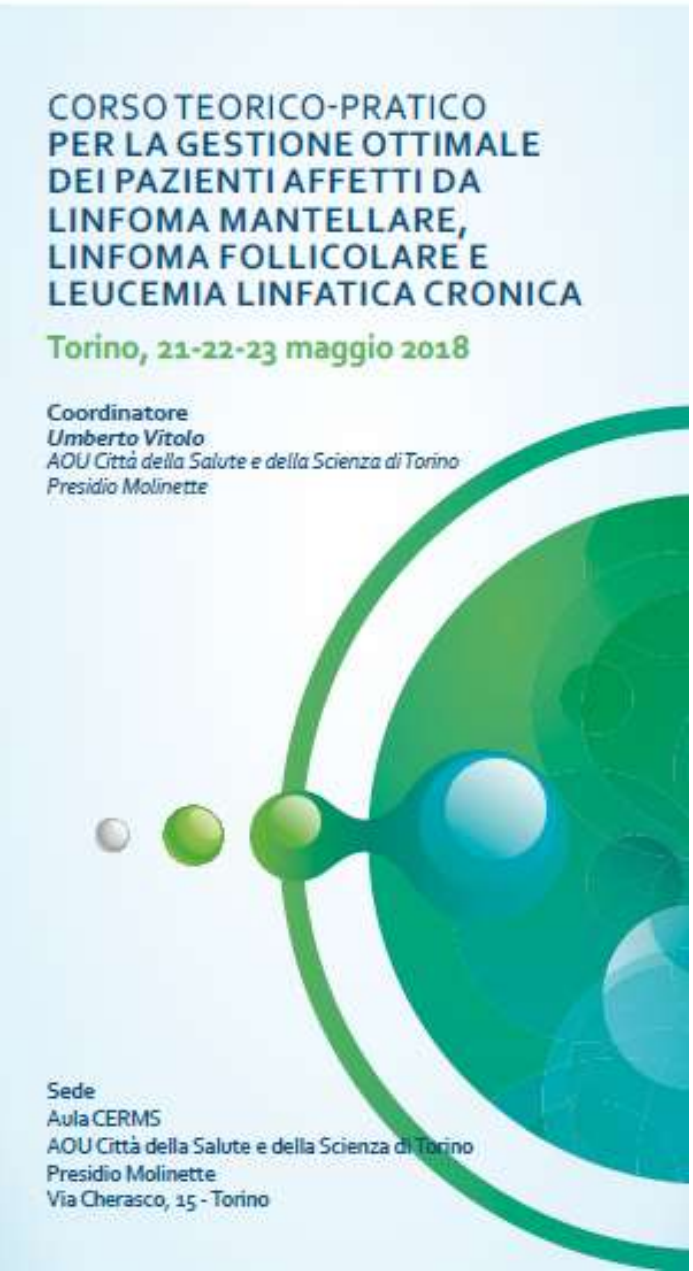


Il trattamento del Linfoma Follicolare in prima linea

Dr.ssa Carola Boccomini

SC Ematologia – Dr. U. Vitolo

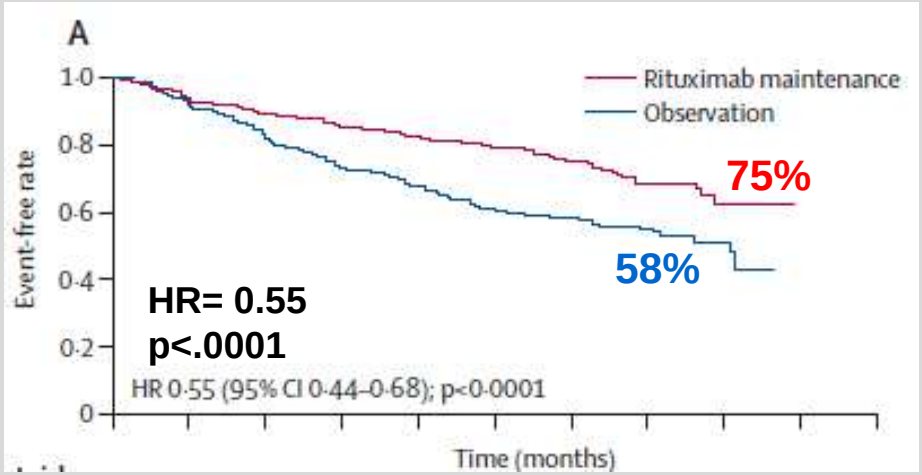
AO Città della Salute e della Scienza

Torino, Italy

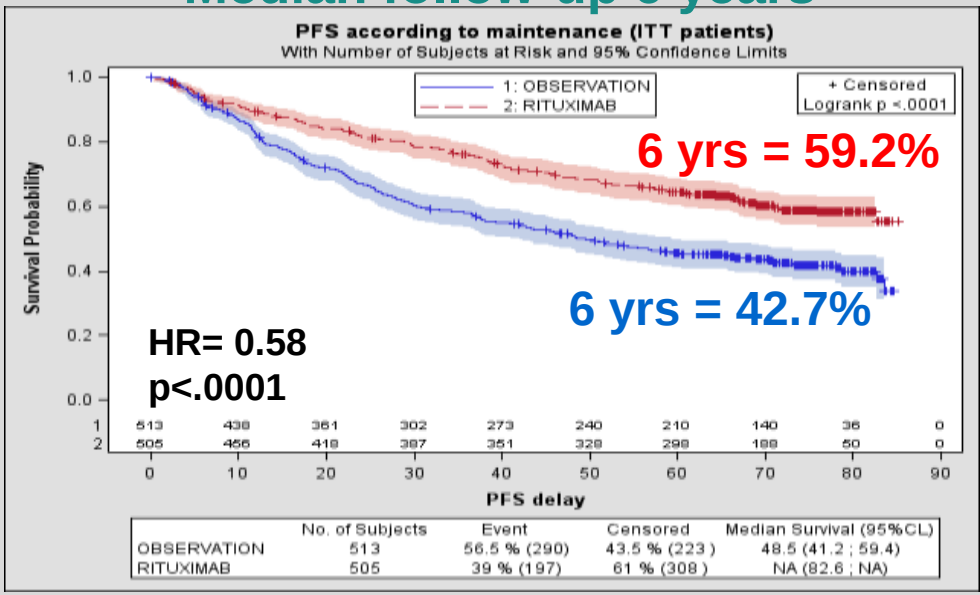
Standard treatment in advanced stage FL

Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial

Median follow-up 3 years



Median follow-up 6 years



At the end of maintenance:

CR 71.5% in maintenance arm vs 52.2% in observation arm (p=0.0001)

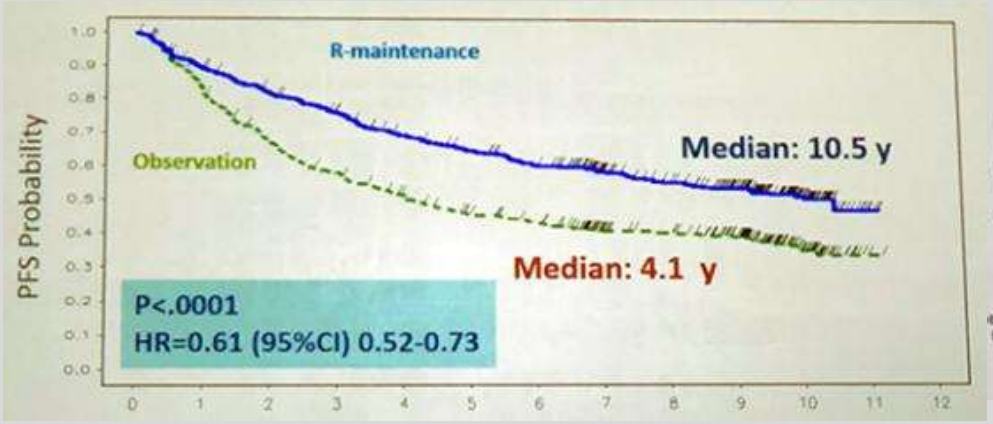
Salles G, et al; Lancet 2011

Salles G, et al; Blood 2013 (abs)

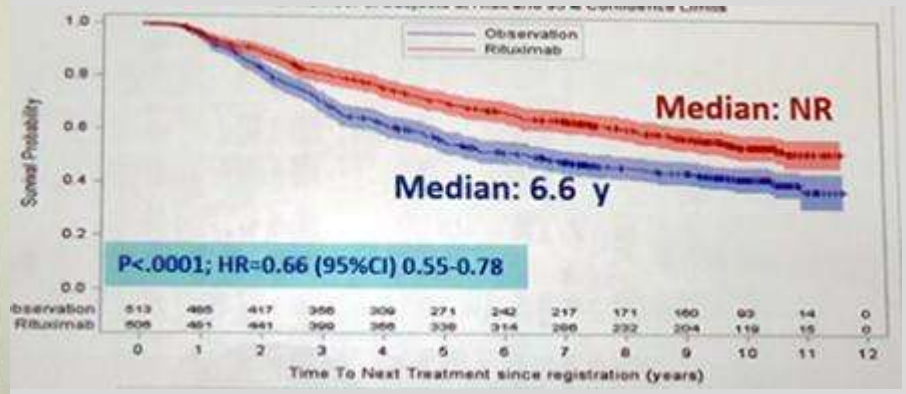
Long Term Follow-up of the PRIMA Study: Half of Patients Receiving Rituximab Maintenance Remain Progression Free at 10 Years

Median follow-up 9 years

Median PFS



Median TTNT

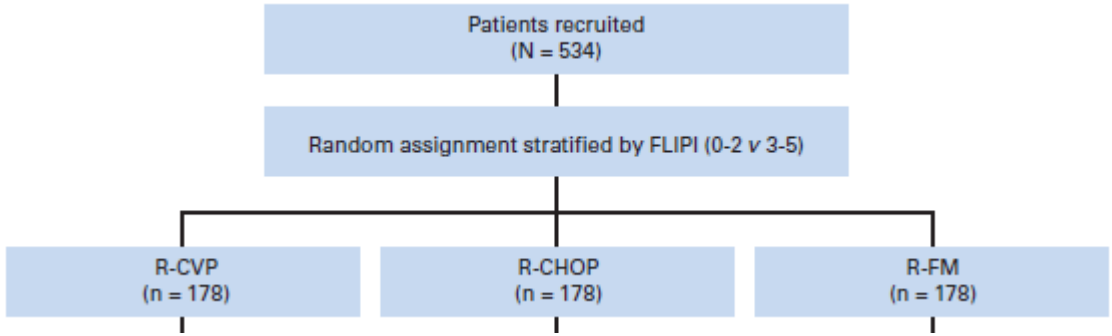


- 51% of pts in R-maintenance arm (vs 35%) free of disease progression
- Benefit of R-maintenance was significant in all patient strata
- Median TTNT not reached in Rituximab maintenance arm with 53% pts not having received a new treatment (vs 41%)
- No new safety signals were indentified with additional 4 years of FU
- OS was identical (80%) in each arm
- **Obtaining truly durable response with 1st line induction and R-maintenance remains an appealing treatment strategy for FL pts**

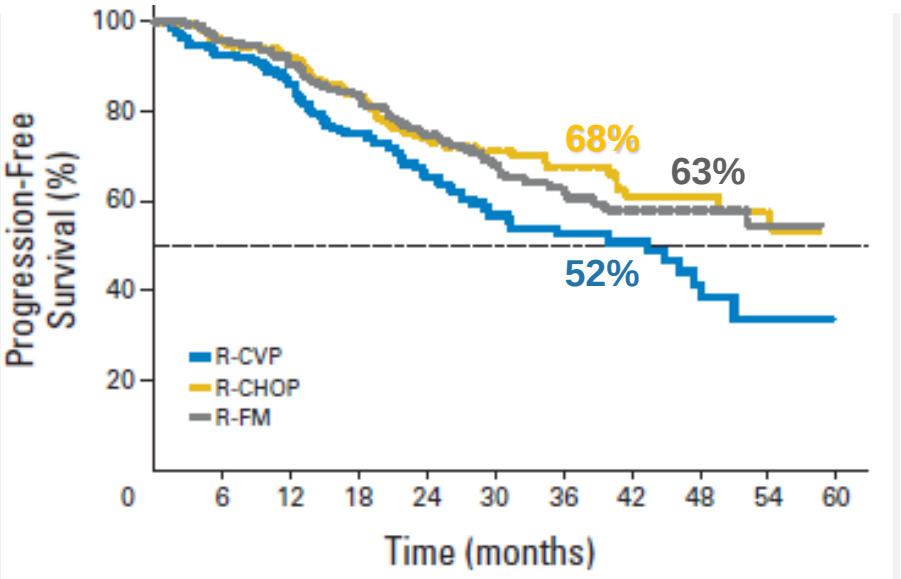
Salles G, et al; Blood 2017 (abs)

Best chemotherapy induction regimen?

