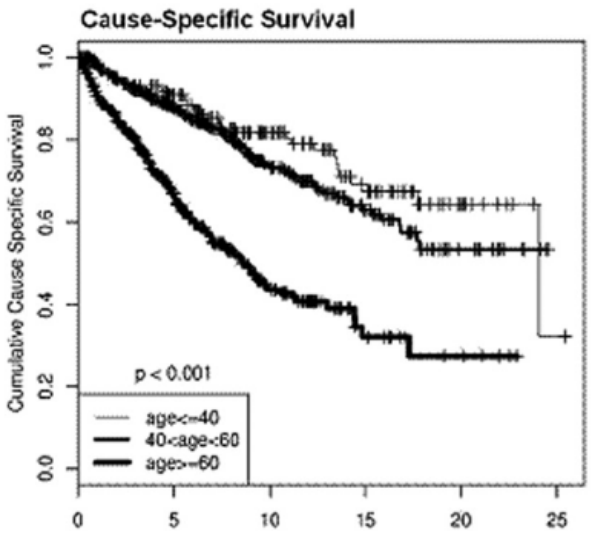


Survival With Transformation

Casulo. JCO. 2015;33:2516. Casulo C. ASH 2017 (abs#412). Maurer MJ et al. Am J Hematol. 2016;91:1096-101. Al-Tourah A, et al JCO 2008.

Impact of Age in Clinical Risk score





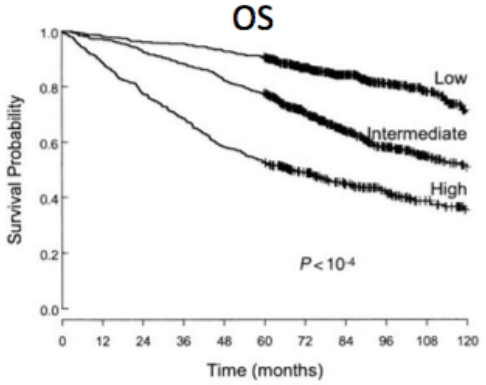
Age (yrs)	n	Overall Survival			Cause-Specific Survival		
		median	10-yr	p-value (<40 vs. 41-59)	median	10-yr	p-value (<40 vs. 41-59)
<=40	153 (15%)	24 yrs	81%	0.01	24 yrs	82%	0.16
41-59	423 (42%)	16 yrs	68%		not reached	74%	
>=60	423 (42%)	6 yrs	32%		9 yrs	44%	

Lobetti-Bodoni C et al. Blood (2011) 118 (21): 1593

Follicular Lymphoma International Prognostic Index

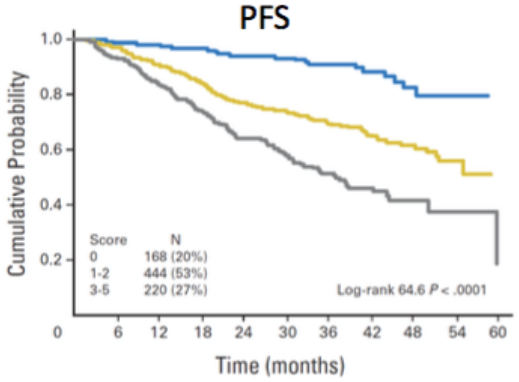
FLIPI Criteria:
LN sites (≤ 4 vs > 4)
LDH (≤ vs > ULN)
Age (≤ 60 vs > 60 yrs)
Ann Arbor stage (I/II vs III/IV)
Hb (≥ 12 vs < 12 g/dL)

FLIPI Risk Group	No. Risk Factors	5-Yr OS,* %	10-Yr OS,* %
Low	0-1	91	71
Intermediate	2	78	51
High	≥ 3	53	36



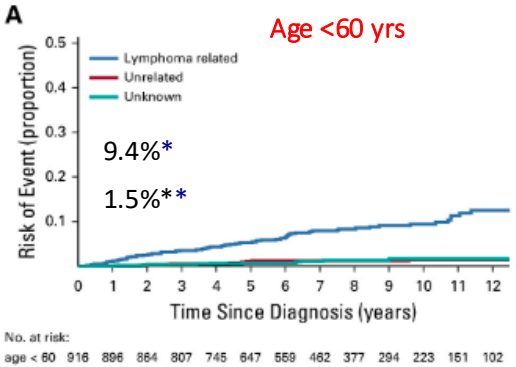
FLIPI-2 Criteria:
Age (≤ 60 vs > 60 years)
Hb (≥ 12 vs < 12 g/dL)
β_2M (≤ vs > ULN)
BM involvement (Y vs N)
> 6 cm dm of LN (Y vs N)

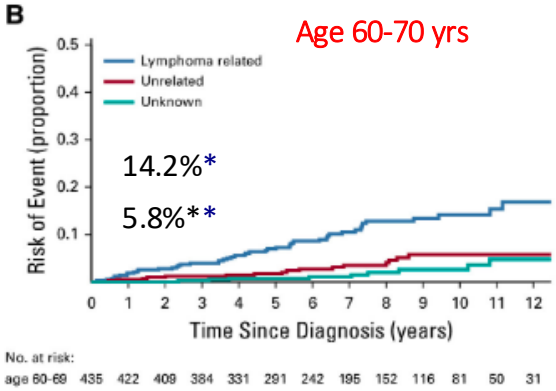
FLIPI-2 Risk Group	No. Risk Factors	3-Yr PFS,* %	5-Yr PFS,* %
Low	0	91	80
Intermediate	1-2	69	51
High	3-5	51	19

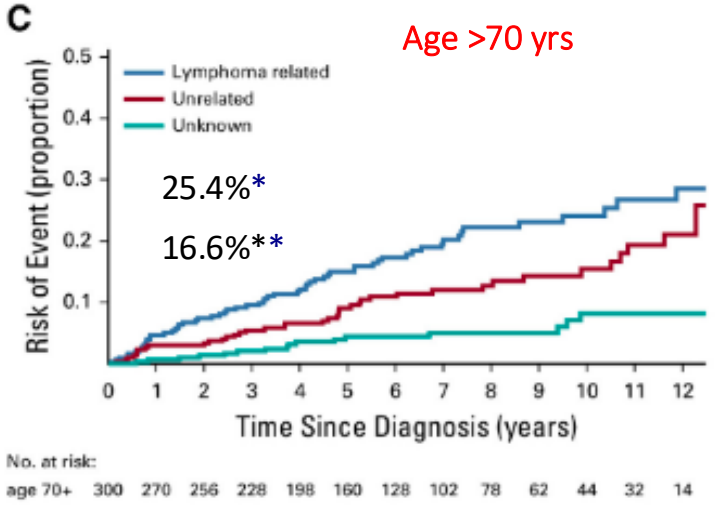


Solal-Celigny P et al. Blood. 2004;104(5):1258-1265 Federico M et al. J Clin Oncol. 2009;27(27):4555-62

Cause of Death in the first Decade of the Rituximab Era







***10-yrs cumulative incidence of lymphoma-related mortality**

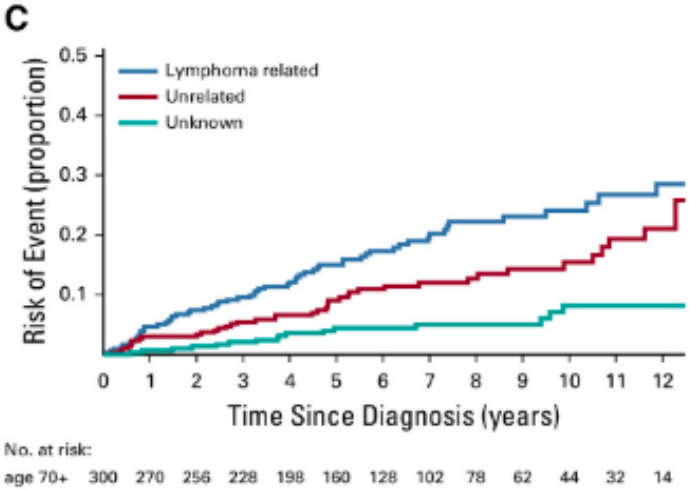
****10-yrs cumulative incidence of non lymphoma-related mortality**

Sarkozy C. et al, J Clin Oncol. 2019;37:144-52.

Impact of Age in Clinical Risk score

lymphoma-related mortality was the major COD in all age groups, even for patients older than age 70 years.

Deaths related to treatment seem to also be a significant burden and new, less-toxic treatment options need to be investigated.



Treatment Related Mortality

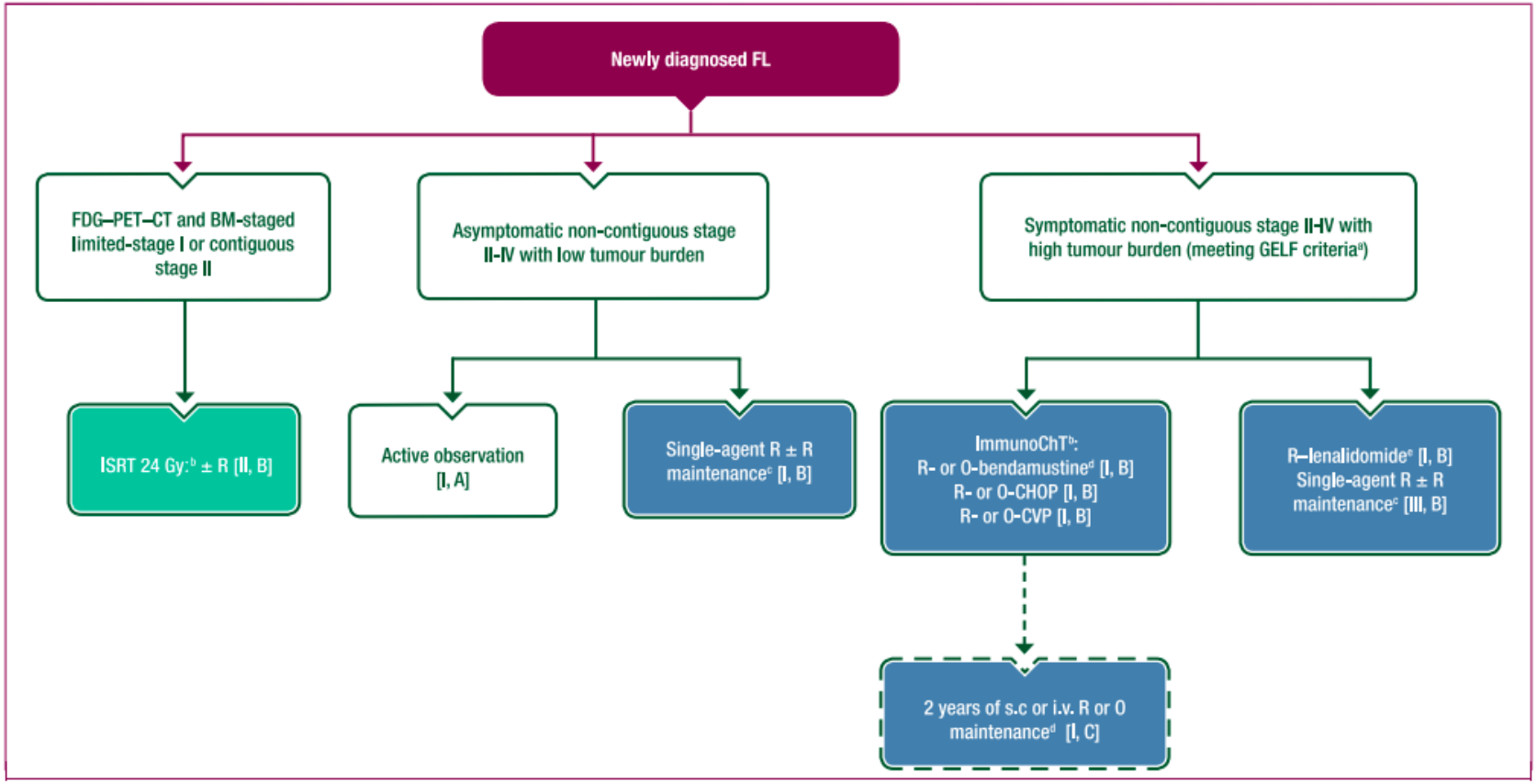
20 (48%) infection

12 (29%) MDS/AML

6 (14%) cardiotoxicity 4 (9%)

other

ESMO Clinical Practice Guideline for Follicular Lymphoma 2025



ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. July 2025

Follicular Lymphoma Treatment Initiation

Stage I/II

ISRT 24-30 Gy
+/- rituximab
[II, B]

In selected cases:
Watch-and-wait
Rituximab monotherapy
INRT 2x2 Gy
[III, B]

≈20%

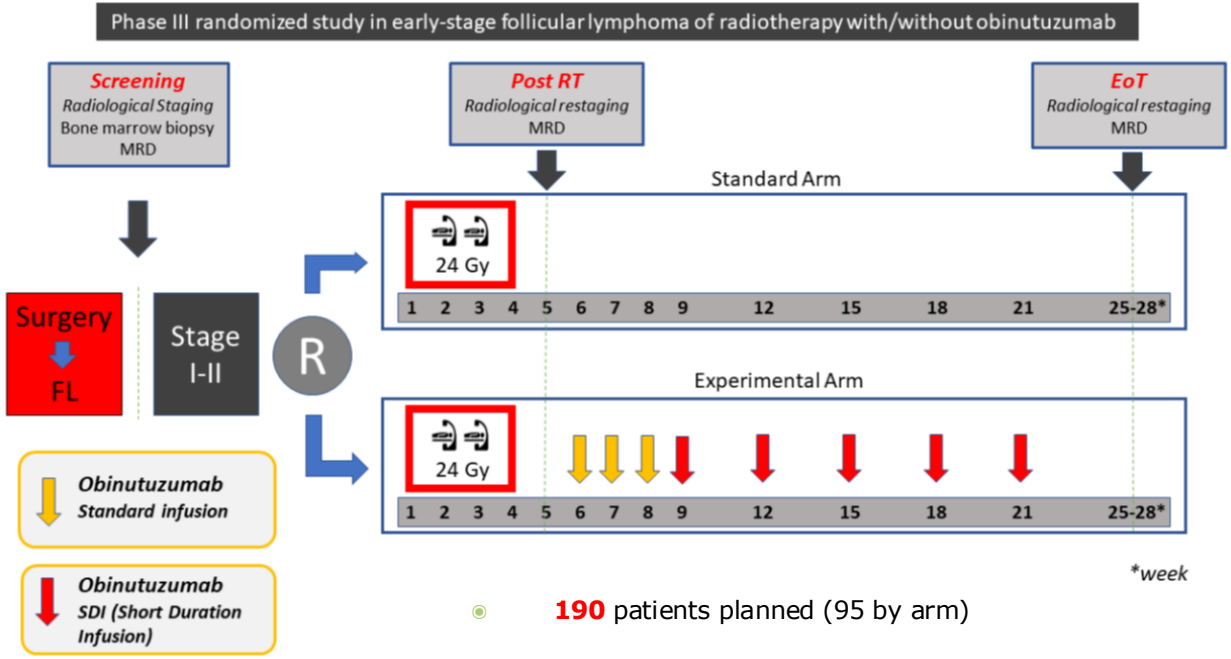
- **Local radiotherapy (24 Gy)**: complete and long-lasting remission in 40–50% of patients
- OS curve: possible plateau (potential for a cure)
- +/- Rituximab (positive results but no evidence from randomized trials –only retrospective or phase II studies)

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020:32;298-308.

Speaker's personale elaboration ESMO Guidelines

FIL-GAZEBO in Early Stage FL

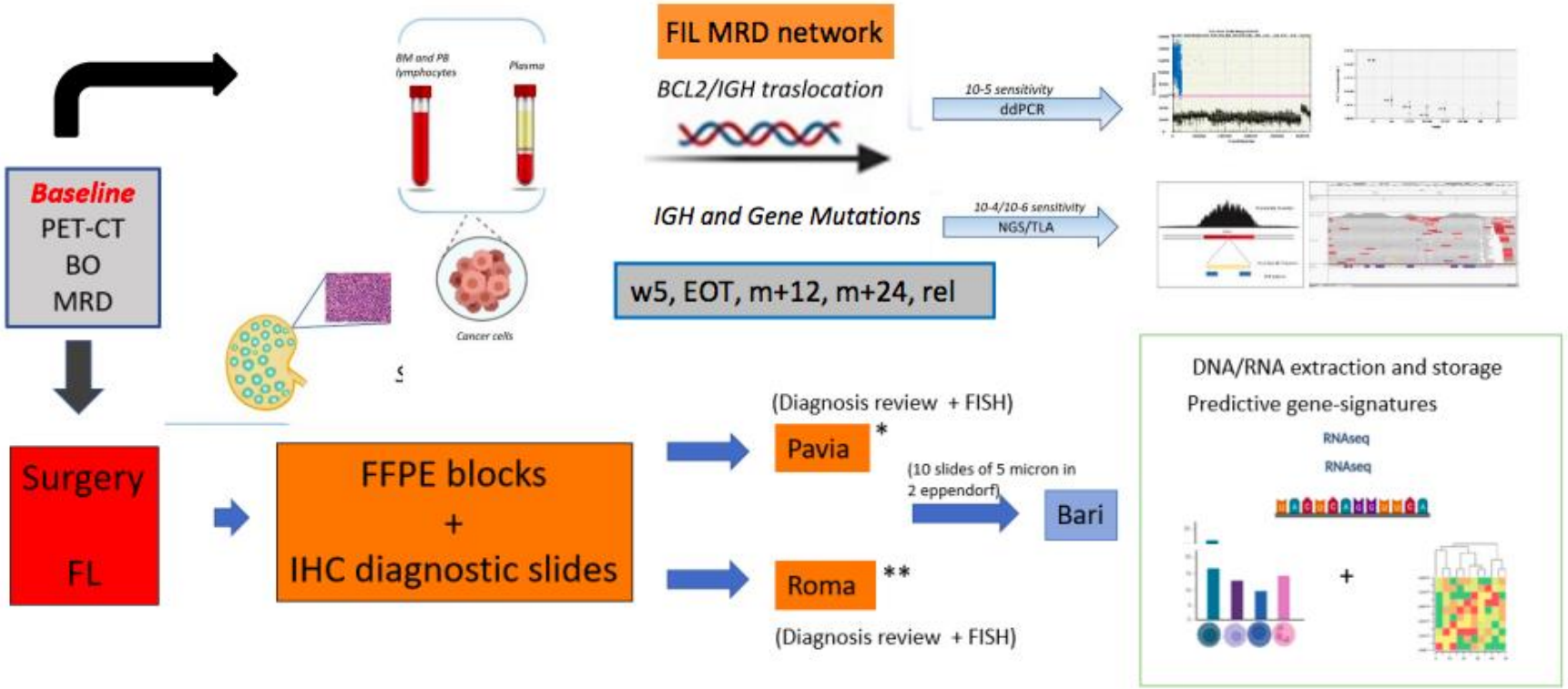
An open-label, randomized phase III trial comparing local radiotherapy alone or combined with Obinutuzumab in early stage Follicular Lymphoma: the **GAZEBO** Trial from the Fondazione Italiana Linfomi



- **190** patients planned (95 by arm)

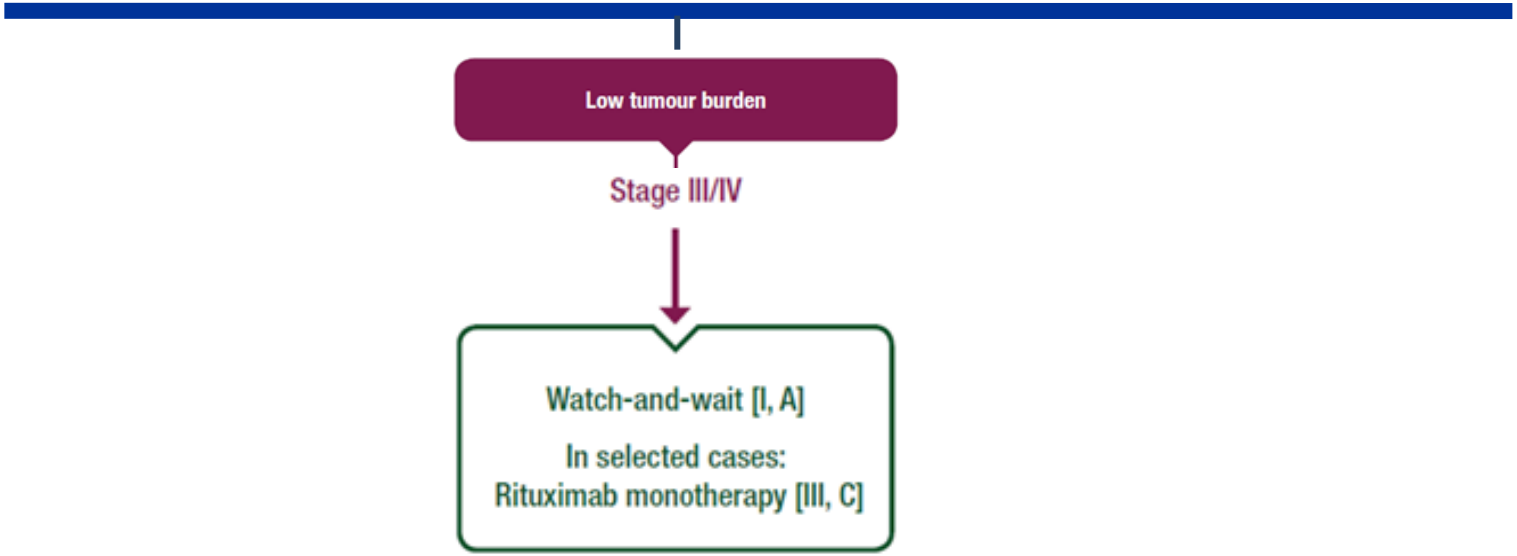
PI: A. Pulsoni, A. Pilippi

BIO-GAZEBO: Explorative Biological Studies



PI: A. Pulsoni, A. Pilippi

Follicular Lymphoma Treatment Initiation



≈35%

Speaker's personale elaboration ESMO Guidelines

Key Studies for Low Tumor Burden FL

- **Ardeshna Study:** In asymptomatic, advanced stage FL, rituximab therapy improves PFS but not OS compared with watchful waiting[1]

- **RESORT:** In patients with low tumor burden FL, maintenance rituximab improves PFS but not OS compared with no maintenance[2]

- **SAKK 35/98:** In patients with low tumor burden FL, short-duration maintenance rituximab improves EFS compared with no maintenance[3]

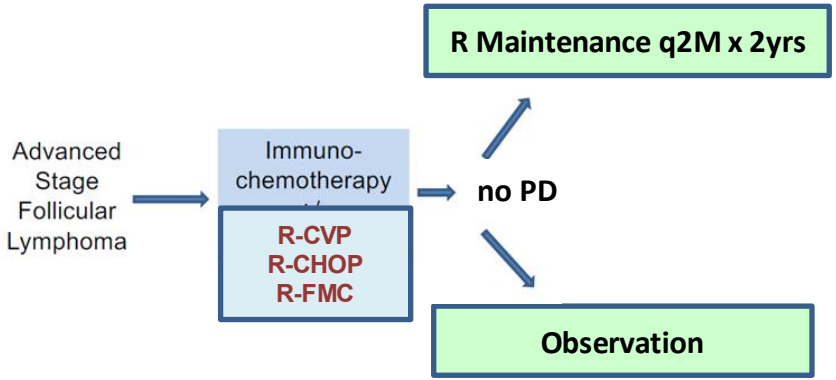
1. Ardeshna. Lancet Oncol. 2014;15:424. 2. Kahl. JCO. 2014;32:3096. 3. Martinelli. JCO. 2010;28:4480.