R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Follicular Lymphoma: Results of the FOLL05 Trial Conducted by the Fondazione Italiana Linfomi



- Similar ORR (88%, 93% e 91%) and CR rate
- 3-yr OS for whole series: 85%
- **R-CHOP and R-FM regimens lead to improved PFS compared to R-CVP**
- Study regimens generally well tolerated, but
- R-FM more toxic in term of grade III-IV neutropenia and second malignancies



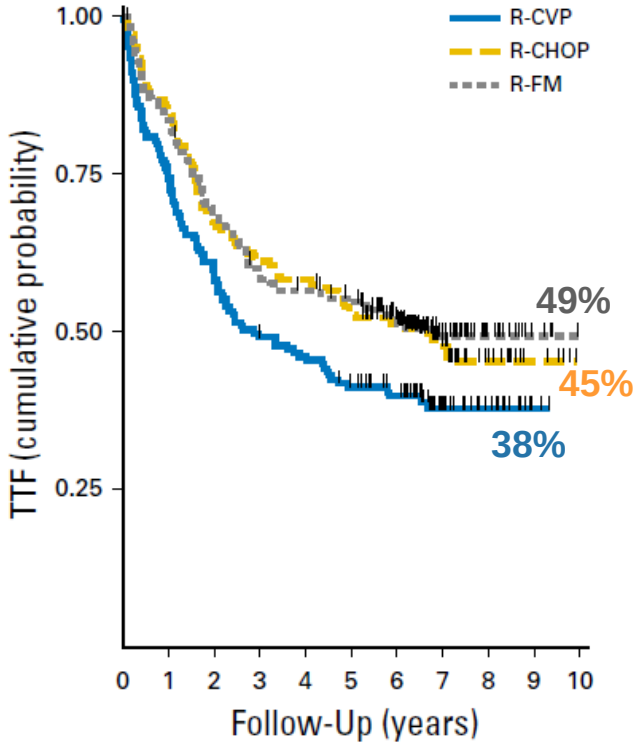
Federico M, et al: JCO 2013

Long-Term Results of the FOLL05 Trial Comparing R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Symptomatic Follicular Lymphoma

14-ICML
14th International Conference on Malignant Lymphoma
Palazzo dei Congressi, Lugano, Switzerland, June 14-17, 2017

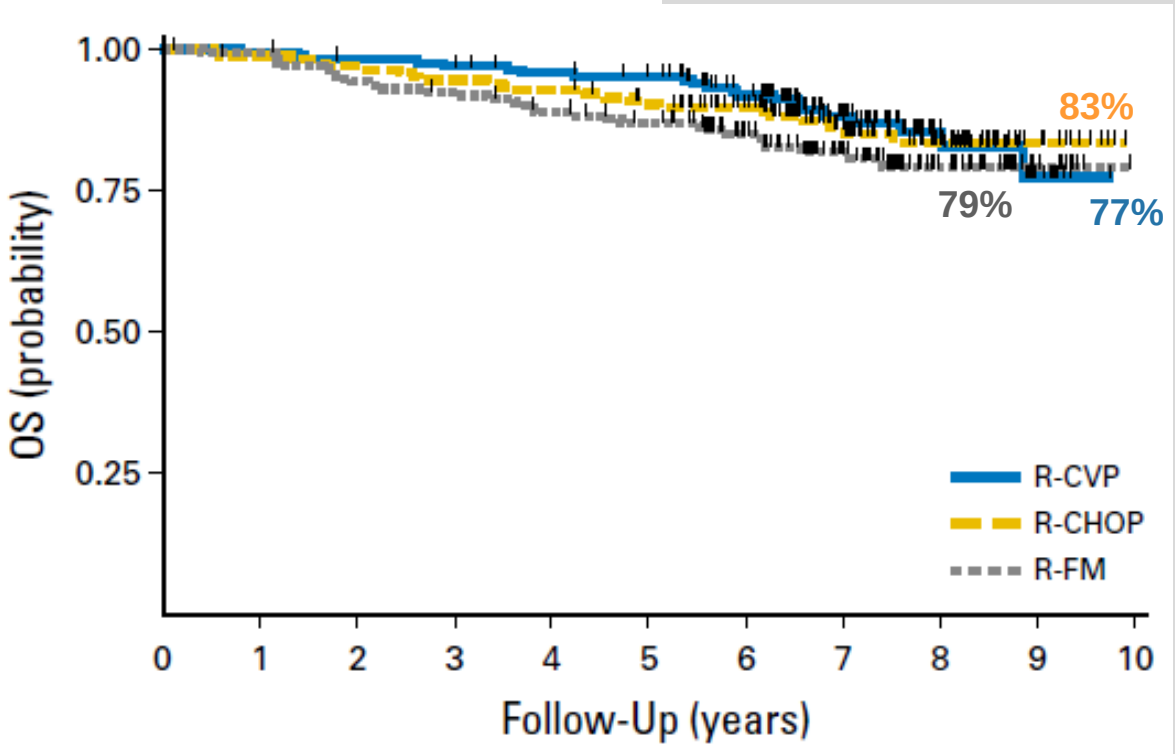
Median follow-up 7 years

TTF



PFS

OS



Luminari S, et al: JCO 2018

Long-Term Results of the FOLL05 Trial Comparing R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Symptomatic Follicular Lymphoma

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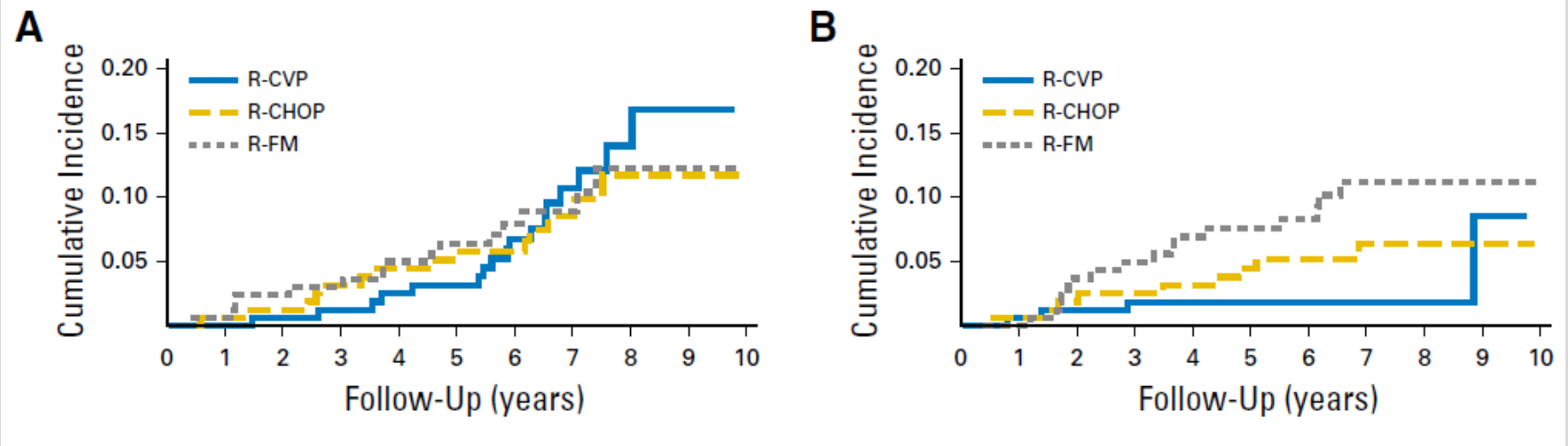

- Long-term FU of FOLL05 trial confirms the favourable outcome of advanced-stage FL treated with immunochemotherapy
- **The three study arms had** similar OS but **different activity and toxicity profiles**
- Pts initially treated with R-CVP had higher risk of lymphoma progression and additional therapy compared to R-CHOP
- Pts treated with R-FM had higher risk of dying as a results of causes unrelated to lymphoma progression

Luminari S, et al: JCO 2018

Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study

Randomized, no-inferiority phase 3 study

447 pts (314 FL pts)

- Dose intensity ≥96% for all drugs ,except for PDN and VCR
- Dose reduction for AEs more common for Bendamustine and VCR
- Neutropenia was the most common reason for treatment delays across the groups
- **Safety profile was different according to treatment**
- Peripheral neuropathy or constipation more frequent in R-CHOP/R-CVP arms
- Hypersensitivity more frequent in BR arm
- **BR is not-inferior to standard therapy in term of CR and OR rates.**

	CR		CR + partial response	
Histologic subtype, n/N (%)	**BR**	**R-CHOP/R-CVP**	**BR**	**R-CHOP/R-CVP**
Indolent NHL	49/178 (28)	43/174 (25)	173/178 (97)	160/174 (92)
Follicular	45/148 (30)	37/149 (25)	147/148 (>99)	140/149 (94)
Marginal zone	5/25 (20)	4/17 (24)	23/25 (92)	12/17 (71)
Lymphoplasmacytic	0/5	1/6 (17)	3/5 (60)	6/6 (100)
MCL	17/34 (50)	9/33 (27)*	32/34 (94)	28/33 (85)*

Flinn IW, et al: Blood 2014

Assessment of Maintenance Rituximab after First-Line Bendamustine-Rituximab in Patients with Follicular Lymphoma: An Analysis from the BRIGHT Trial

ASH

- Pts responding to BR who received Rituximab maintenance had a significantly better PFS (HR 0.50; p = 0.0295) than pts who did not receive Rituximab maintenance
- Pts responding to R-CHOP/R-CVP who received Rituximab maintenance had a trend towards better PFS (HR 0.66; p = 0.1443) than pts who did not receive maintenance
- **OS tended to be better in pts assigned to Rituximab maintenance**
- **These results support the use of Rituximab maintenance also after BR therapy**

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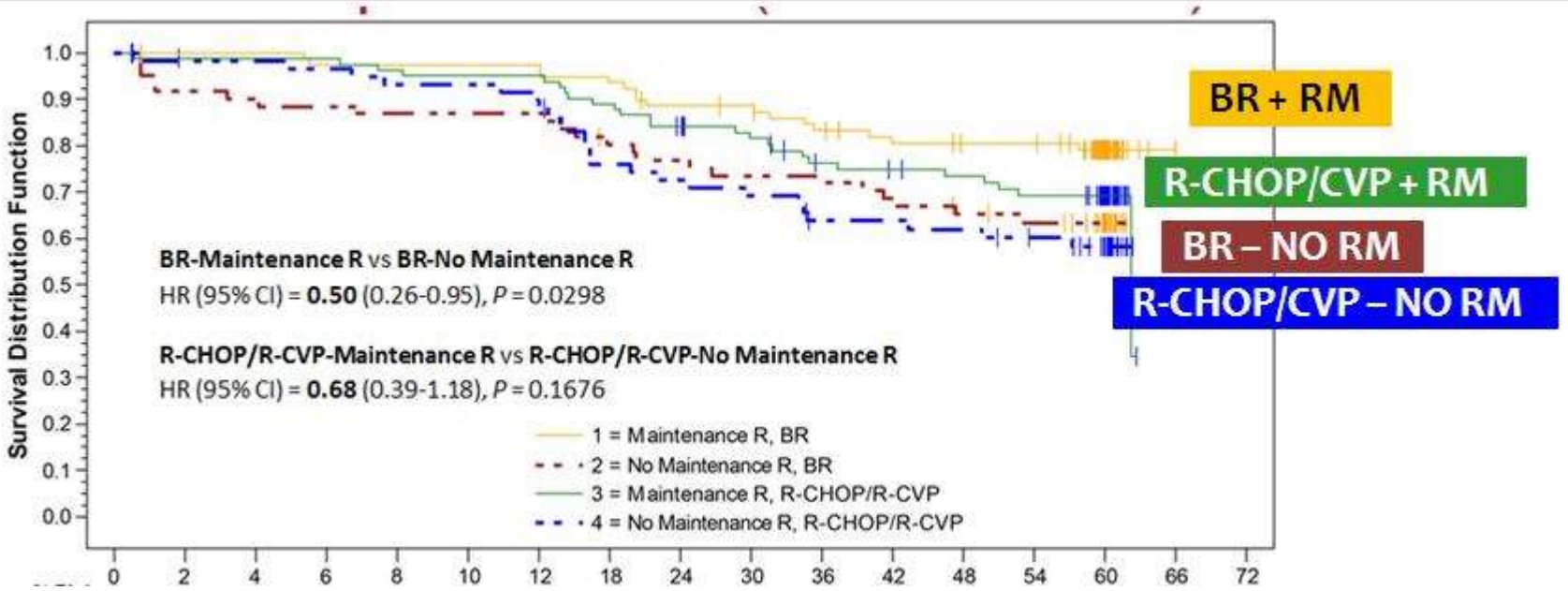


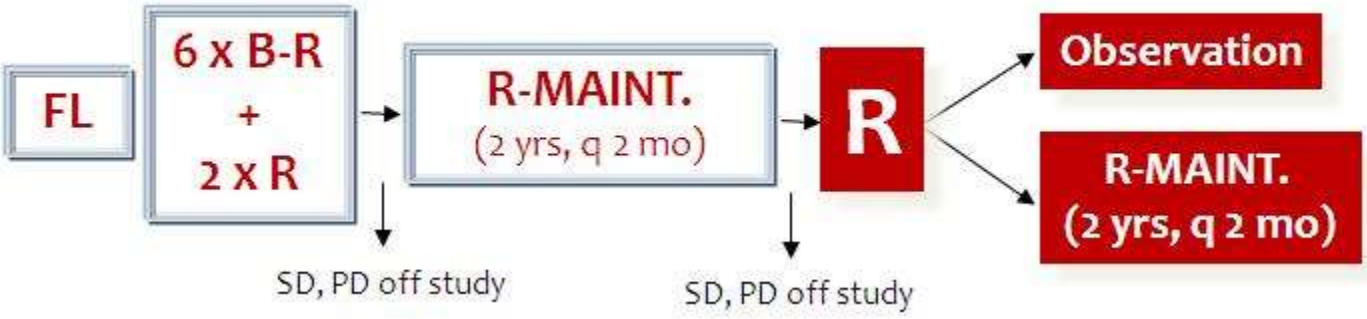
Kahl BS, Blood 2017 (Abs)

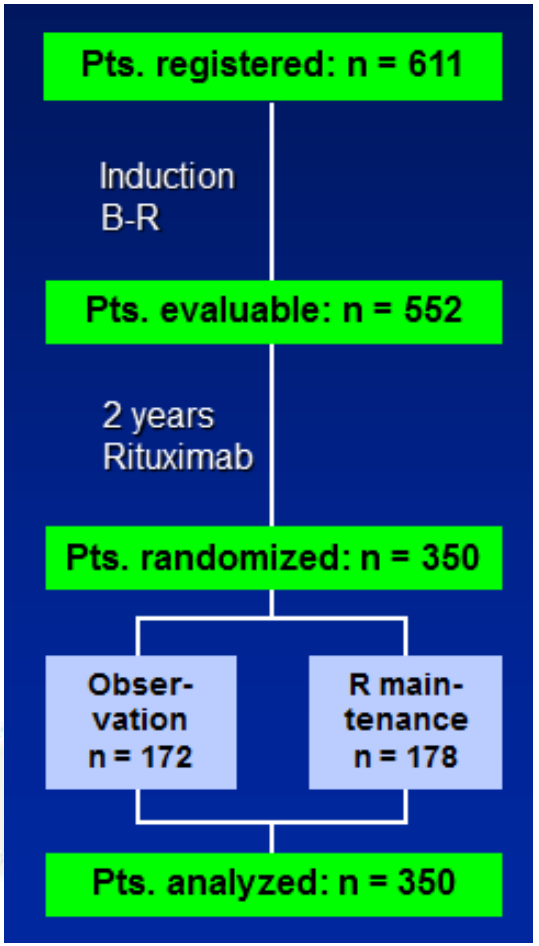
Four Versus Two Years of Rituximab Maintenance (R-maintenance) Following Bendamustine Plus Rituximab (B-R): Initial Results of a Prospective, Randomized Multicenter Phase 3 Study in First-Line Follicular Lymphoma (the StiL NHL7-2008 MAINTAIN study)

ASH

StiL NHL 7-2008 - MAINTAIN

- **612 FL pts – stage II bulky, III or IV disease**
- Median age 60 years
- pts treated with up to 6 cycles of BR + 2 additional R
- All responding pts received 2 years R-maintenance
- **Pts who tolerated treatment for the entire 2 years and who were still in CR were subsequently randomized to 2 more years of R-maintenance or observation**





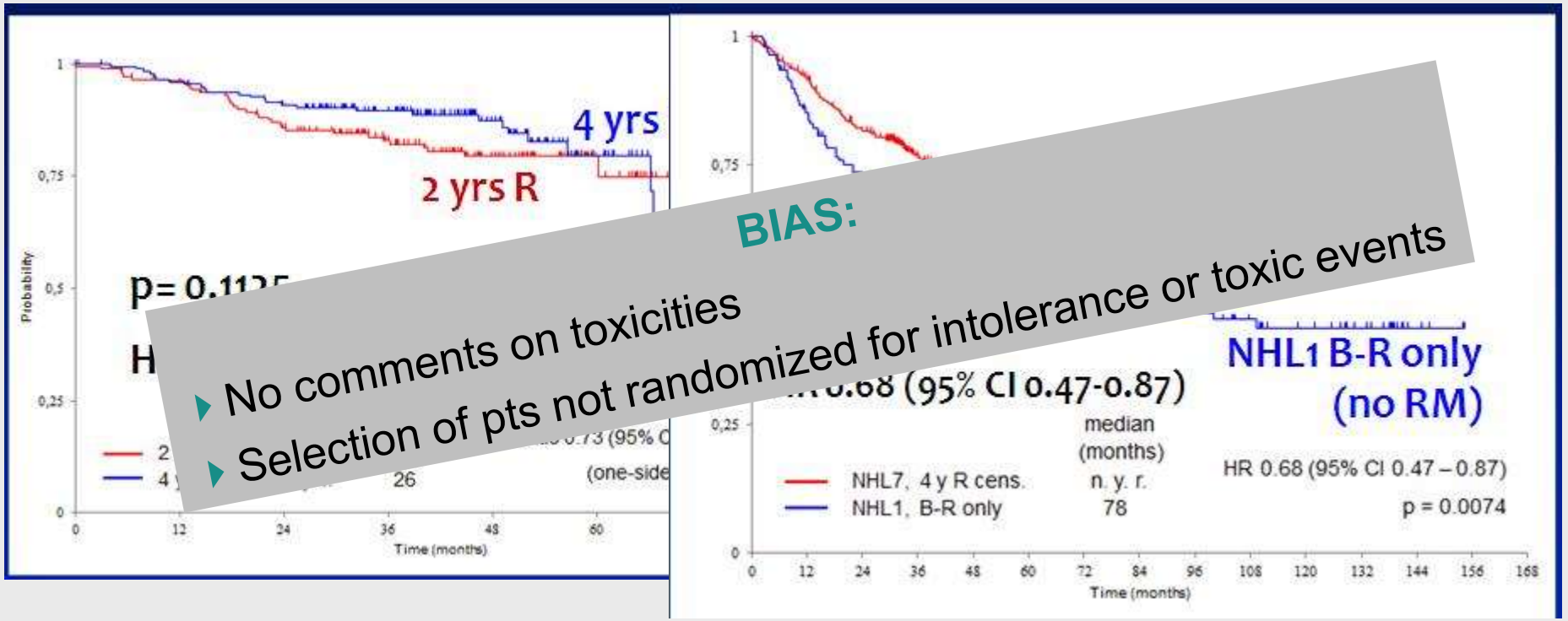
Rummel MJ, Blood 2017 (Abs)

Four Versus Two Years of Rituximab Maintenance (R-maintenance) Following Bendamustine Plus Rituximab (B-R): Initial Results of a Prospective, Randomized Multicenter Phase 3 Study in First-Line Follicular Lymphoma (the StiL NHL7-2008 MAINTAIN study)

ASH

Median FU: 36 months from randomization (75 months from registration)

- Median PFS and OS not reached in either arms
- PFS appears superior with 4 years vs 2 years of R-maintenance but there was no difference in OS between groups



BIAS:

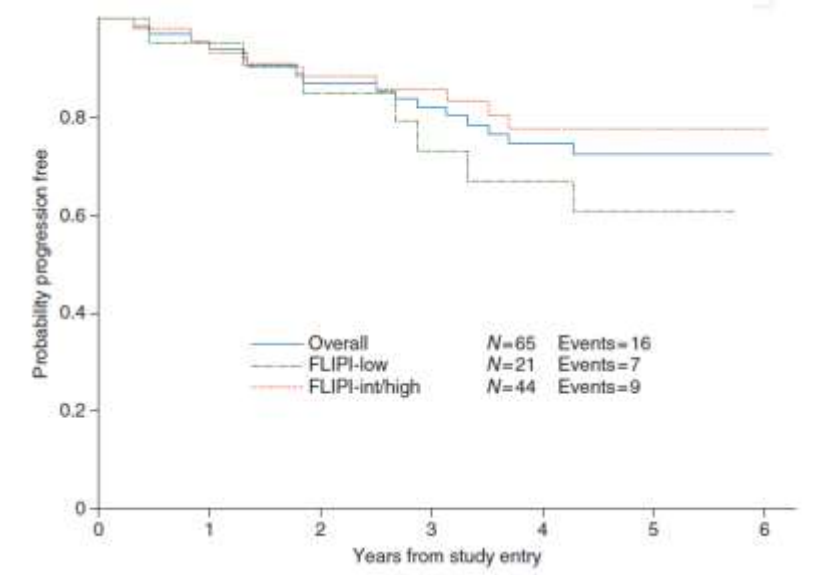
- No comments on toxicities
- Selection of pts not randomized for intolerance or toxic events

- A historical comparison for PFS between MAINTAIN study and the former StiL NHL1 study (BR vs R-CHOP) appears to favor R-maintenance

Rummel MJ, Blood 2017 (Abs)

A phase II trial of lenalidomide plus rituximab in previously untreated follicular non-Hodgkin's lymphoma (NHL): CALGB 50803 (Alliance)

- **ORR: 95% with CR rate 72%**
- Median FU: 5 years
- 2- and 5-yrs PFS: 86% and 70% respectively
- 5-yrs OS 100%

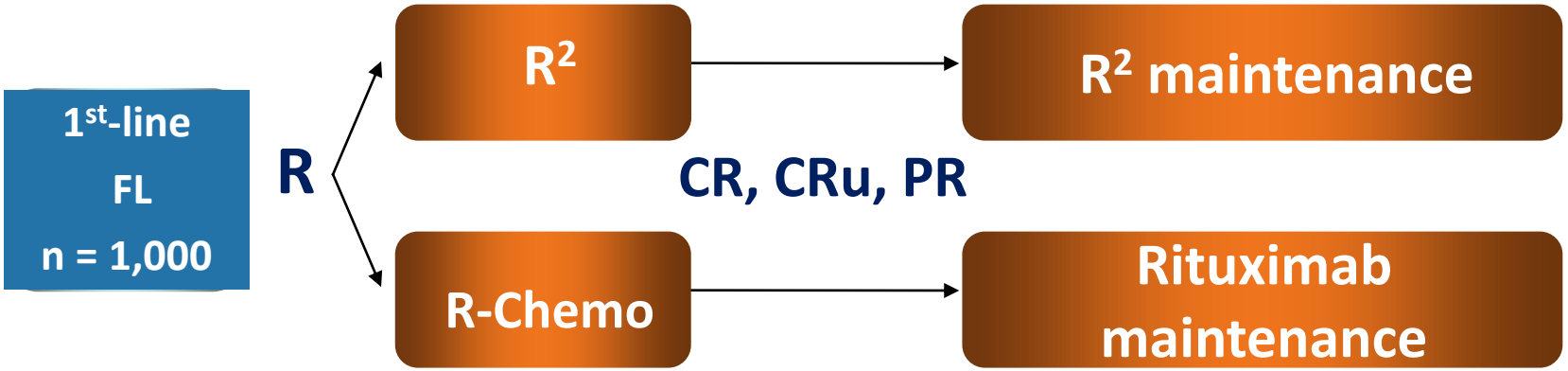


- **Lenalidomide plus Rituximab was associated with low rate of grade 3-4 toxicity, leading a CR rate and a PFS similar to chemotherapy-based regimens and may represent a reasonable alternative to immunochemotherapy in previously untreated FL.**

Martin P, et al: Ann Oncol 2017

RELEVANCE trial: Rituximab and Lenalidomide vs any chemotherapy

International, phase 3, multi-centre, randomized study
(Frank Morchhauser, Nathan Fowler)