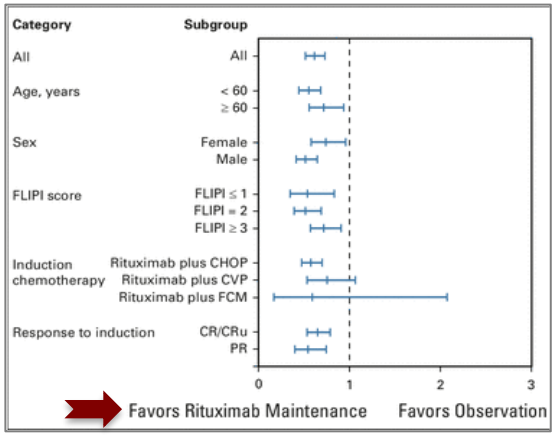
Treatment Initiation for High Tumor Burden Follicular Lymphoma

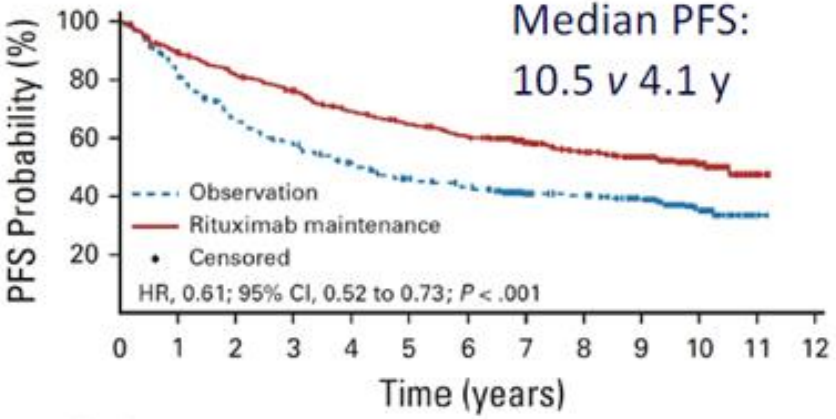
≈45%

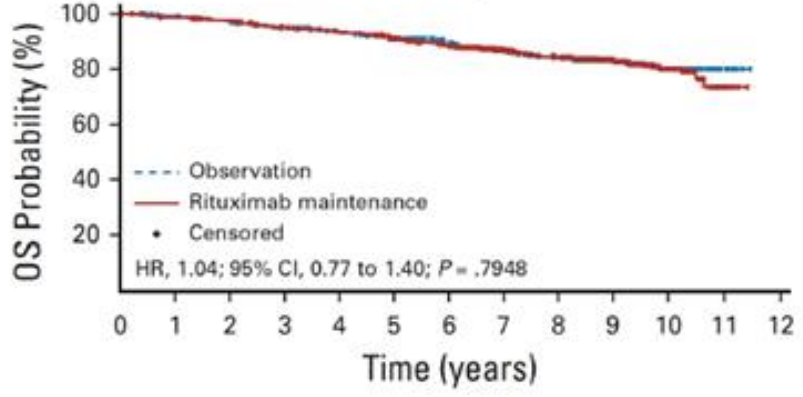
Speaker's personale elaboration ESMO Guidelines

PRIMA Trial: R-Maintenance after R-Chemotherapy Induction









Salles G. et al, Lancet. 2011 Apr 2;377(9772):1154. Bachy E et al, JCO 2019;37(31):2815-282

GALLIUM Trial: R-Chemio vs G-Chemio in Untreated FL

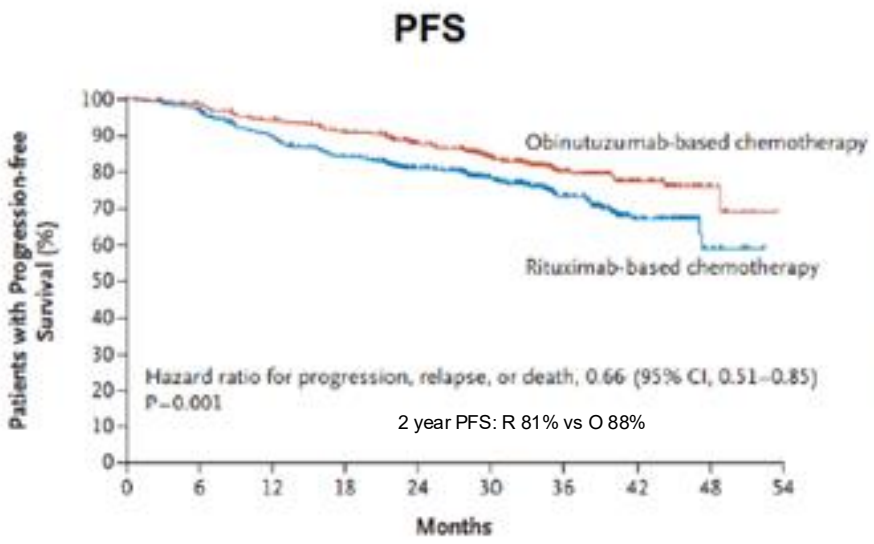
Table 1. Baseline Patient Demographics and Disease Characteristics by Treatment Arm and by Chemotherapy Regimen (follicular lymphoma intention-to-treat population)

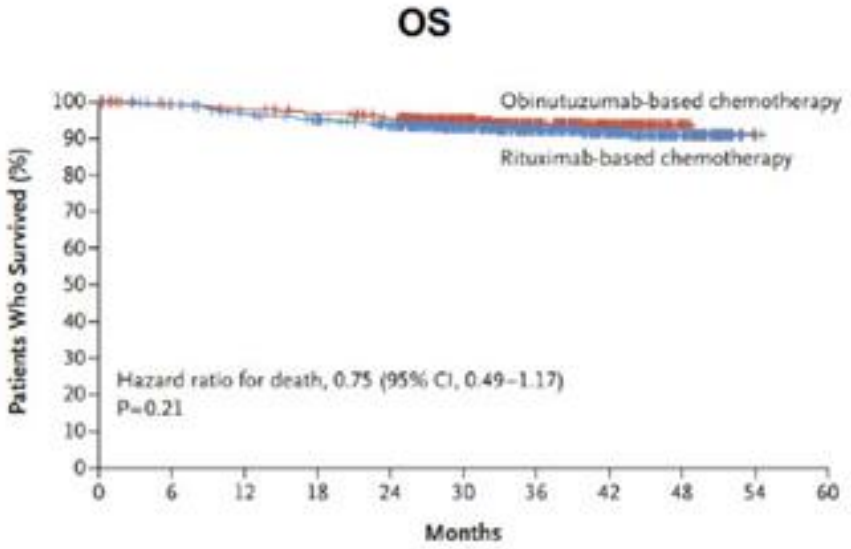
Characteristic	Obinutuzumab Plus Chemotherapy (n = 601)	Rituximab Plus Chemotherapy (n = 601)	Bendamustine (n = 686)	CHOP (n = 399)	CVP (n = 117)
Age, years	60 (26-88)	58 (23-85)	60 (23-88)	57 (31-85)	59 (32-85)
Age ≥ 70	97 (16)	106 (18)	122 (18)	56 (14)	25 (21)
Age ≥ 80	11 (2)	19 (3)	23 (3)	3 (1)	4 (3)
Male	283 (47)	280 (47)	332 (48)	177 (44)	54 (46)
Ann Arbor stage at diagnosis, patients with data*					
I and II†	51 of 598 (9)	52 of 597 (9)	57 of 680 (8)	31 of 399 (8)	15 of 116 (13)
III and IV	547 of 598 (91)	545 of 597 (91)	623 of 680 (92)	368 of 399 (92)	101 of 116 (87)
FLIPI					
Low (0-1)	127 (21)	125 (21)	149 (22)	75 (19)	28 (24)
Intermediate (2)	225 (37)	223 (37)	263 (38)	137 (34)	48 (41)
High (≥ 3)	249 (41)	253 (42)	274 (40)	187 (47)	41 (35)
Bone marrow involvement, patients with data	318 of 592 (54)	295 of 598 (49)	354 of 676 (52)	197 of 397 (50)	62 of 117 (53)
Extranodal involvement‡	392 (65)	396 (66)	460 (67)	251 (63)	77 (66)
Bulky disease (≥ 7 cm), patients with data	255 of 600 (43)	271 of 600 (45)	274 of 686 (40)	206 of 398 (52)	46 of 116 (40)
Time from initial diagnosis to random assignment, months	1.5 (0.1-121.6)	1.4 (0.0-168.1)	1.5 (0.1-103.5)	1.4 (0-168.1)	1.2 (0.2-86.4)
Charlson Comorbidity Index score ≥ 1§	114 (19)	140 (23)	163 (24)	69 (17)	22 (19)

Marcus et al, NEJM 2017,377:1331.

GALLIUM Trial: R-Chemio vs G-Chemio in Untreated FL

Efficacy Analysis





- **Median follow-up: 34.5 months**

Most benefit in intermediate-high risk FLIPI

Marcus et al, NEJM 2017,377:1331.

GALLIUM Trial: R-Chemio vs G-Chemio in Untreated FL

Safety Analysis

Table 4. Summary of Adverse Events in the FL Safety Population by Treatment Arm and Chemotherapy Regimen

Patients Reporting ≥ 1 AE	G Plus Bendamustine (n = 338)	R Plus Bendamustine (n = 338)	G Plus CHOP (n = 193)	R Plus CHOP (n = 203)	G Plus CVP (n = 61)	R Plus CVP (n = 56)	G Plus Chemotherapy (n = 595)	R Plus Chemotherapy (n = 597)
AEs (any grade)	338 (100)	331 (98)	191 (99)	201 (99)	61 (100)	56 (100)	593 (100)	585 (98)
Grade 3-5 AEs	233 (69)	228 (67)	171 (89)	151 (74)	42 (69)	30 (54)	449 (75)	409 (69)
Neutropenia	100 (30)	102 (30)	137 (71)	111 (55)	28 (46)	13 (23)	265 (45)	226 (38)
Leucopenia	11 (3)	15 (4)	39 (20)	34 (17)	1 (2)	1 (2)	51 (9)	50 (8)
Febrile neutropenia	18 (5)	13 (4)	22 (11)	14 (7)	2 (3)	2 (4)	42 (7)	29 (5)
Infusion-related reactions	18 (5)	10 (3)	17 (9)	9 (4)	2 (3)	3 (5)	40 (7)	22 (4)
Pneumonia	23 (7)	17 (5)	5 (3)	8 (4)	0	4 (7)	28 (5)	29 (5)
Thrombocytopenia	20 (6)	11 (3)	15 (8)	5 (2)	1 (2)	0	36 (6)	16 (3)
Anemia	8 (2)	5 (1)	15 (8)	8 (4)	1 (2)	0	24 (4)	13 (2)
Dyspnea	6 (2)	3 (1)	8 (4)	3 (1)	2 (3)	3 (5)	17 (3)	9 (2)
Serious AEs	176 (52)	160 (47)	76 (39)	67 (33)	26 (43)	19 (34)	281 (47)	246 (41)
Deaths*	28 (8)	37 (11)	11 (6)	9 (4)	3 (5)	6 (11)	42 (7)	52 (9)
Fatal AEs	20 (6)	16 (5)	3 (2)	4 (2)	1 (2)	1 (2)	24 (4)	21 (4)
Fatal AEs occurring before start of NACT	16 (5)	14 (4)	3 (2)	4 (2)	1 (2)	1 (2)	20 (3)	19 (3)
AEs causing treatment discontinuation	52 (15)	48 (14)	32 (17)	31 (15)	11 (18)	9 (16)	98 (16)	88 (15)
Selected AE categories of special interest (grade 3-5)								
Neutropenia†	107 (32)	107 (32)	142 (74)	115 (57)	29 (48)	14 (25)	278 (47)	236 (40)
Infections‡	89 (26)	66 (20)	23 (12)	25 (12)	8 (13)	7 (13)	121 (20)	98 (16)
Opportunistic infections, including herpes zoster§	10 (3)	6 (2)	5 (3)	2 (1)	0	0	15 (3)	8 (1)
Second neoplasms‖	21 (6)	12 (4)	7 (4)	7 (3)	1 (2)	2 (4)	29 (5)	21 (4)
Nonmelanoma skin cancer	7 (2)	3 (1)	0	0	1 (2)	0	8 (1)	3 (1)
Hematologic tumors¶	3 (1)	0	3 (2)	0	0	0	6 (1)	0
Other solid tumors	11 (3)	9 (3)	4 (2)	7 (3)	0	2 (4)	15 (3)	18 (3)
Cardiac events#	13 (4)	12 (4)	6 (3)	5 (2)	4 (7)	0	23 (4)	17 (3)

Marcus et al, NEJM 2017,377:1331. Hiddemann W et al. J Clin Oncol 2018; 10;36(23):2395-2404

GALLIUM Trial: R-Chemio vs G-Chemio in Untreated FL

Safety Analysis

- 81 deaths during the trial
- 44 due to AE: 24 (4.0%) in the obinutuzumab group and 20 (3.4%) in the rituximab group

- Non relapse-related fatal AE more common among patients received bendamustine (5.6% in the obinutuzumab group and 4.4% in the rituximab group) than CHOP (1.6% and 2.0%) or CVP (1.6% and 1.8%).