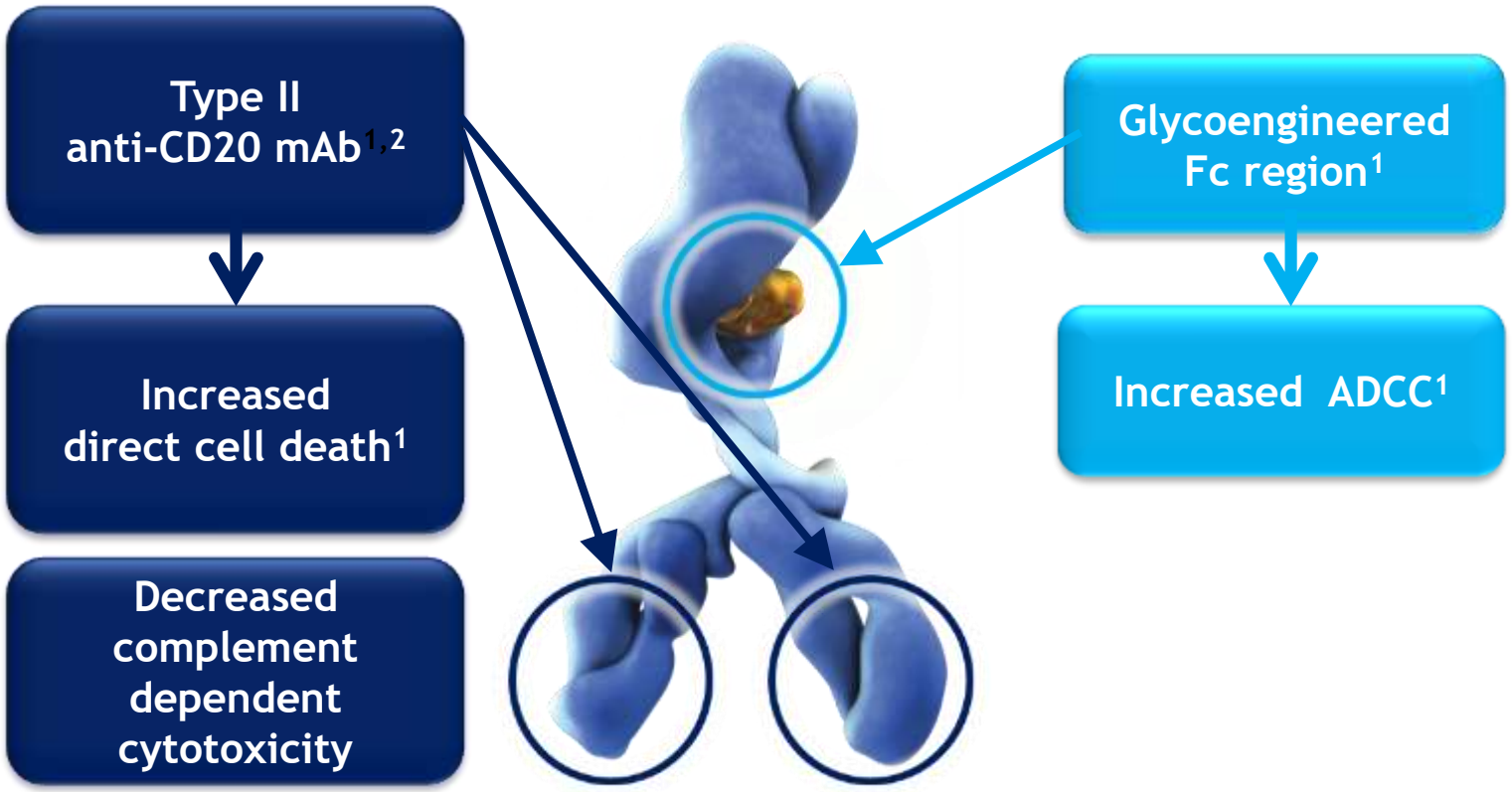


- **R-Chemo** according to investigator choice of **R-CHOP, R-CVP, R-B**
- **R + Lenalidomide 20 mg x 6 cycles; if CR then 10 mg; if PR 20 mg x further 3-6 cycles and then 10 mg for up to 18 cycles**
- Co-primary end-points
  - surrogate end-point: CR/CRu rate at 1.5 years
  - PFS

NCT01476787. Available from: http://clinicaltrials.gov.

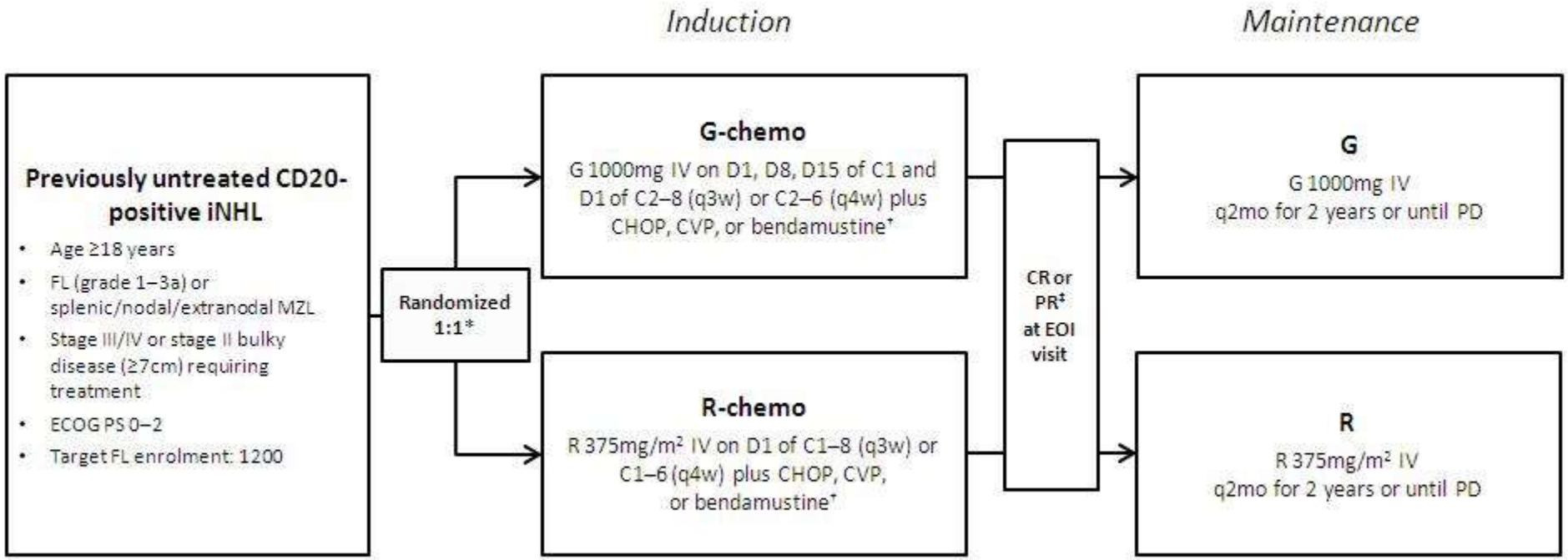
Obinutuzumab: GA-101

GA101 has increased direct cell death and antibody-dependent cellular cytotoxicity (ADCC), as well as decreased complement dependent cytotoxicity (CDC) compared with non-glycoengineered, type I mAbs



Mössner E, Blood 2010

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma



- **1202 enrolled pts**
- Median age 58-60 years (range 23-88)

Marcus R, et al; NEJM 2017

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

Pts and disease characteristics

Characteristic	*R-chemo, n=601*	*G-chemo, n=601*
Median age, years (range)	58 (23–85)	60 (26–88)
Male, % (n)	46.6% (280)	47.1% (283)
Ann Arbor stage at diagnosis, % (n)		
I	1.3% (8)*	1.7% (10)†
II	7.4% (44)*	6.9% (41)†
III	35.0% (209)*	34.8% (208)†
IV	56.3% (336)*	56.7% (339)†
FLIPI risk group, % (n)		
Low (0–1)	20.8% (125)	21.3% (128)
Intermediate (2)	37.1% (223)	37.3% (224)
High (≥3)	42.1% (253)	41.4% (249)
B symptoms, % (n)	34.3% (206)‡	33.4% (201)
Bone marrow involvement, % (n)	49.3% (295)†	53.7% (318)§
Extranodal involvement, % (n)	65.9% (396)	65.2% (392)
Bulky disease (≥7cm), % (n)	45.2% (271)‡	42.5% (255)‡
Median (range) time from diagnosis to randomization, months	1.4 (0–168.1)	1.5 (0.1–121.6)¶

Marcus R, et al; NEJM 2017

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

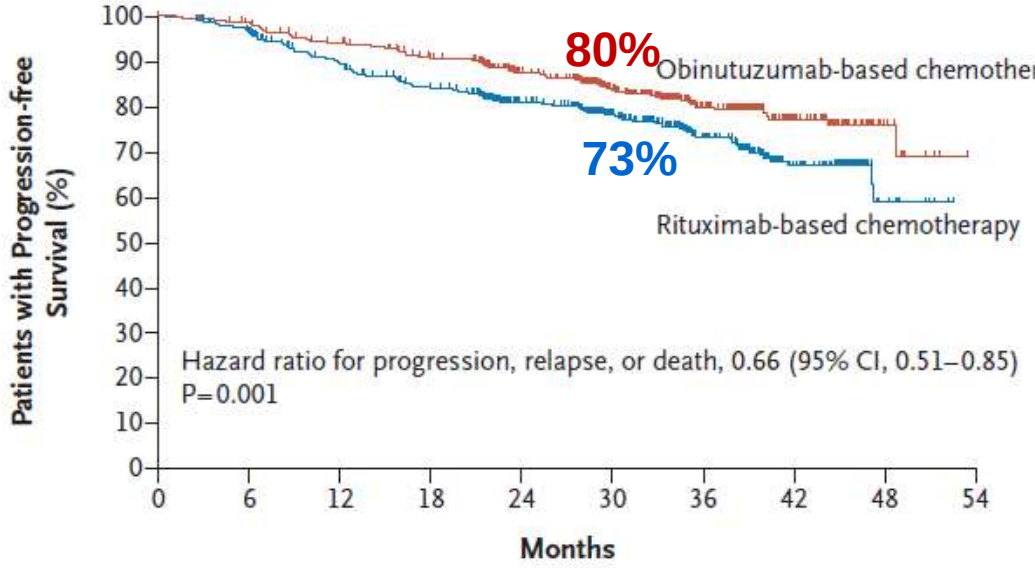
Response rates at the end of induction

% (n); 95% CI	*R-chemo, n=601*	*G-chemo, n=601*
ORR	**86.9% (522); 83.9, 89.5**	**88.5% (532); 85.7, 91.0**
CR	**23.8% (143); 20.4, 27.4**	**19.5% (117); 16.4, 22.9**
PR	63.1% (379)	69.1% (415)
SD	1.3% (8)	0.5% (3)
PD	4.0% (24)	2.3% (14)
Not evaluable / missing	3.5% (21) / 4.3% (26)	4.0% (24) / 4.7% (28)

Marcus R, et al; NEJM 2017

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

3-yrs PFS
Median FU 34.5 months

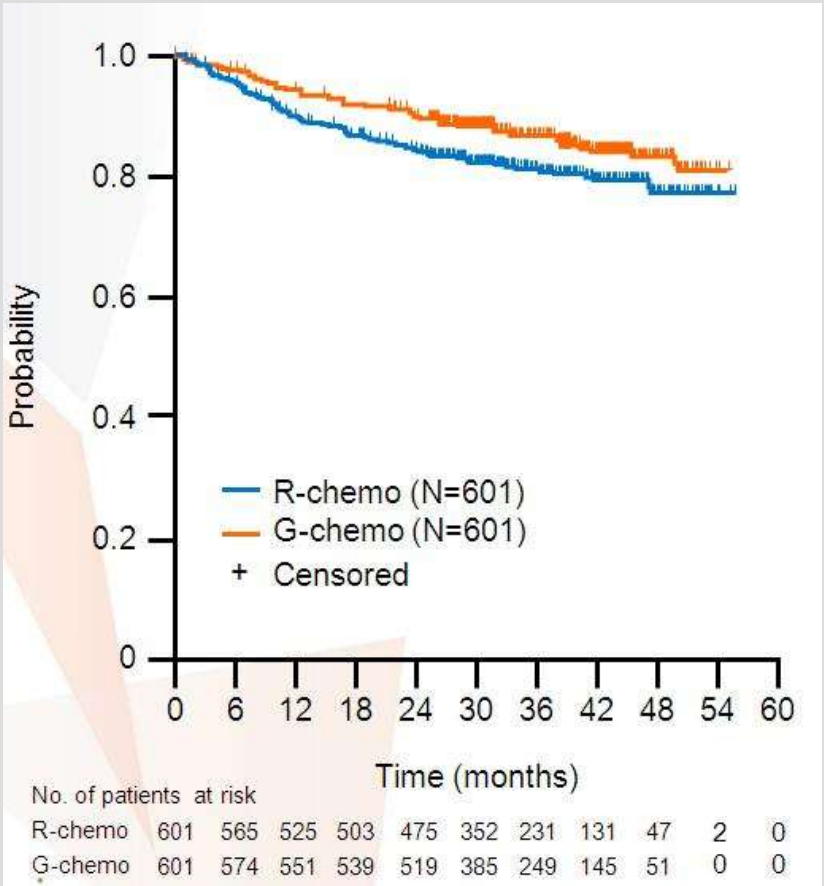


	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	144 (24.0)	101 (16.8)
3-yr PFS, % (95% CI)	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)
HR (95% CI), p-value*	0.66 (0.51, 0.85), p=0.0012	

34% reduction in the risk of progression, relapse or death

Marcus R, et al; NEJM 2017

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma



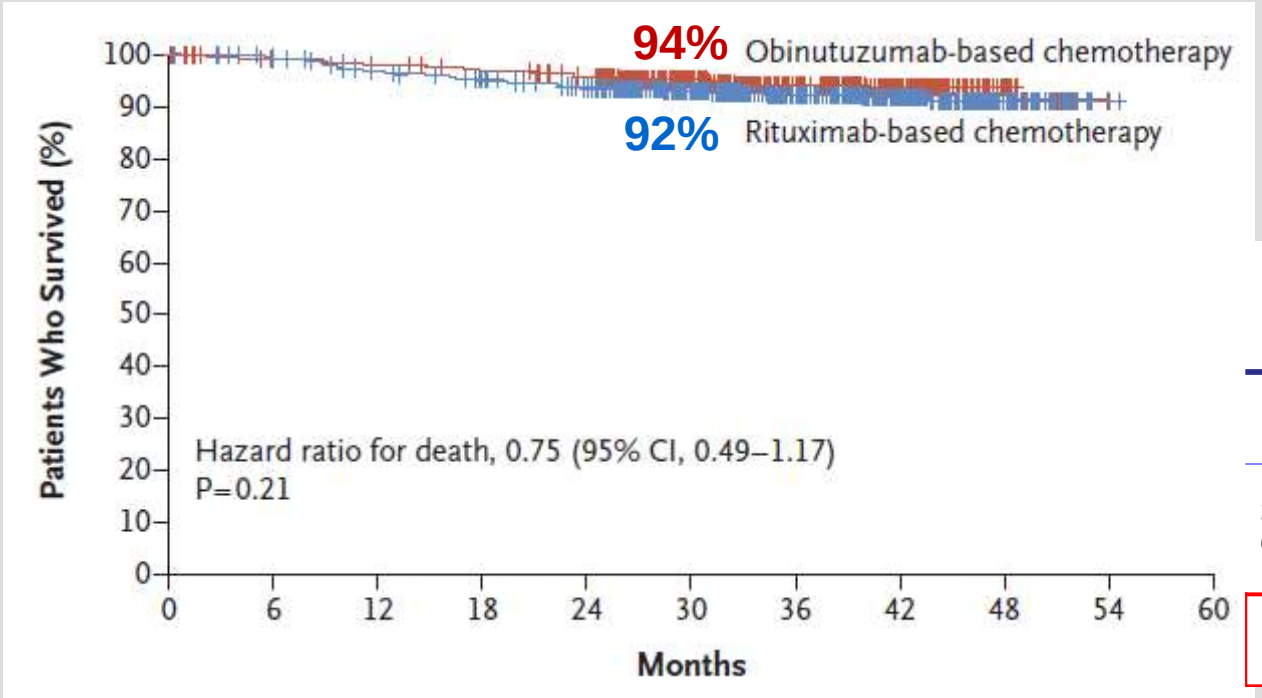
3-yrsTTNT

	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	111 (18.5)	80 (13.3)
3-yr TTNT, % (95% CI)	81.2 (77.6, 84.2)	87.1 (84.0, 89.6)
HR (95% CI), p-value*	0.68 (0.51, 0.91), p=0.0094	

Marcus R, et al; NEJM 2017

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

3-yrs OS



	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	46 (7.7)	35 (5.8)
3-yr OS, % (95% CI)	92.1 (89.5, 94.1)	94.0 (91.6, 95.7)
HR (95% CI), p-value*	0.75 (0.49, 1.17), p=0.21	

Marcus R, et al; NEJM 2017

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

Event	Overall Trial†		Induction Phase		Maintenance and Observation Phases	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=548)	Rituximab Group (N=535)
No. of events	10,311	9343	7012	6533	3002	2578
Patients with ≥1 adverse event — no. (%)						
Any event	592 (99.5)	587 (98.3)	580 (97.5)	577 (96.6)	501 (91.4)	458 (85.6)
Event of grade 3 to 5	444 (74.6)	405 (67.8)	357 (60.0)	336 (56.3)	205 (37.4)	169 (31.6)
Event of grade 5‡	24 (4.0)	20 (3.4)§	4 (0.7)	3 (0.5)	10 (1.8)	10 (1.9)
Patients with ≥1 serious adverse event — no. (%)	274 (46.1)	238 (39.9)	166 (27.9)	144 (24.1)	134 (24.5)	110 (20.6)
Treatment-related adverse event — no. (%)						
Any event	564 (94.8)	547 (91.6)	—	—	—	—
Event leading to withdrawal of treatment	75 (12.6)	65 (10.9)	—	—	—	—
Event leading to any dose reduction	103 (17.3)	89 (14.9)	—	—	—	—
Serious adverse event leading to withdrawal of treatment — no. (%)	44 (7.4)	36 (6.0)	—	—	—	—
Serious adverse event leading to dose reduction — no. (%)	12 (2.0)	10 (1.7)	—	—	—	—

- **More pts in GA101-group had grade 3-5 AE or SAEs** but AEs that led to the discontinuation of treatment were similar in the 2 arms

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

Category	All Adverse Events		Adverse Events of Grade 3 to 5		Serious Adverse Events	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)
	number of patients (percent)					
Infection*	460 (77.3)	418 (70.0)	119 (20.0)	93 (15.6)	108 (18.2)	86 (14.4)
Neutropenia	301 (50.6)	269 (45.1)	273 (45.9)	236 (39.5)	50 (8.4)	44 (7.4)
Infusion-related event†						
Any event	406 (68.2)	349 (58.5)	74 (12.4)	40 (6.7)	33 (5.5)	14 (2.3)
Antibody-related event	353 (59.3)	292 (48.9)	63 (10.6)	30 (5.0)	28 (4.7)	12 (2.0)
Tumor lysis syndrome	6 (1.0)	3 (0.5)	6 (1.0)	3 (0.5)	3 (0.5)	1 (0.2)
Cardiac event‡	78 (13.1)	58 (9.7)	22 (3.7)	17 (2.8)	26 (4.4)	12 (2.0)
Thrombocytopenia	68 (11.4)	45 (7.5)	36 (6.1)	16 (2.7)	4 (0.7)	1 (0.2)
Second neoplasm§	43 (7.2)	30 (5.0)	28 (4.7)	16 (2.7)	31 (5.2)	17 (2.8)
Nonmelanoma skin cancer	18 (3.0)	14 (2.3)	7 (1.2)	3 (0.5)	9 (1.5)	3 (0.5)
Hematologic event¶	6 (1.0)	0	6 (1.0)	0	6 (1.0)	0
Other	22 (3.7)	18 (3.0)	17 (2.9)	15 (2.5)	18 (3.0)	16 (2.7)
Myelodysplastic syndrome	2 (0.3)	0	2 (0.3)	0	2 (0.3)	0
Gastrointestinal perforation	4 (0.7)	3 (0.5)	3 (0.5)	0	3 (0.5)	0
Hemorrhagic event	57 (9.6)	62 (10.4)	5 (0.8)	7 (1.2)	6 (1.0)	5 (0.8)

- The most common AEs of any grade in the whole trial were: infusion-related reactions (GA 59% vs R 48.9%), nausea and neutropenia

Marcus R, et al; NEJM 2017

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

Event	Overall Trial†		Induction Phase		Maintenance and Observation Phases	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=548)	Rituximab Group (N=535)
Grade 3 to 5 event, according to chemotherapy regimen — no./total no. (%)						
Neutropenia	—	—				
Bendamustine	—	—	73/338 (21.6)	87/338 (25.7)	49/312 (15.7)	29/305 (9.5)
CHOP	—	—	124/193 (64.2)	103/203 (50.7)	36/179 (20.1)	26/187 (13.9)
CVP	—	—	24/61 (39.3)	13/56 (23.2)	5/57 (8.8)	2/43 (4.7)
Infection¶	—	—				
Bendamustine	—	—	27/338 (8.0)	26/338 (7.7)	52/312 (16.7)	39/305 (12.8)
CHOP	—	—	14/193 (7.3)	13/203 (6.4)	7/179 (3.9)	11/187 (5.9)
CVP	—	—	3/61 (4.9)	4/56 (7.1)	5/57 (8.8)	1/43 (2.3)
Second neoplasm‖	—	—				
Bendamustine	—	—	0	0	21/312 (6.7)	18/305 (5.9)
CHOP	—	—	0	0	8/179 (4.5)	8/187 (4.3)
CVP	—	—	0	0	0	1/43 (2.3)

- **AEs were generally less common during maintenance phase than during induction**
- **During induction phase:** most frequent AEs were neutropenia, infusion-related reactions and febbrile neutropenia
- **During maintenance phase**: most common AE/SAE were neutropenia and pneumonia

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

Event	Overall Trial†		Induction Phase		Maintenance and Observation Phases	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=548)	Rituximab Group (N=535)
Grade 3 to 5 event, according to chemotherapy regimen — no./total no. (%)						
Neutropenia	—	—				
Bendamustine	—	—	73/338 (21.6)	87/338 (25.7)	49/312 (15.7)	29/305 (9.5)
CHOP	—	—	124/193 (64.2)	103/203 (50.7)	36/179 (20.1)	26/187 (13.9)
CVP	—	—	24/61 (39.3)	13/56 (23.2)	5/57 (8.8)	2/43 (4.7)
Infection¶	—	—				
Bendamustine	—	—	27/338 (8.0)	26/338 (7.7)	52/312 (16.7)	39/305 (12.8)
CHOP	—	—	14/193 (7.3)	13/203 (6.4)	7/179 (3.9)	11/187 (5.9)
CVP	—	—	3/61 (4.9)	4/56 (7.1)	5/57 (8.8)	1/43 (2.3)
Second neoplasm‖	—	—				
Bendamustine	—	—	0	0	21/312 (6.7)	18/305 (5.9)
CHOP	—	—	0	0	8/179 (4.5)	8/187 (4.3)
CVP	—	—	0	0	0	1/43 (2.3)

- Bendamustine associated with higher rates of infection or 2nd neoplasm during maintenance/FU whereas CHOP with higher rate of neutropenia during induction phase

Marcus R, et al; NEJM 2017

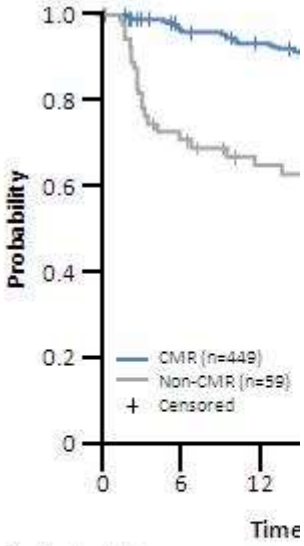
Comparison of contrast-enhanced CT-based response with PET assessment after first-line therapy for follicular lymphoma in the Phase III GALLIUM study

Assessment criteria, n (%)	R-chemo, n=298	G-chemo, n=297	p-value
CT CR response[1*]	82 (27.5)	96 (32.3)	0.28
PET CR/CMR response			
IHP 2007[1]	178 (59.7)	212 (71.4)	0.006
Lugano 2014[2,3†]	217 (72.8)	232 (78.1)	0.18

- There is a higher PET-CR rate with G-Chemo vs R-chemo according to IHP 2007 criteria and a strong trend favouring G-chemo with Lugano 2014 criteria