- CCI score ≥1, or were ≥ 80 years of age, or ECOG PS 2 are risk factors

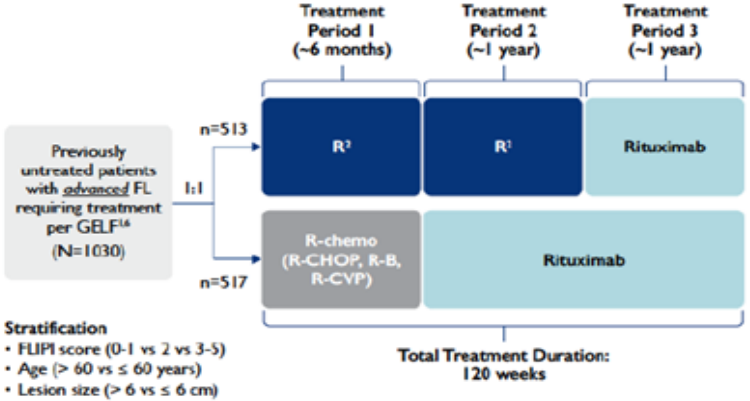
- age ≥ 70 years, fatal events more common with bendamustine (16/119, 13%) than CHOP (1/55, 2%) and CVP (1/25, 4%)

- < 70 years, the incidence was similar (14/557, 3%; 6/341, 2%; 1/92, 1%)

Marcus et al, NEJM 2017,377:1331. Hiddemann W et al. J Clin Oncol 2018; 10;36(23):2395-2404

Lenalidomide Plus Rituximab (R2) Followed by R Maintenance

Figure 1. RELEVANCE Study Design



Stratification
- FLIPI score (0-1 vs 2 vs 3-5)
- Age (> 60 vs ≤ 60 years)
- Lesion size (> 6 vs ≤ 6 cm)

Dosing schedule
- **R:** Lenalidomide 20 mg/d, d2-22/28 until CR/CRu at 6, 9, or 12 cycles, then 10 mg/d (total 18 cycles) and rituximab 375 mg/m/wk c1 and d1 c2-6; continued in responders q8wk for 12 cycles
- **R-chemo:** 3 options (R-CHOP, R-B, R-CVP) plus 2 years rituximab Maintenance (§ Included 72% R-CHOP, 23% R-B, and 5% R-CVP)

Median age 59 yrs (range, 23-89)

≥ 70 yrs 15%

6 years updated

Figure 3: Progression-Free Survival by IRC, FDA Censoring Rules

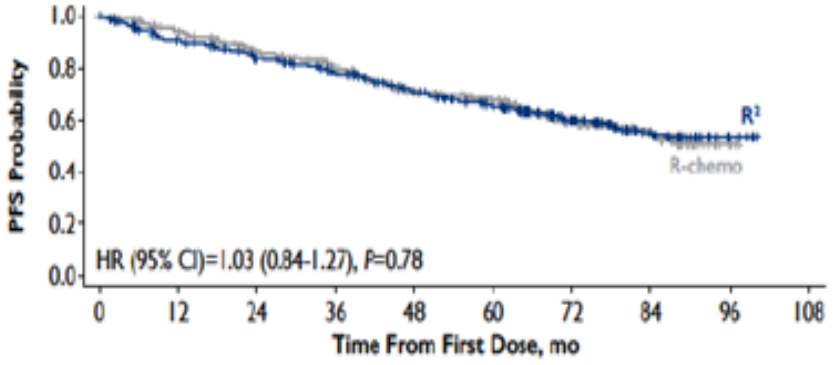
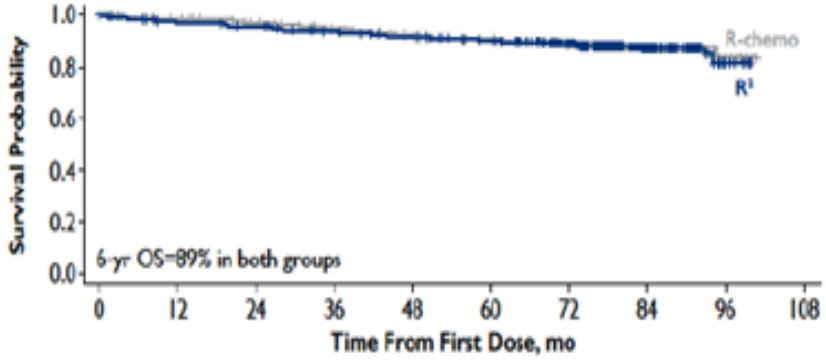
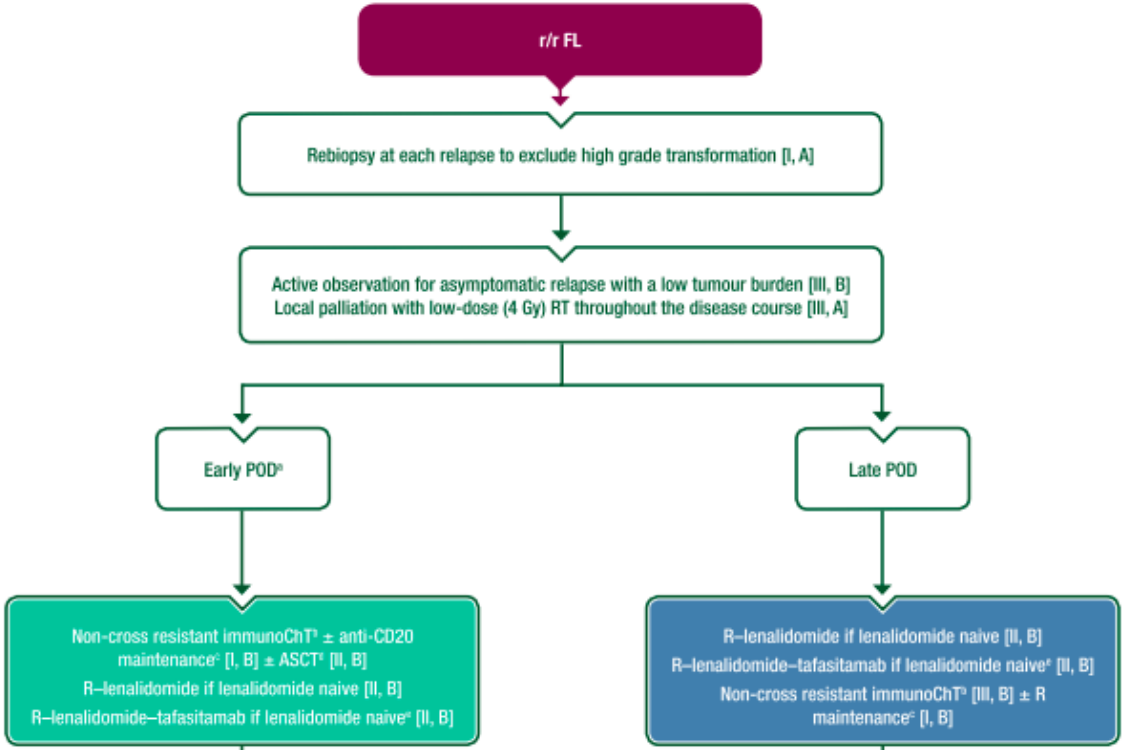


Figure 6: Overall Survival



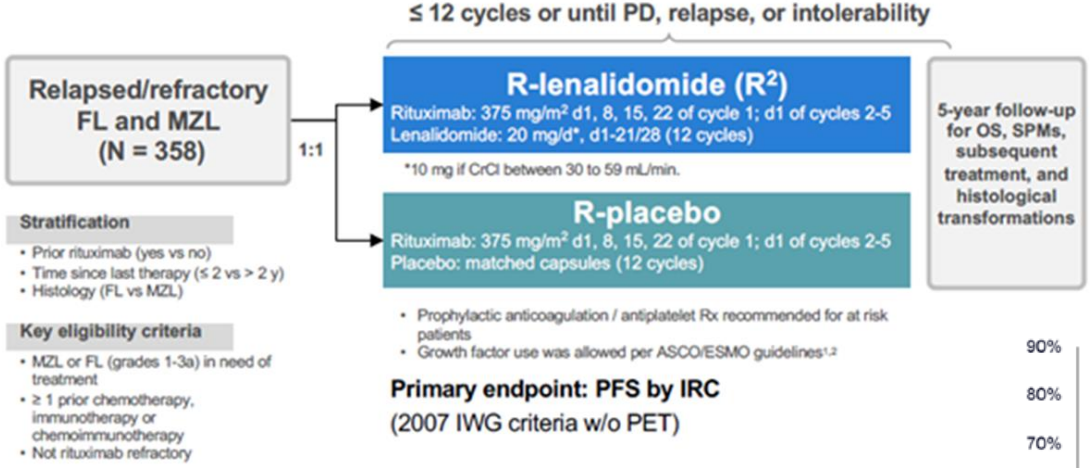
Morschhauser F, et al JCO 2022 1;40(28):3239-3245

ESMO Clinical Practice Guideline for Follicular Lymphoma 2025



ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. July 2025

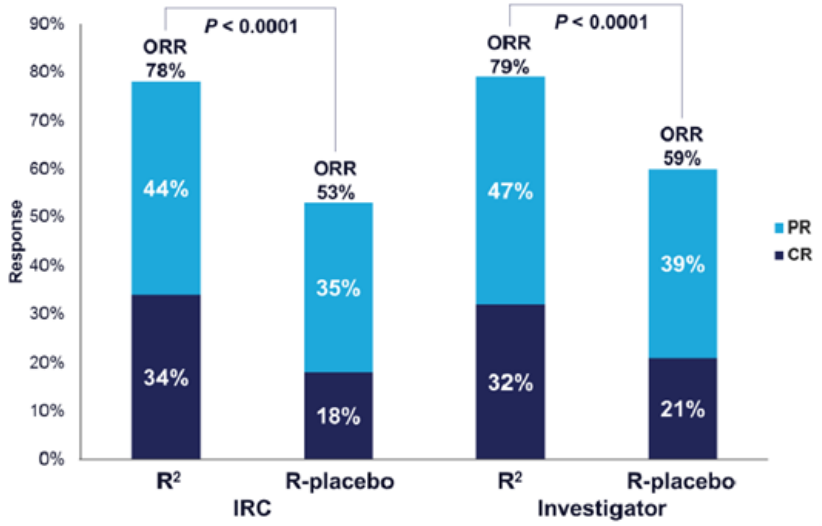
AUGMENT Study: R2 vs Rituximab Monotherapy in R/R iNHL



Median age 63 yrs (range, 26-88)