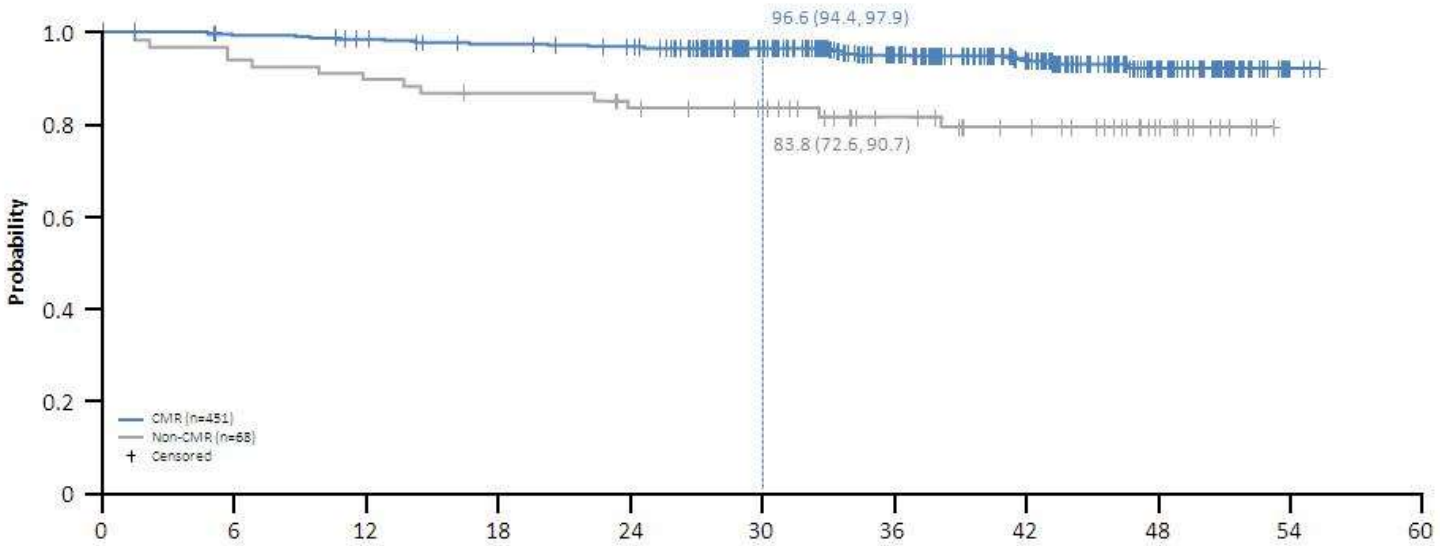
Comparison of contrast-enhanced CT-based response with PET assessment after first-line therapy for follicular lymphoma in the Phase III GALLIUM study

PFS



HR, 0.2

OS



HR, 0.22 (95% CI: 0.11, 0.45); p<0.0001

Trotman J, et al

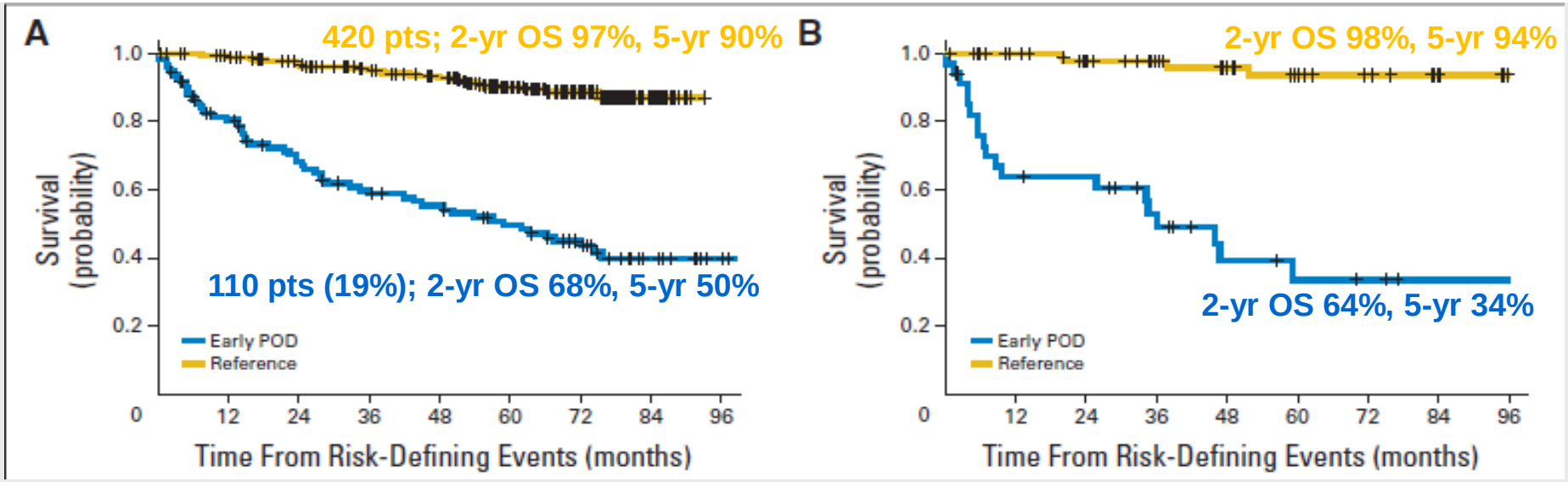
Comparison of contrast-enhanced CT-based response with PET assessment after first-line therapy for follicular lymphoma in the Phase III GALLIUM study

Multivariate analysis for PFS and OS:
Lugano 2014 criteria

	PFS, n=508		OS,† n=519	
Parameter*	HR (95% CI)	p-value	HR (95% CI)	p-value
PET status (non-CMR vs CMR)	**0.2 (0.1, 0.3)**	**<0.0001**	**0.2 (0.1, 0.5)**	**<0.0001**
Treatment arm (R-chemo vs G-chemo)	**0.6 (0.4, 0.8)**	**0.005**	0.8 (0.4, 1.5)	0.42
Induction chemo (Benda vs CHOP/CVP)	0.9 (0.6, 1.5)	0.76	0.5 (0.2, 1.1)	0.09
FLIPI category (Low vs intermediate)	1.1 (0.6, 1.9)	0.84	0.8 (0.3, 2.1)	0.61
(Low vs high)	1.6 (0.9, 2.7)	0.09	2.0 (0.8, 4.8)	0.13

Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study

JOURNAL OF CLINICAL ONCOLOGY



Pts with early progression had an increased risk of death with an HR=20.0

Group	R-CHOP Total No.	R-CHOP No. of Deaths	HR	95% CI
Reference	420	44		
Early POD	110	57		
FLIPI adjusted	110	57	6.44	4.33 to 9.58
Unadjusted	420	44	7.17	4.83 to 10.65

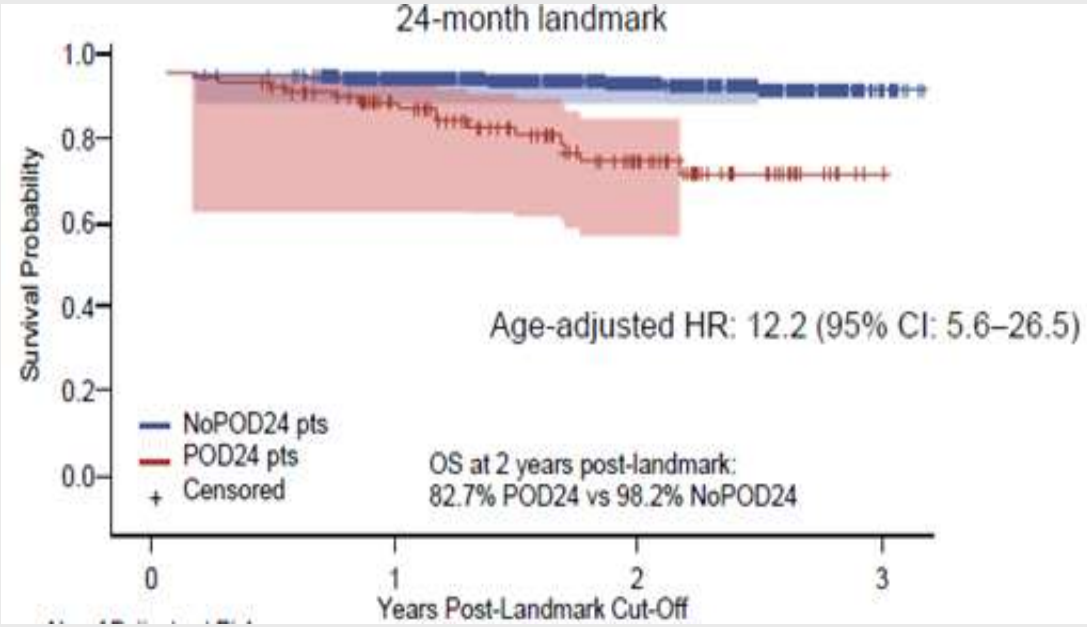
Trend maintained after adjustement for FLIPI

Casulo C, et al; JCO 2015

Early Disease Progression Predicts Poorer Survival in Patients with Follicular Lymphoma (FL) in the GALLIUM Study

ASH

- Explanatory analysis aimed to assess whether POD24 and POD at time points other than 24 months predicted OS in GALLIUM trial
- The risk of death increased 26-fold following a POD24 event



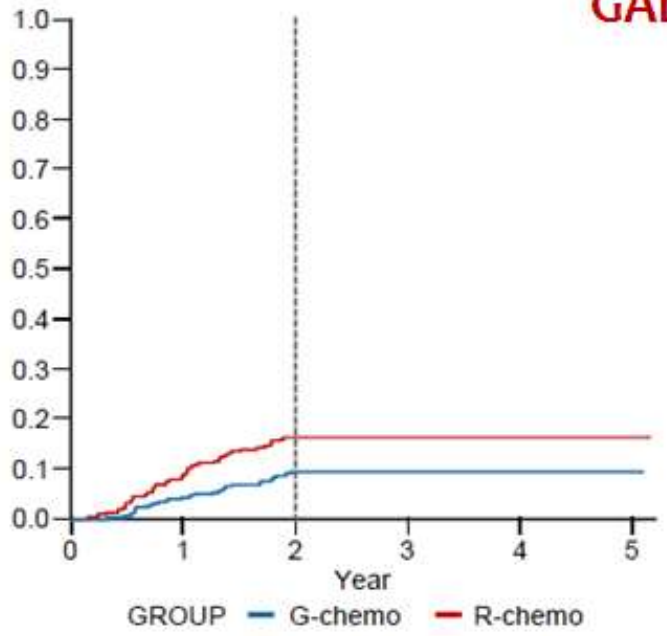
2-yrs OS	POD	NO POD
6 months	20%	95,8%
12 months	58,4%	97,6%
18 months	76,5%	97,8%

- Mortality risk was higher the earlier patient progressed but early progressors cannot be identified in advance
- Analysis of POD24 in GALLIUM study confirms Casulo data

Early Disease Progression Predicts Poorer Survival in Patients with Follicular Lymphoma (FL) in the GALLIUM Study

ASH

GALLIUM: POD24



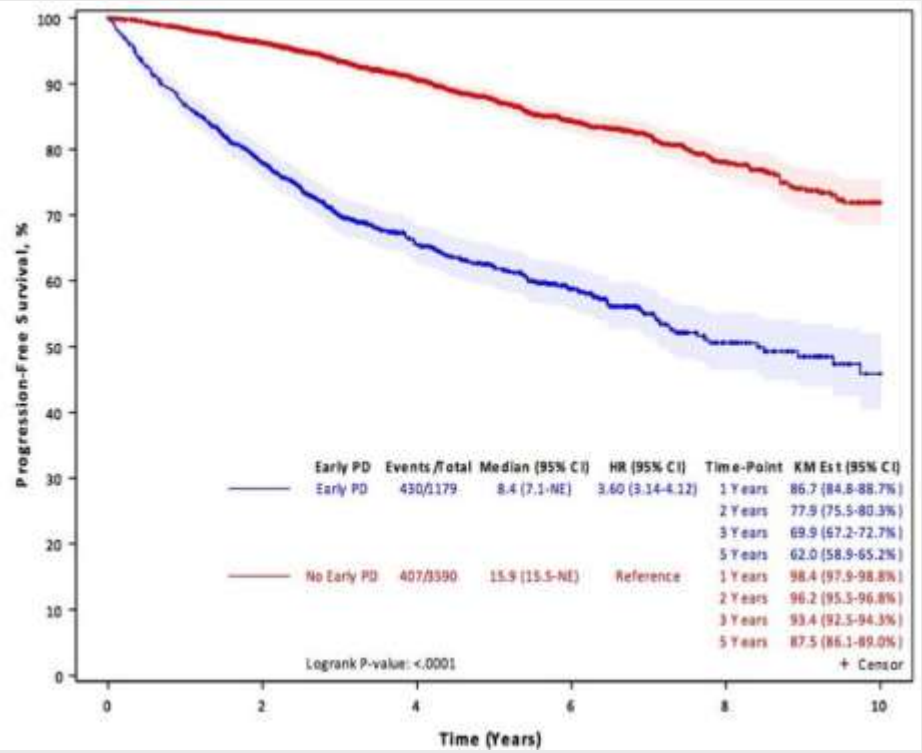
	R-chemo, N=601	G-chemo, N=601	Risk reduction G-chemo vs R-chemo
POD24 events*, %	16.7	9.7	41.5%†
POD24 events, n	72	43	

- G-chemo was associated with a reduced relative risk of a POD24 event by 42% compared to R-chemo: **demonstration of the superiority of G-chemo over R-chemo**
- Post-progression survival for POD24 pts appeared to be similar in the 2 arms: **suggestion that post-progression survival is not compromised by 1st line G-chemo**

Validation of POD24 As a Robust Early Clinical Endpoint of Poor Survival in Follicular Lymphoma: Results from the Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) Investigation Using Individual Data from 5,453 Patients on 13 Clinical Trials

ASH

- **POD24 was associated with poor subsequent OS (HR 5.24) after adjusting for gender, PS, FLIPI and B2M**



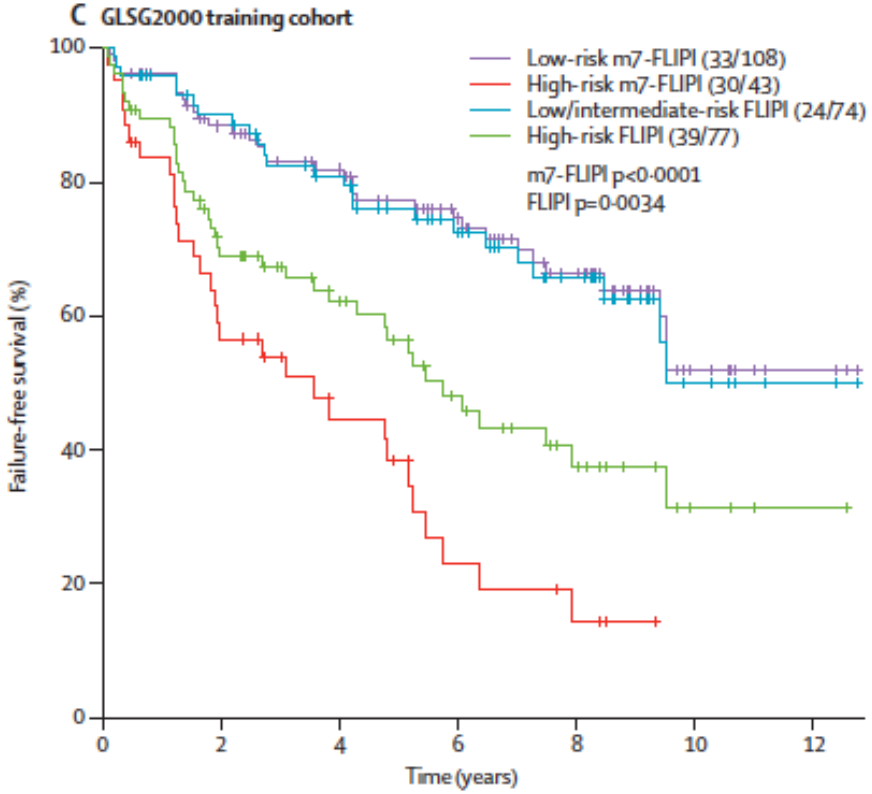
- This trial validates early progression as robust indicator of poor FL survival
- Male gender, poor PS, high FLIPI score and elevated baseline B2M are predictors of early death and progression
- **POD24 can be used as early clinical endpoint in prospective clinical trials**

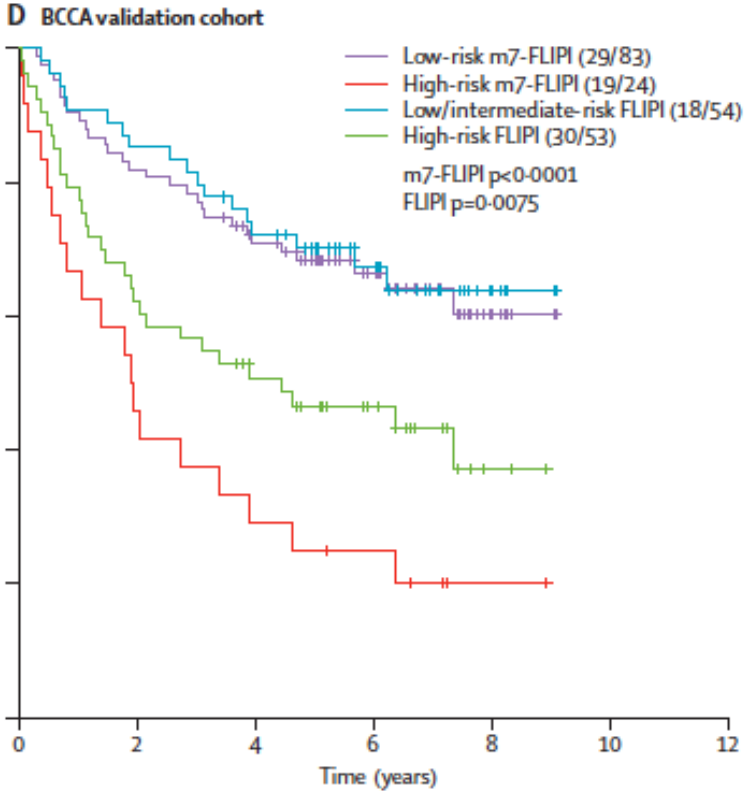
How can we identify high risk patients?

- FLIPI or FLIPI2 or M7-FLIPI
- BCL2/IgH rearrangement
- Post-induction PET
- Minimal residual disease
- Post-induction PET + Minimal residual disease
- Total Metabolic Tumor Volume (TMTV)
- TMTV + post-induction PET

Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry

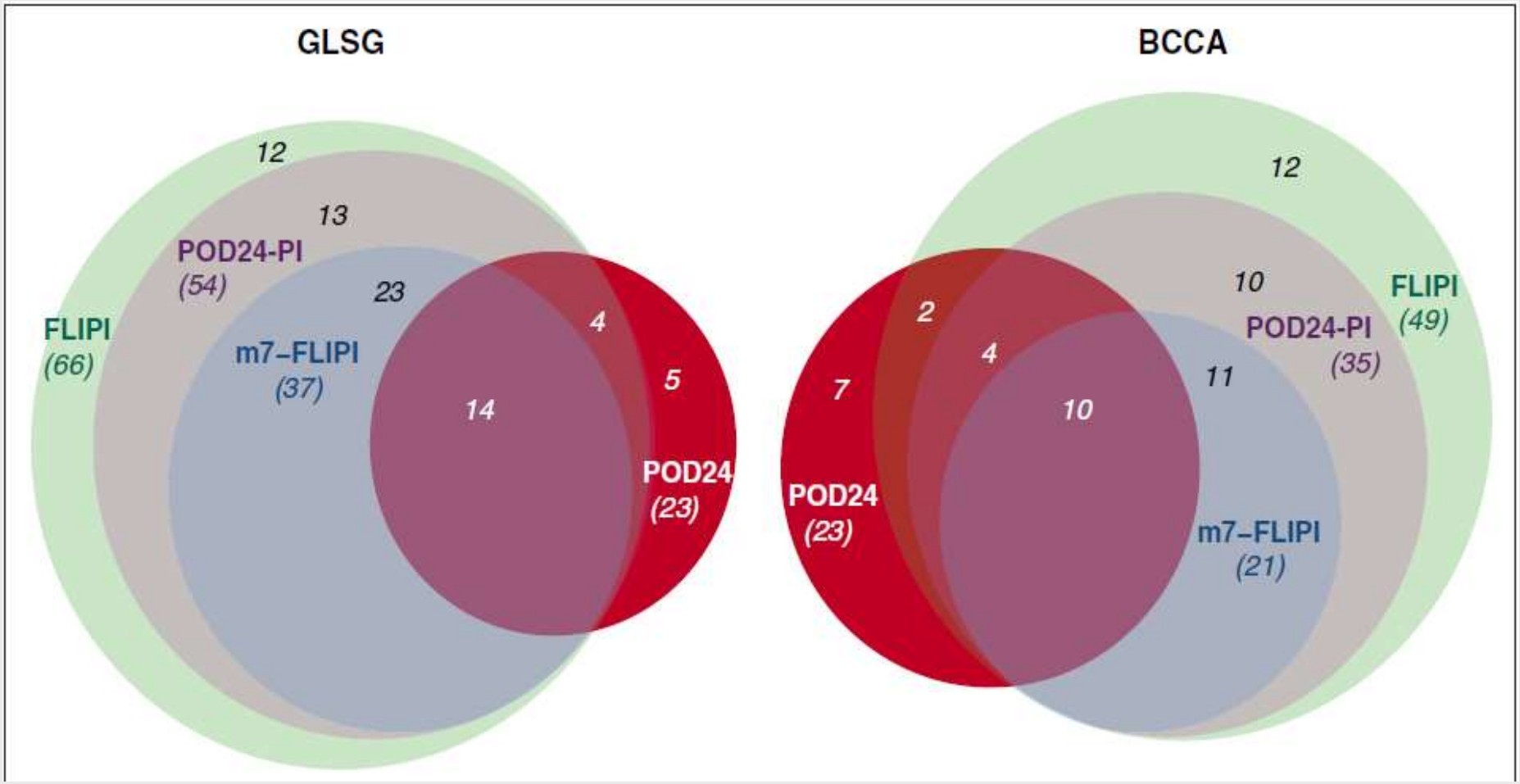
- 151 follicular lymphoma biopsy specimens within 1 year before beginning (R-CHOP) between 2000-2010





Pastore A, et al; Lancet oncol 2015

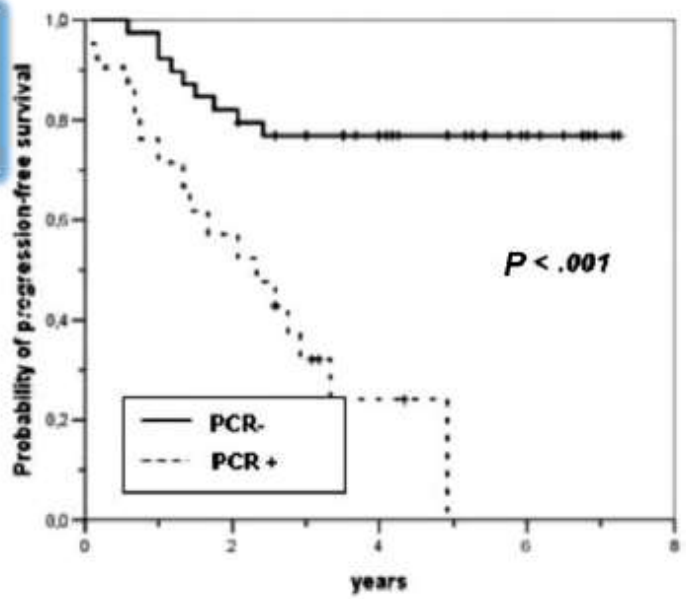
Clinicogenetic risk models predict early progression of follicular lymphoma after first-line immunochemotherapy



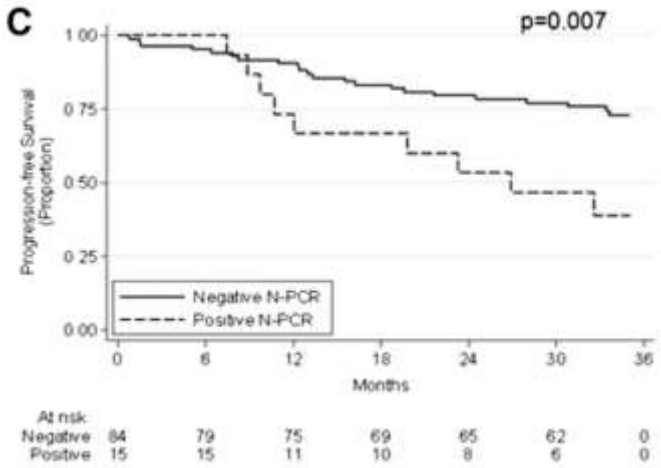
- 22%-30% of pts with POD24 were still not correctly identified as high risk by any of the pre-treatment risk models