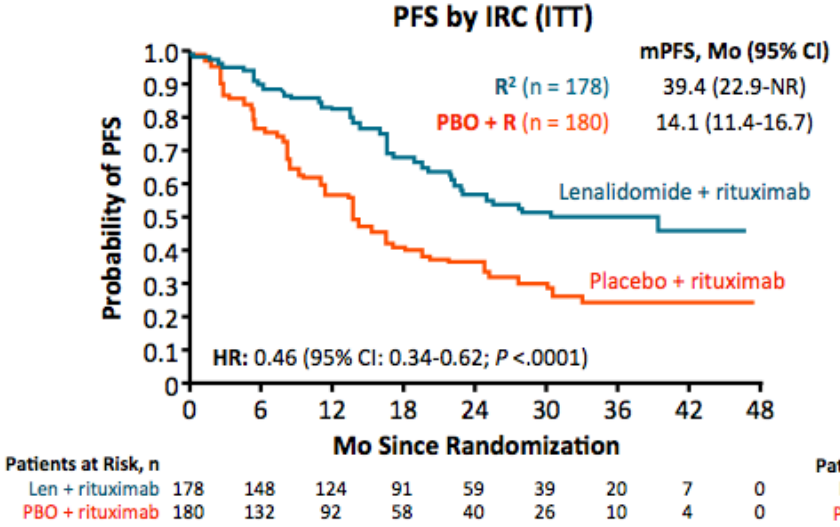
≥ 65 yrs 43%

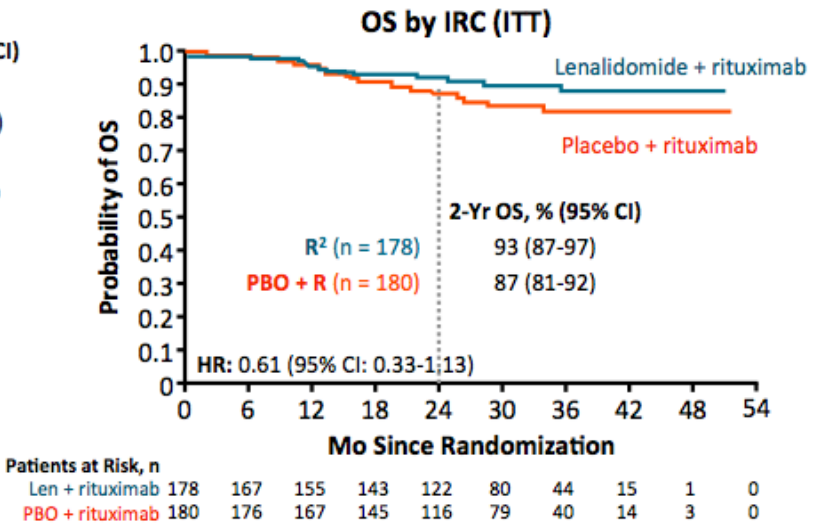
ORR: 78%; CR 34%



Leonard. ASH 2022. Abstract #230. Leonard, et al; *JCO* 2019 37:1188-1199

AUGMENT Study: R2 vs Rituximab Monotherapy in R/R iNHL





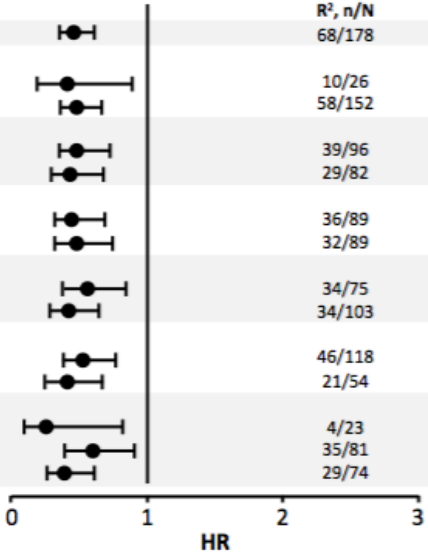
Median DoR: 36.6 mo
Median PFS: 39.4 mo, median OS: NR

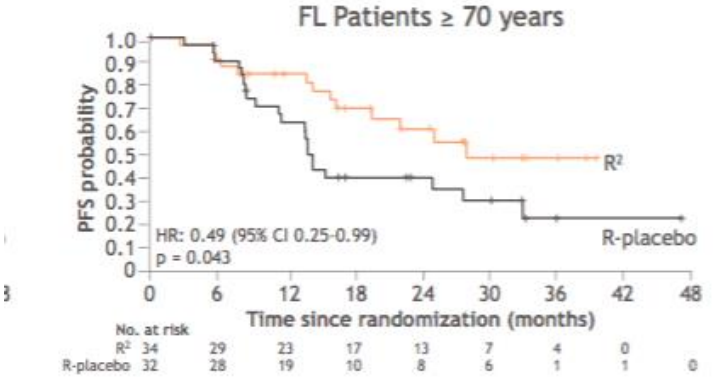
Leonard. ASH 2022. Abstract #230. Leonard, et al; *JCO* 2019 37:1188-1199

AUGMENT Study: R2 vs Rituximab Monotherapy in R/R iNHL

IRC-Assessed PFS by Subgroup (ITT)

Subgroup	R², n/N	R-Placebo, n/N	HR (95% CI)
Overall	68/178	115/180	0.46 (0.34-0.62)
Rituximab naive			
Yes	10/26	17/30	0.40 (0.18-0.89)
No	58/152	98/150	0.47 (0.34-0.66)
Age			
< 65 yrs	39/96	66/107	0.49 (0.33-0.73)
≥ 65 yrs	29/82	49/73	0.43 (0.27-0.68)
Yrs since last antilymphoma therapy			
≤ 2	36/89	62/92	0.45 (0.30-0.69)
> 2	32/89	53/88	0.48 (0.31-0.75)
Sex			
Men	34/75	65/97	0.56 (0.37-0.85)
Women	34/103	50/83	0.42 (0.27-0.65)
Race			
White	46/118	73/115	0.53 (0.37-0.77)
Other races	21/54	41/64	0.40 (0.23-0.67)
Region			
United States	4/23	9/17	0.25 (0.08-0.83)
Europe	35/81	54/84	0.60 (0.39-0.91)
Other	29/74	52/79	0.39 (0.25-0.62)

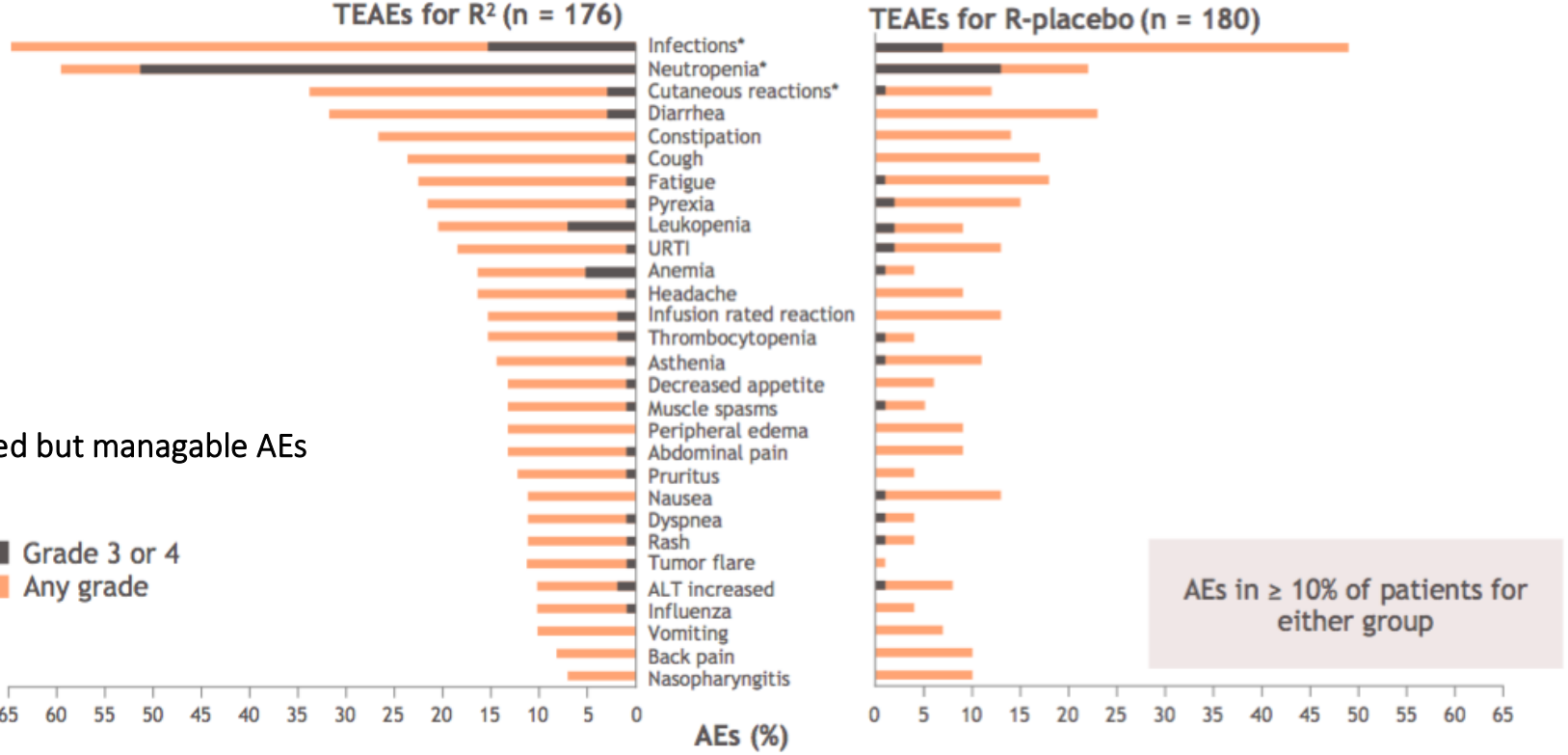




FL ≥ 70 years		Total	
R² (n = 34)	R-Placebo (n = 32)	R² (n = 178)	R-Placebo (n = 180)
28.0 (16.4-NR)	14.3 (11.3-27.7)	39.4 (22.9-NR)	14.1 (11.4-16.7)
0.49 (0.25-0.99)		0.46 (0.34-0.62)	

Trněny M, et al. ASH 2019;abs 347. Leonard. ASH 2022.Leonard, et al; *JCO* 2019 37:1188-1199

AUGMENT Study: TEAEs with R2 vs Rituximab Monotherapy



Increased but managable AEs

Leonard, et al; *JCO* 2019 37:1188-1199

Beyond Second Line

Phase II study Fixed-duration Mosunetuzumab in R/R FL

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

Key inclusion criteria

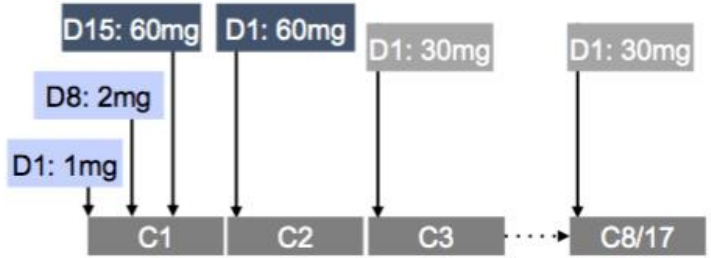
- FL Grade 1–3a
- ECOG PS 0–1
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator

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



Dreyling M, et al. J Clin Oncol 2017; Budde LE, et al. Lancet Oncol 2022;23:1055–1065; Bartlett N.L., et al. Blood (2022) 140 (Supplement 1): 1467–1470.

Baseline Patient Characteristics

All patients (n=90)	
Median age, years (range)	60 (29–90)
Male	55 (61.1)
ECOG PS 0, n (%)	53 (58.9)
Ann Arbor stage III–IV**, n (%)**	69 (76.7)
Median N of prior Tx, n (range)	3 (2–10)
Refractory to last prior therapy, n (%)	62 (68.9)
Double refractory, n (%)	48 (53.3)
POD24, n (%)	47 (52.2)

Prior systemic therapy, n (%)

Anti-CD20 therapy	90 (100)
Alkylator therapy	90 (100)
Prior ASCT	19 (21.1)
PI3K inhibitor	17 (18.9)
IMiD	13 (14.4)
CAR-T	3 (3.3)

Dreyling M, et al. J Clin Oncol 2017; Budde LE, et al. Lancet Oncol 2022;23:1055–1065; Bartlett N.L., et al. Blood (2022) 140 (Supplement 1): 1467–1470.

Pivotal Phase II study: Responses Rate

Efficacy Endpoint (best response)	IRF n (%)
ORR	72 (80%)
CR	54 (60%)
Time to first complete response, months (range)	3.0 (1.4-5.7)
24-month DoR, % (95% CI)	53%

CR rate significantly greater ($p<0.0001$) than 14% historical control CR rate in a similar patient population receiving the pan-class I PI3K inhibitor copanlisib

Median follow-up: 28.3 mo

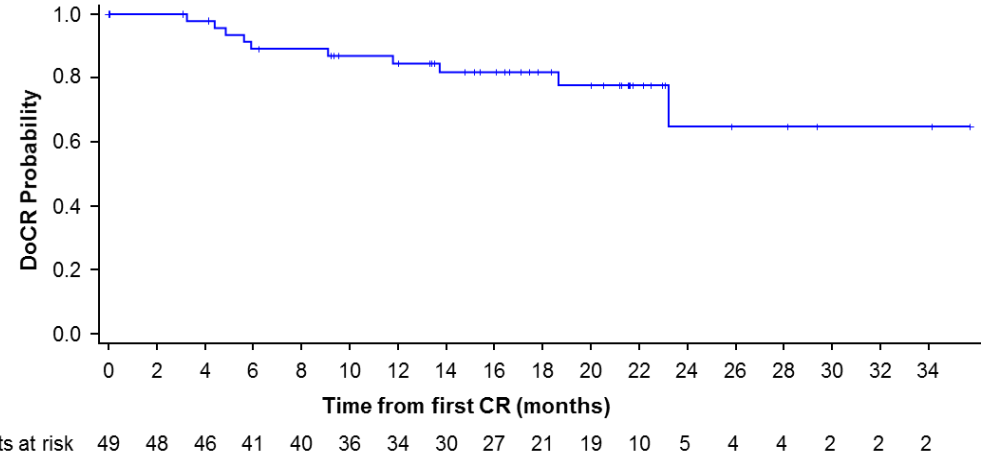
Dreyling M, et al. J Clin Oncol 2017; Budde LE, et al. Lancet Oncol 2022;23:1055–1065; Bartlett N.L., et al. Blood (2022) 140 (Supplement 1): 1467–1470.

Pivotal Phase II study: Responses Rate

Efficacy Endpoint (best response)	IRF n (%)
ORR	72 (80%)
CR	54 (60%)
Time to first complete response, months (range)	3.0 (1.4-5.7)
24-month DoR, % (95% CI)	53%

	n=49
Median, months (95% CI)	**NE** (23.2–NE)
24-month DoCR, % (95% CI)	**65** (39–90)

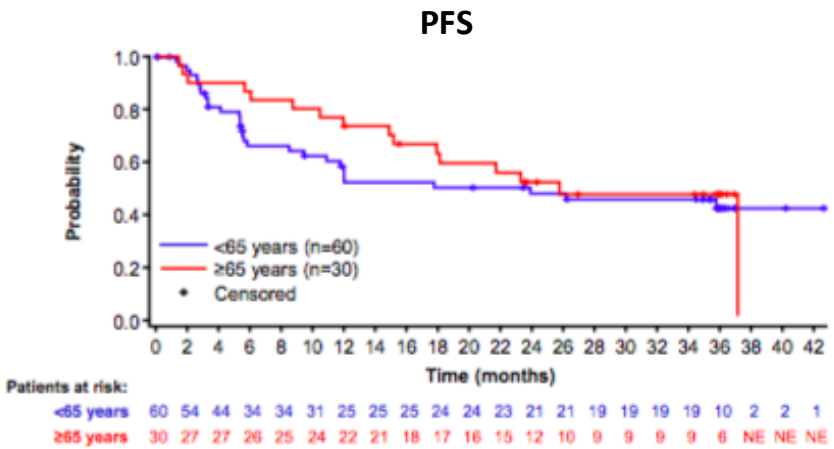
Duration of Response (DoCR)

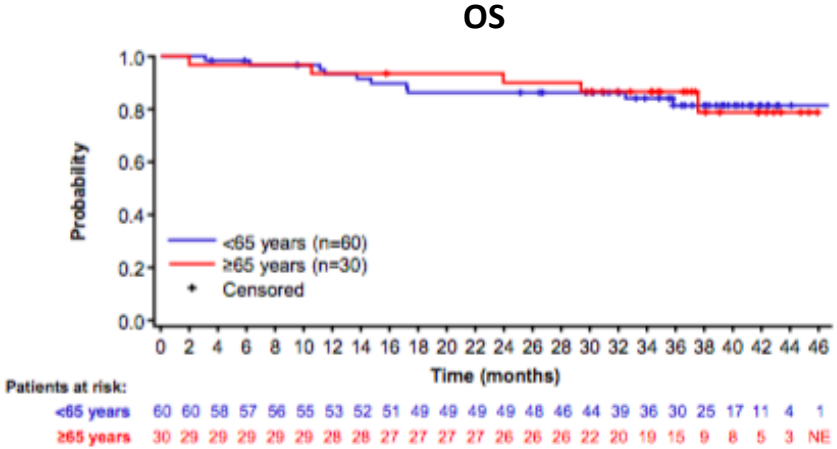


Durable Responses in patients who achieved a CR at EOT

Dreyling M, et al. J Clin Oncol 2017; Budde LE, et al. Lancet Oncol 2022;23:1055–1065; Bartlett N.L., et al. Blood (2022) 140 (Supplement 1): 1467–1470.

Fixed-duration Mosunetuzumab in R/R FL: PFS and OS by Age





	Overall population (N=90)	<65 years (n=60)	≥65 years (n=30)
Median PFS, months (95% CI)	24.0 (12.0–NE)	17.8 (9.4–NE)	25.8 (15.2–NE)
36-month PFS, % (95% CI)	43 (31.8–54.7)	42 (27.3–55.8)	47 (28.1–65.8)

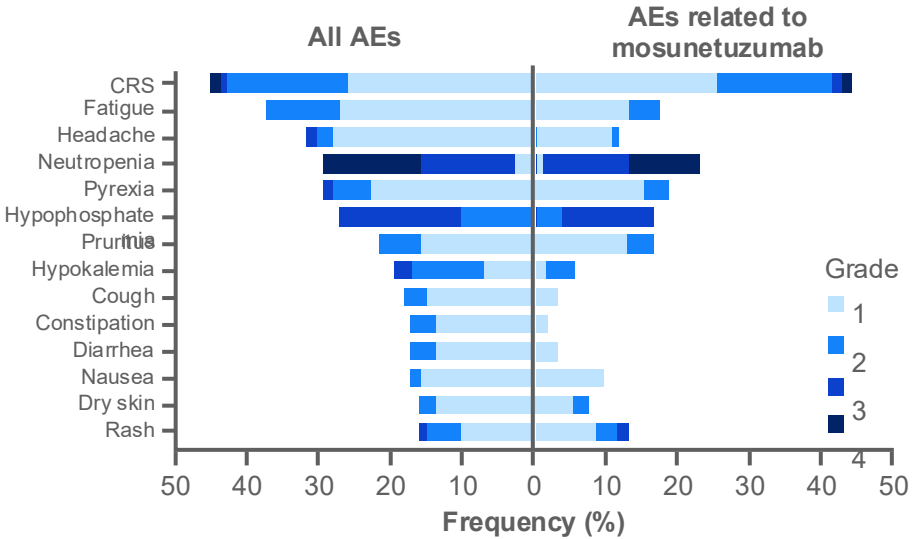
	Overall population (N=90)	<65 years (n=60)	≥65 years (n=30)
Median OS, months (95% CI)	NR (NE)	NR (NE)	NR (NE)
36-month OS, % (95% CI)	83 (74.6–91.2)	81 (70.6–91.9)	86 (74.0–98.8)

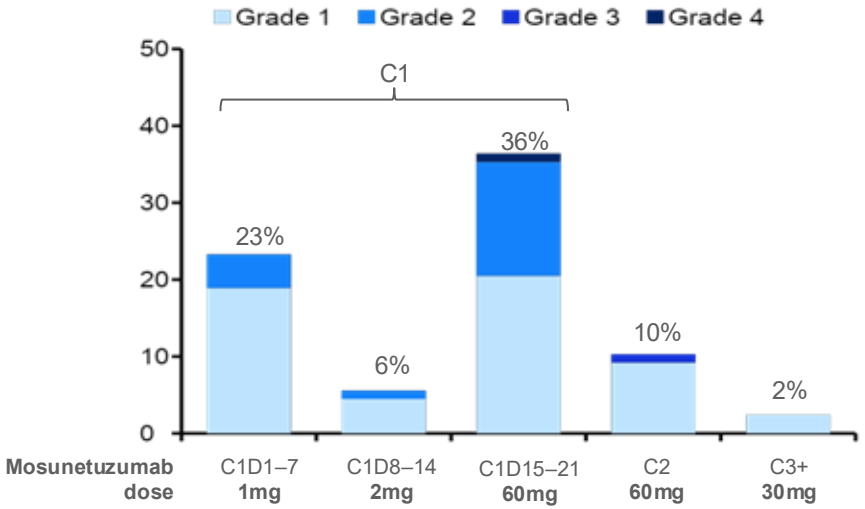
36-month PFS and OS rates in patients ≥65 years were consistent with the overall population

Assouline S et al. EHA 2024, S233

Pivotal Phase II study: Safety Analysis

AEs (≥15%) by grade





No new events were reported with 10 months of additional follow-up

No correlation between occurrence of CRS and tumor response

Dreyling M, et al. J Clin Oncol 2017; Budde LE, et al. Lancet Oncol 2022;23:1055–1065; Bartlett N.L., et al. Blood (2022) 140 (Supplement 1): 1467–1470.

Updated Safety Analysis by Risk Factors and Age

AE	Overall population (N=90)	POD24 status		Line of therapy		Age	
		Non-POD24 (n=43)	POD24 (n=47)	3L therapy (n=35)	4L+ therapy (n=55)	<65 years (n=60)	≥65 years (n=30)
CRS by ASTCT Grade 1 Grade 2 Grade 3 Grade 4	40 (44%) 23 (26%) 15 (17%) 1 (1%) 1 (1%)	16 (37%) 10 (23%) 5 (12%) 1 (2%) 0	24 (51%) 13 (28%) 10 (21%) 0 1 (2%)	14 (40%) 9 (26%) 4 (11%) 0 1 (3%)	26 (47%) 14 (26%) 11 (20%) 1 (2%) 0	31 (52%) 17 (28%) 13 (22%) 0 1 (2%)	9 (30%) 6 (20%) 2 (7%) 1 (3%) 0
Neutropenia	26 (29%)	7 (16%)	19 (40%)	10 (29%)	16 (29%)	19 (32%)	7 (23%)
Serious infections	18 (20%)	5 (12%)	13 (28%)	8 (23%)	10 (18%)	13 (22%)	5 (17%)

Incidence of serious infections in patients ≥65 yrs was consistent with the overall population

Assouline S et al. EHA 2024, S233

BiTe for R/R Follicular Lymphoma

Monotherapy

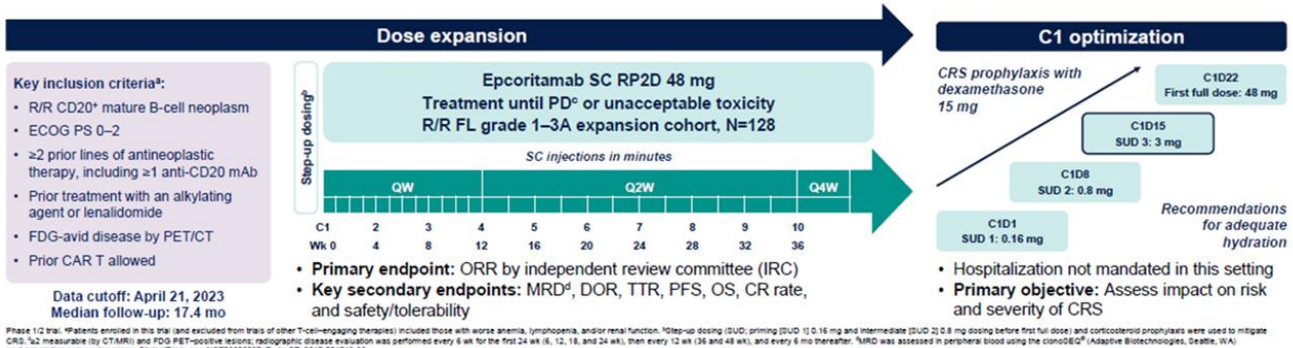
Agent and trial	Phase	Administration	Pts n	POD24 %	Prior tx median	ORR (CR), %	Follow-up median mo	PFS median mo	OS, median mo	CRS-ICANS (any/ gr ≥3), %	Infections gr ≥3, %
Mosunetuzumab (GO29781)[1,2]	II	EV, fixed duration	90	52	3 (2-4)	80 (60)	28.3	24	NR	44/2 5/0	18
Odronextamab (ELM-2)[3,4]	II	EV, Until PD	131	48	3 (2-13)	82 (75)	22.4	20.2	NR	56/4 1/0	32
Epcoritamab[5]	I/II	SC, Until PD	12	NA	4.5 (2.5-8)	90 (50)	13.6	NA	NA	59/0 6/3	NA
Glofitamab[6,7]	I	EV, Fixed duration	53	36	3 (1-12)	81 (70)	NA	NA	NA	66/1 NA	NA

In combination

Agent and trial	Phase	Administration	Pts n	POD24 %	Prior tx median	ORR (CR), %	Follow-up median mo	PFS median mo	OS, median mo	CRS-ICANS (any/ gr ≥3), %	Infections gr ≥3, %
Epco+Lena+Rit[8] (EPCORE NHL-2)	I/II	SC+OS+EV/SC Fixed duration	109	36	2 (1-9)	97 (86)	8.8	6mo: 93%	NA	46/2 2/0	NA
Mosu + Lena[9]	Ib	EV+OS Fixed duration	27	11	1 (1-4)	92 (77)	NA	NA	NA	30/0 NA	NA

1. Budde L.E., et al. Lancet Oncol 2022. 2. Bartlett N.L., et al. Blood 2022- 3 Kim T.M., et al. Blood 2022. 4 Bannerji R et al, Lancet Hematol 2022; 5. Hutchings M. et al, Lancet 2021. 6. Morschhauser F. et al, Blood 2022. 8.Hutchings M. et al, J Clin Oncol 2021. 8. Belada D., et al. J. Clin. Oncol. 2023. 9. Morschhauser F. et al, Blood 2021.

Pivotal EPCORE NHL-1 Study in R/R FL

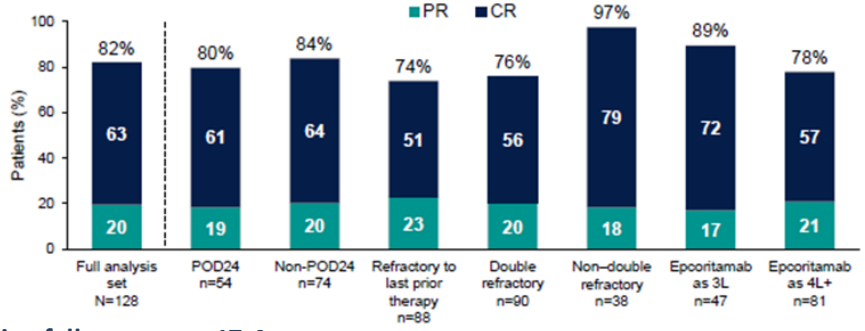


Phase 1/2 trial. [a]Patients enrolled in this trial (and excluded from trials of other T-cell–engaging therapies) included those with worse anemia, lymphopenia, and/or renal function. [b]Step-up dosing (SUD; priming [SUD 1] 0.16 mg and intermediate [SUD 2] 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [c]≥2 measurable (by CT/MRI) and FDG PET–positive lesions; radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [d]MRD was assessed in peripheral blood using the clonoSEQ® (Adaptive Biotechnologies, Seattle, WA) next-generation sequencing assay. ClinicalTrials.gov: NCT03625037; EudraCT: 2017-001749-36.

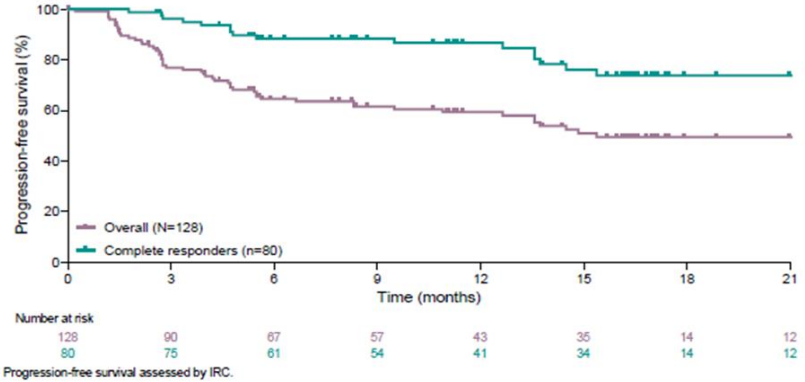
≥4 prior lines, n (%)	40 (31)
POD24,[a] n (%)	54 (42)
Double refractory,[b,c] n (%)	90 (70)
Primary refractory,[b] n (%)	69 (54)
Refractory[b] to last prior systemic therapy, n (%)	88 (69)

Efficacy Results

ORRs and CR Rates Were High Regardless of Subgroup



Complete Response Was Associated With Favorable Long-Term Outcomes

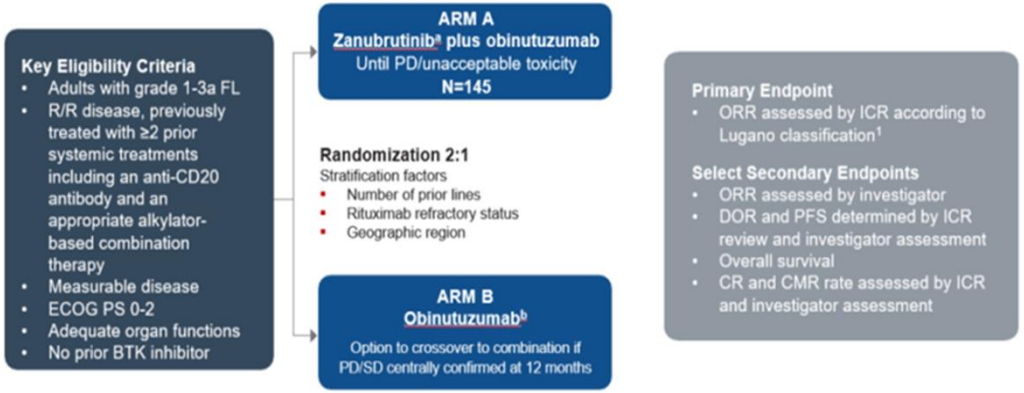


Progression-free survival assessed by IRC.

median follow-up was 17.4 mo

Zanubrutinib Combined With Obinutuzumab in RR FL

*Global, open label, randomized, Phase II study in rituximab-refractory iNHL patients (**ROSEWOOD trial**)*



*Zanubrutinib dosed at 160 mg PO BID. Obinutuzumab dosed at 1000 mg IV on Days 1, 8, and 15 of Cycle 1; Day 1 of cycles 2-6 and then Q8W up to a maximum of 20 doses. †Patients assigned to obinutuzumab with centrally confirmed PD or no response at 12 mo could crossover to receive combination therapy.

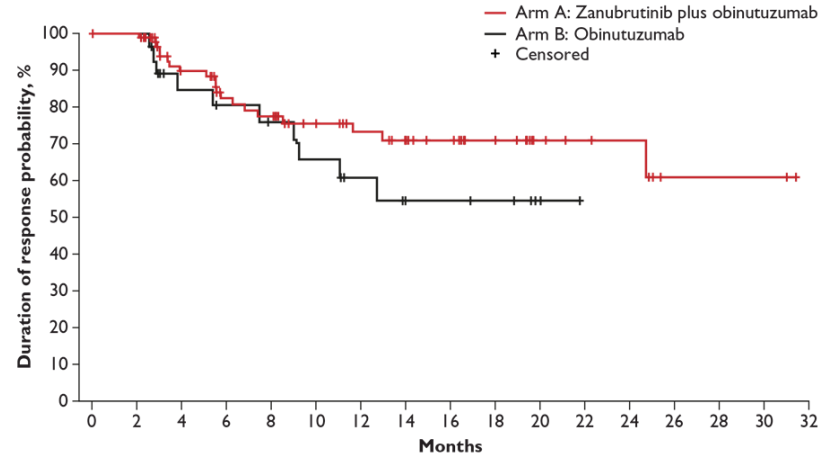
- **Primary endpoint:** ICR-assessed ORR (Lugano classification)
- **Secondary endpoints:** inv-ORR, CR, DoR, PFS, OS, safety

	Zanubrutinib + Obinutuzumab (n = 145)	Obinutuzumab (n = 72)
Median age, yr (range)	63 (31-84)	65.5 (32-88)
Male, %	51.7	45.8
FLIPI, % ▪ Low (0-1) ▪ Intermediate (2) ▪ High (≥3)	 19.3 24.8 53.1	 12.5 33.3 51.4 2.8
ECOG PS ≥1, %	40.7	56.9
Bulky disease	39.3	43.1
Elevated LDH, %	34.5	40.3
Elevated β_2-M, %	44.8	51.4
Median prior lines of therapy, no. (range)	3 (2-11)	3 (2-9)
≥3 lines of therapy, %	28.3	25.0
Refractory to rituximab, %	53.8	50.0
Refractory to recent line of therapy, %	32.4	40.3
PD within 24 months of first-line therapy, %	34.5	41.7

Zinzani P, et al. ASCO 2022. Abstract 7510

ROSEWOOD trial Efficacy in RR FL

Duration of Response

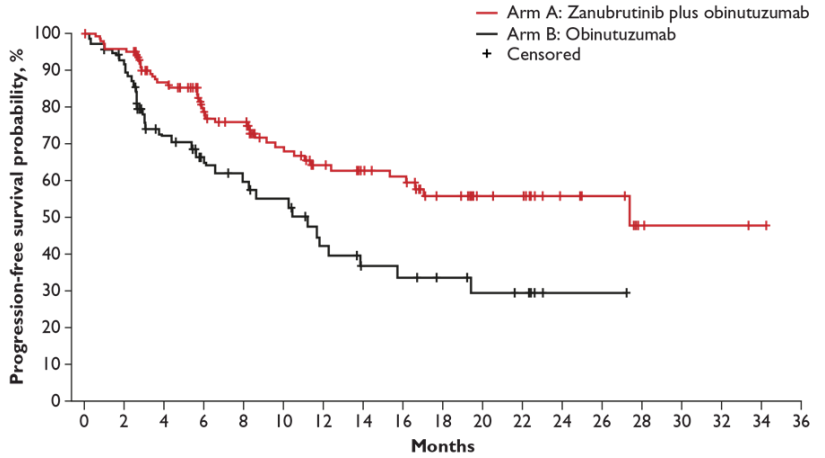


Number of patients at risk:

Arm A	99	92	66	49	46	36	32	27	24	19	10	8	7	2	2	2	0
Arm B	33	28	20	17	15	13	10	6	6	5	2	0					

DOR rate at 18 months:
70.9% Arm A vs 54.6% Arm B

Progression-Free Survival



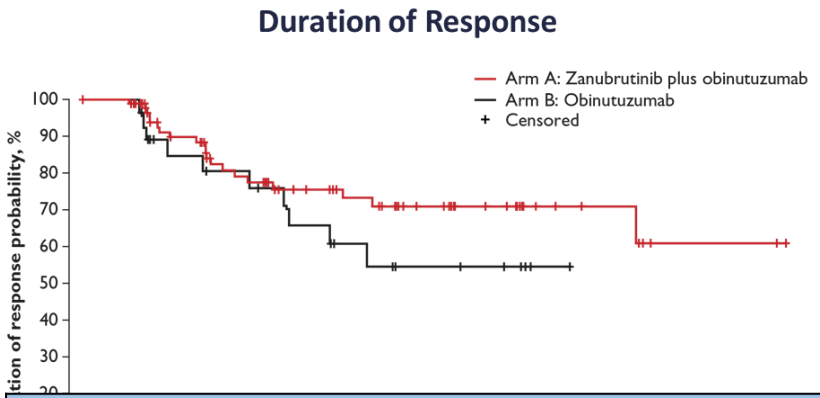
Number of patients at risk:

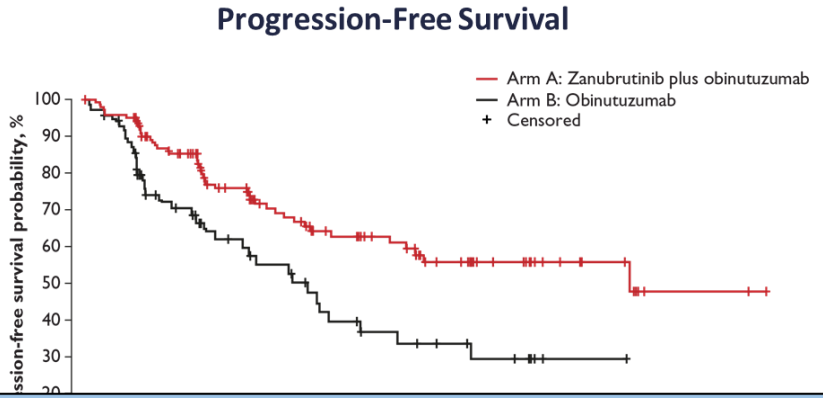
Arm A	145	135	111	83	76	56	46	40	37	27	19	18	10	8	3	2	2	1	0
Arm B	72	63	39	29	26	23	16	12	11	9	7	6	1	1	0				

Median PFS, months (95% CI):
27.4 (16.1, NE) Arm A vs 11.2 (6.5, 15.7) Arm B

Zinzani P, et al. ASCO 2022. Abstract 7510

ROSEWOOD trial Efficacy in RR FL

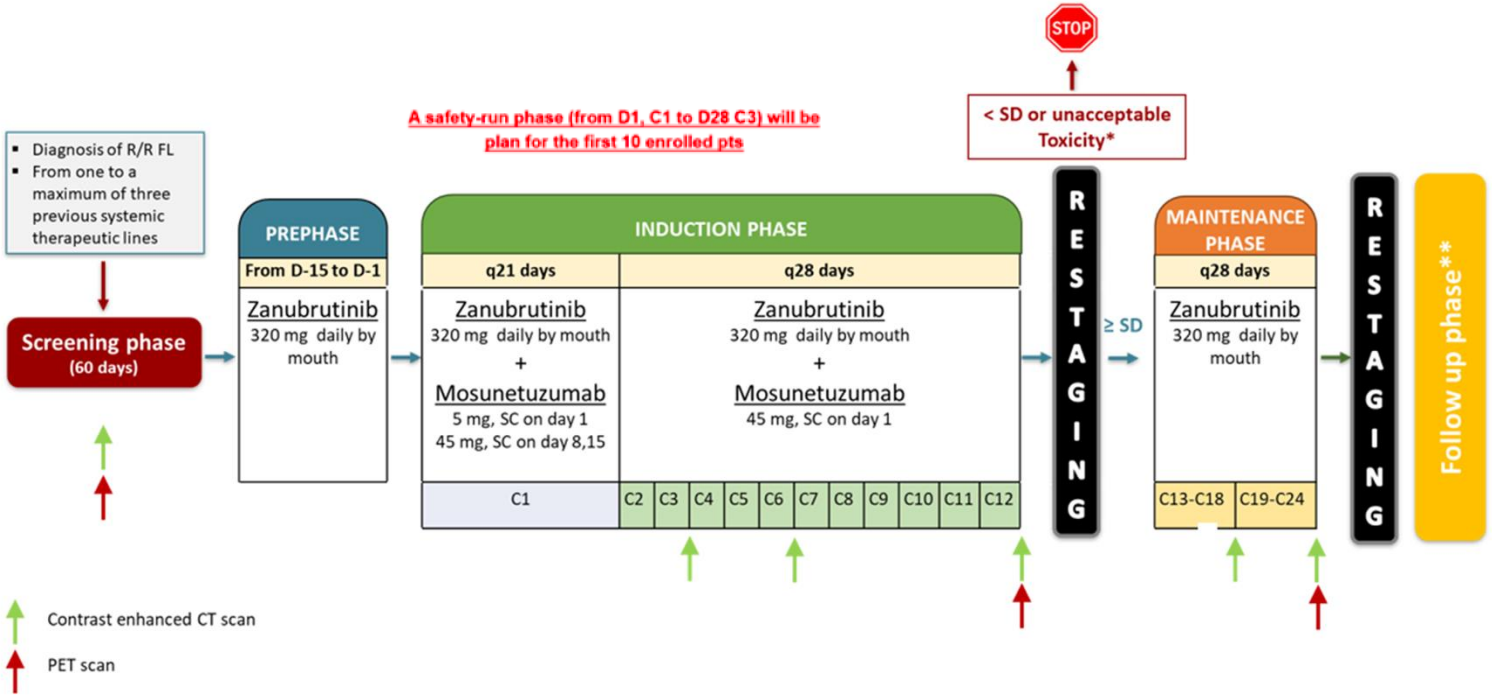




Response by ICR	Zanubrutinib + Obinutuzumab (n = 145)	Obinutuzumab (n = 72)	*P* Value
ORR, %	68.3	45.8	.0017
Best overall response, n (%)			
▪ CR	54 (37.2)	14 (19.4)	.0083
▪ PR	45 (31.0)	19 (26.4)	NR
▪ SD	25 (17.2)	14 (19.4)	NR
▪ PD	13 (9.0)	15 (20.8)	NR

Zinzani P, et al. ASCO 2022. Abstract 7510

MOsunetuzumab and Zanubrutinib in Relapsed/refracTory FL



*Patients with progressive disease at any time during protocol treatment will discontinue it and will be addressed to salvage therapy at clinician discretion.
**Follow-up visits will occur every 12 weeks for the first year, every 24 weeks for the next two years. In the last 2 years visits will occur every 24 weeks to assess disease status, survival status (alive, dead, lost to follow-up), second neoplasia and long-term toxicity.

PI: M. Ladetto, S. Luminari

The "Safety Run In" Phase

n = 10 patients

Safety Report

Induction treatment	Grade 1-2		Grade 3		Grade 4	
Hematological events	**n**	**%**	**n**	**%**	**n**	**%**
Neutropenia	0	-	1	10	0	-
Thrombocytopenia	1	10	0	-	0	-
	Grade 1-2		**Grade 3**		**Grade 4**	
Extrahematological events	**n**	**%**	**N**	**%**	**N**	**%**
Gastrointestinal disorders	2	20	0	-	0	-
General disorders and administration site conditions	5	50	0	-	0	-
Immune system disorders	4	40	0	-	0	-
Injury/poisoning/procedural complications	3	30	0	-	0	-
Investigations	1	10	0	-	0	-
Musculoskeletal and connective tissue disorders	1	10	0	-	0	-
Skin and subcutaneous tissue disorders	4	40	0	-	0	-
Vascular disorders	2	20	0	-	0	-

Preliminary Efficacy Report

	Response after 3 cycles			Total
Response 6cy	CR	PR	SD	
CR	2	4	2	**8**
PR	1	1	-	**2**
Total	**3**	**5**	**2**	**10**

After C6 (ORR 8/10, 80% 95%CI 44-97)

Five relevant safety events (4 grade 1-2 CRS, 1 grade 3 neutropenia) occurred, **not exceeding the threshold defined for early stopping**.
The DSMC recommends that the **study proceeds without changes**

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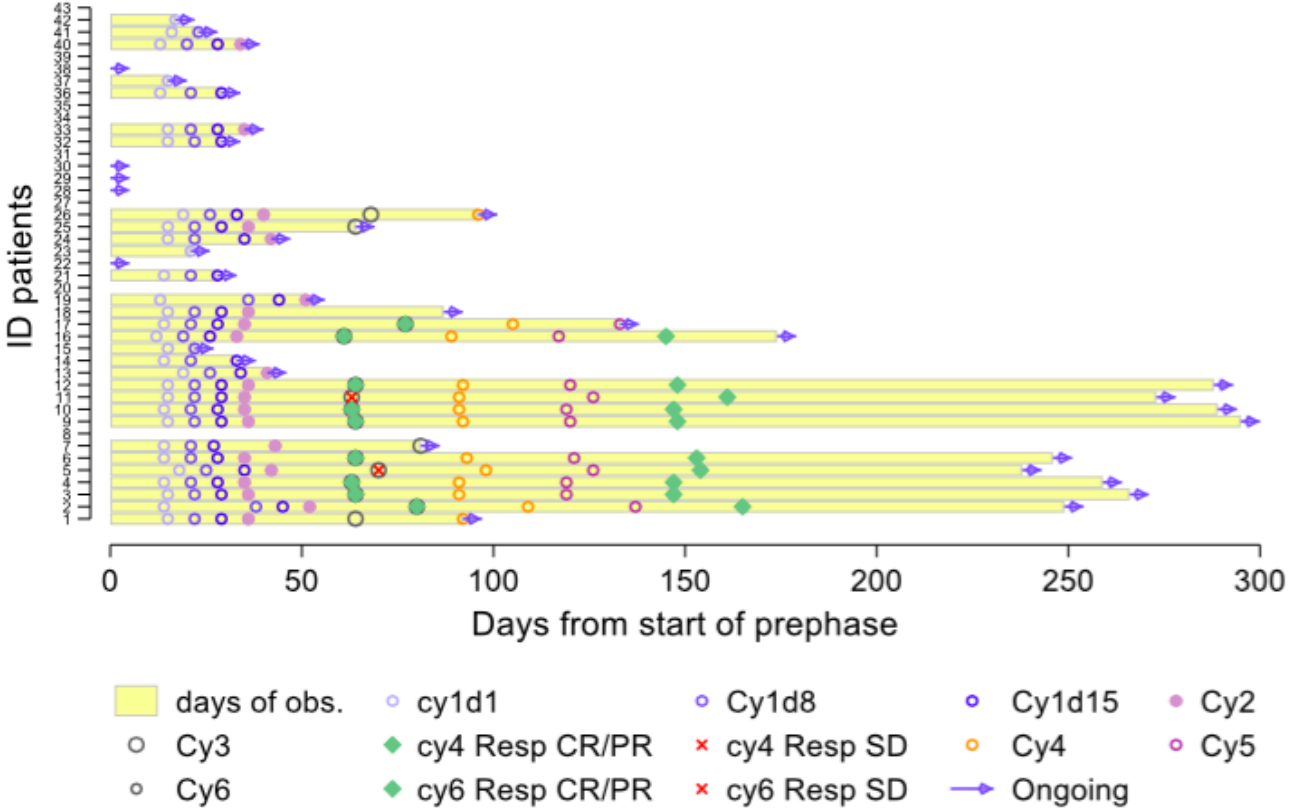
Preliminary Efficacy Analysis All Population



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Conclusions

- FL heterogeneous disease: median OS is approaching 20 years, in modern era
- Poor outcome for early relapse, refractory disease, tFL
- Lymphoma remain the principal cause of death at 10 yrs
- However, toxicity represents an important morbidity factor in elderly subjects
- patients' age and comorbid conditions → Key decisional ← fitness, QoL
- Improving treatment options for patients with follicular lymphoma, including clinical trial participation challenges
- Chemo-free approaches represent a good treatment option in elderly patients
- On going clinical trials are exploring their use in combination (Lenalidomide, Zanubrutinib, Tafasitamab, Tazemotast) or the application in the first-line setting
- Lenalidomide back-bone could represent an overlapping drug…

“Current goal of treatment: maintain best QoL by delaying disease progression”

"Current goal of treatment: maintain best QoL by delaying disease progression"

".....will this translate into an OS benefit with longer follow-up?"

Grazie per l'attenzione