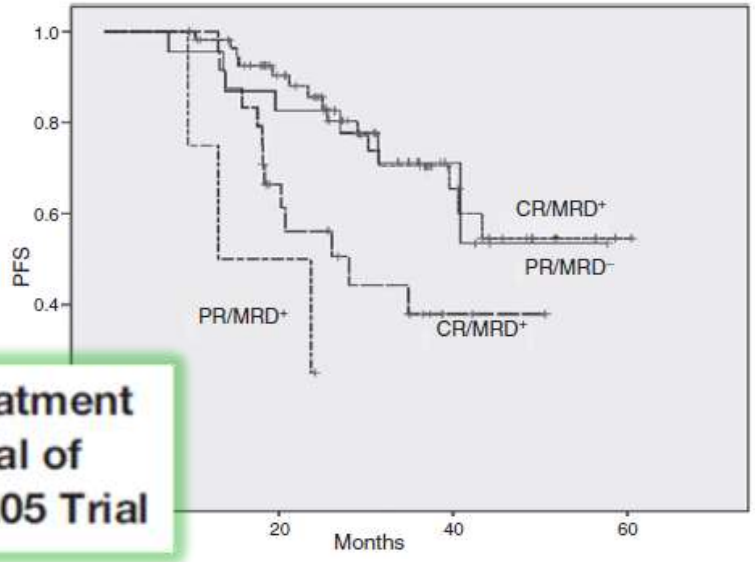
Jurinovic V, et al; Blood 2018

Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage



Persistence of minimal residual disease in bone marrow predicts outcome in follicular lymphomas treated with a rituximab-intensive program



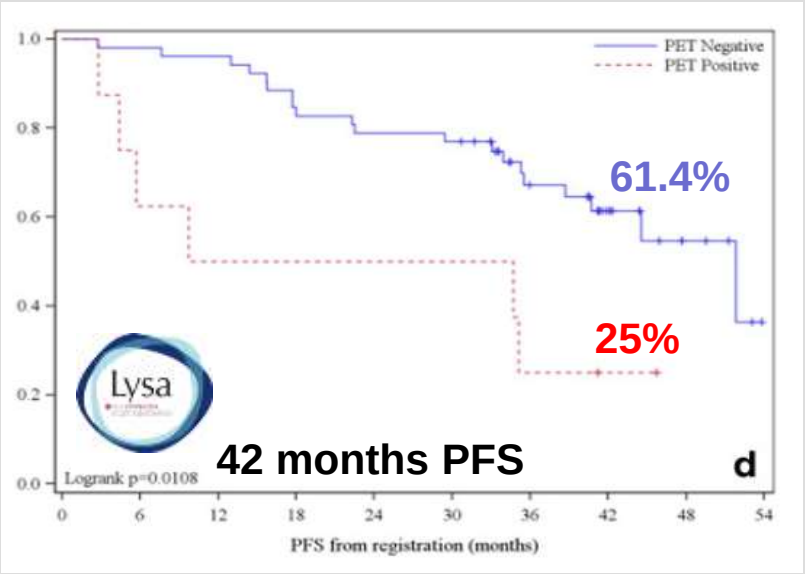


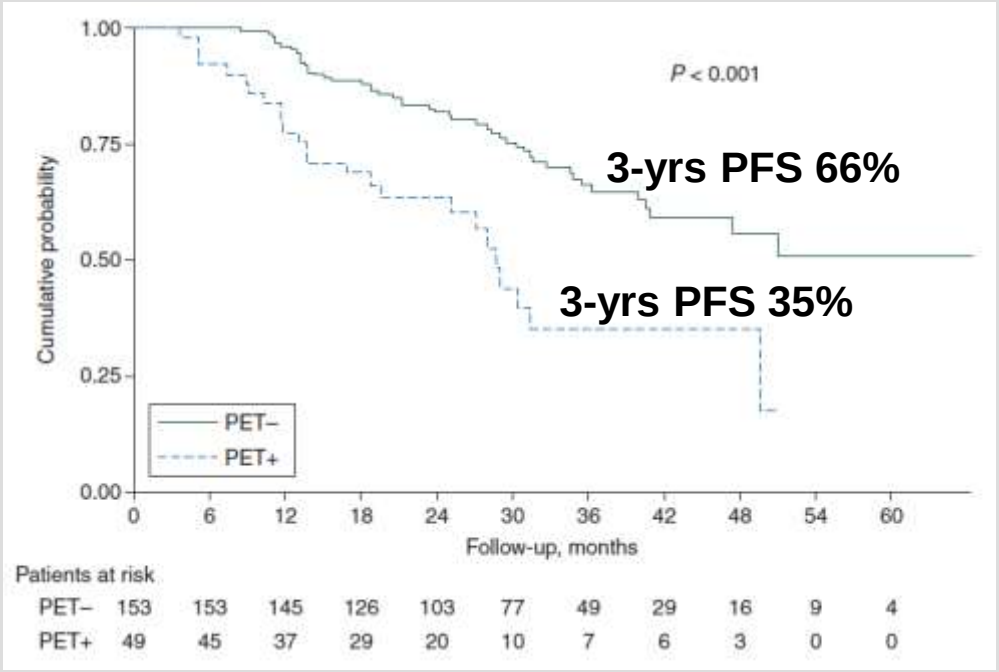
Minimal Residual Disease after Conventional Treatment Significantly Impacts on Progression-Free Survival of Patients with Follicular Lymphoma: The FIL FOLL05 Trial

Ladetto M, et al : Blood 2008
Ladetto M, et al : Blood 2013
Galimberti S, et al : Clin Cancer Res 2014

PET is strongly predictive of outcome after first-line immunochemotherapy for Follicular Lymphoma

The prognostic role of post-induction FDG-PET in patients with follicular lymphoma: a subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi (FIL)





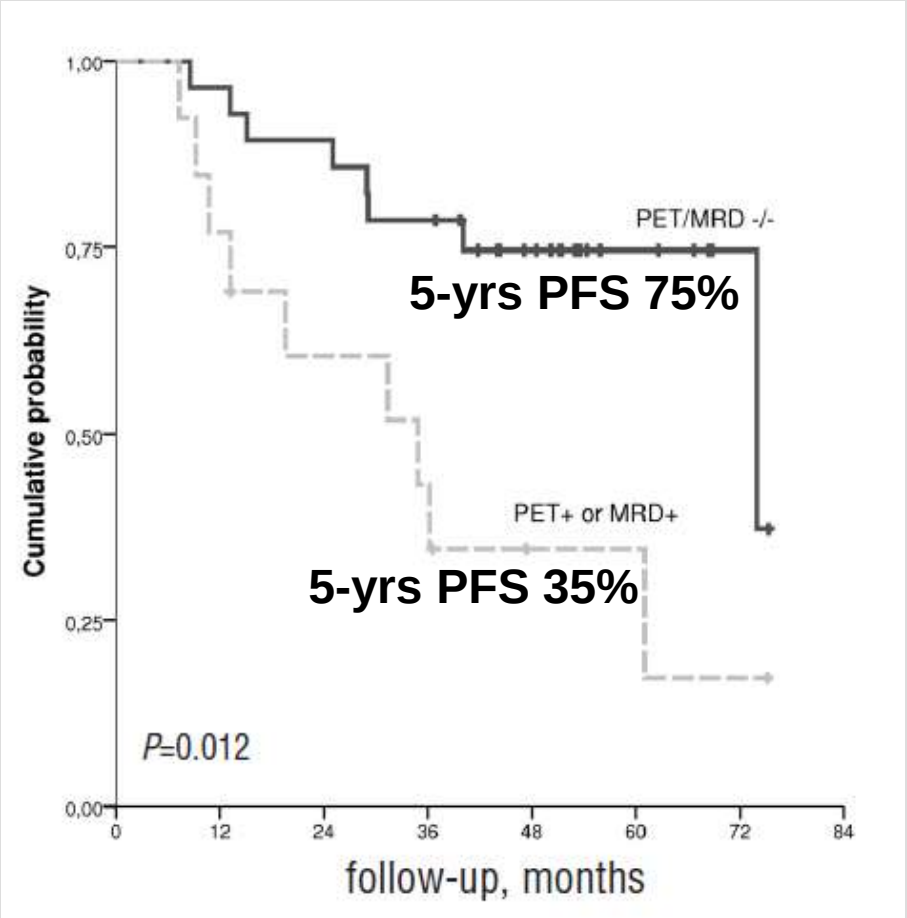
Tychyj-Pinel C, et al: Eur J Nucl Med Mol Imaging 2014

Luminari S, et al : Annals Oncol 2014

Positron emission tomography response and minimal residual disease impact on progression-free survival in patients with follicular lymphoma. A subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi

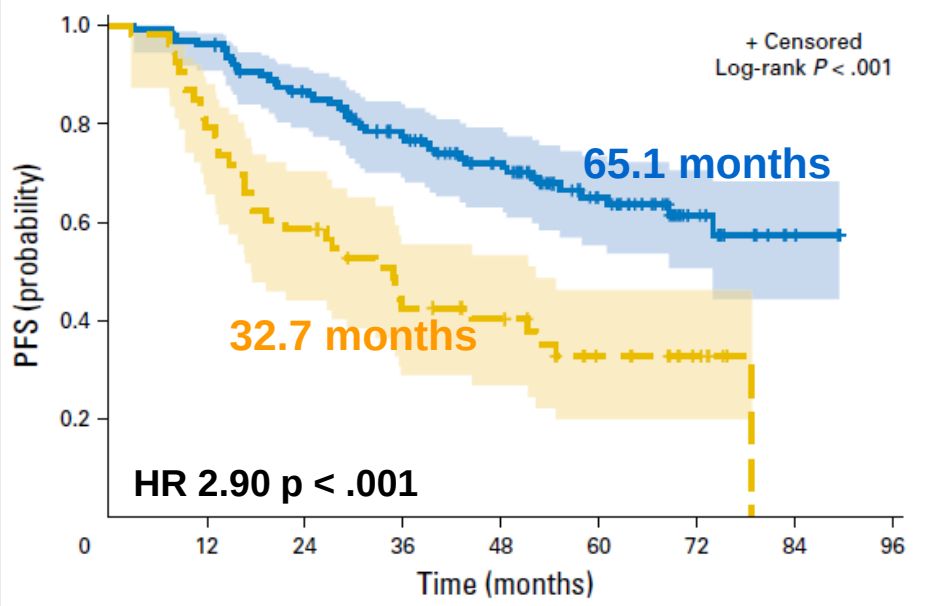
- 41 pts with data on both PET and BCL2/IGH at the EOT (FOLL05)

- Median FU: 53 months



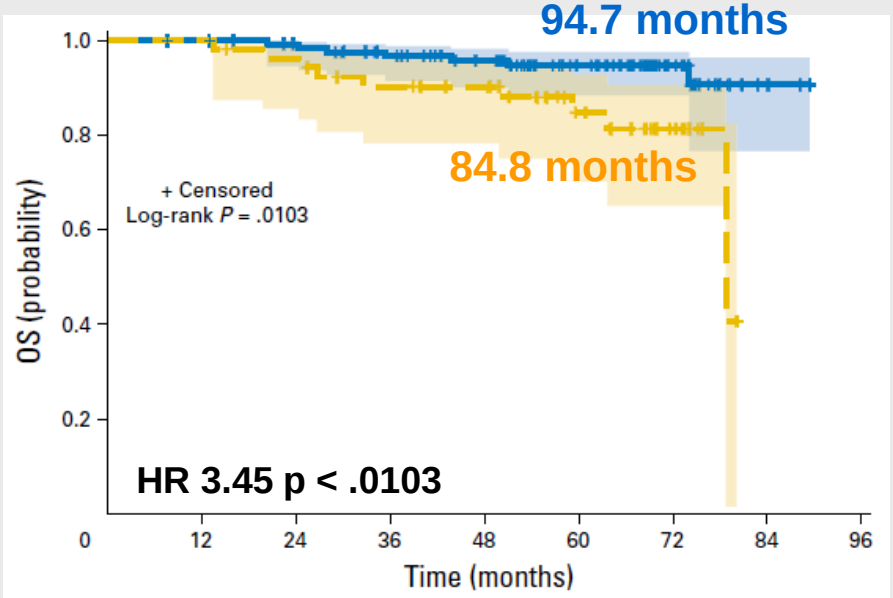
Luminari S, et al : Hematologica 2016

Baseline Metabolic Tumor Volume Predicts Outcome in High–Tumor-Burden Follicular Lymphoma: A Pooled Analysis of Three Multicenter Studies



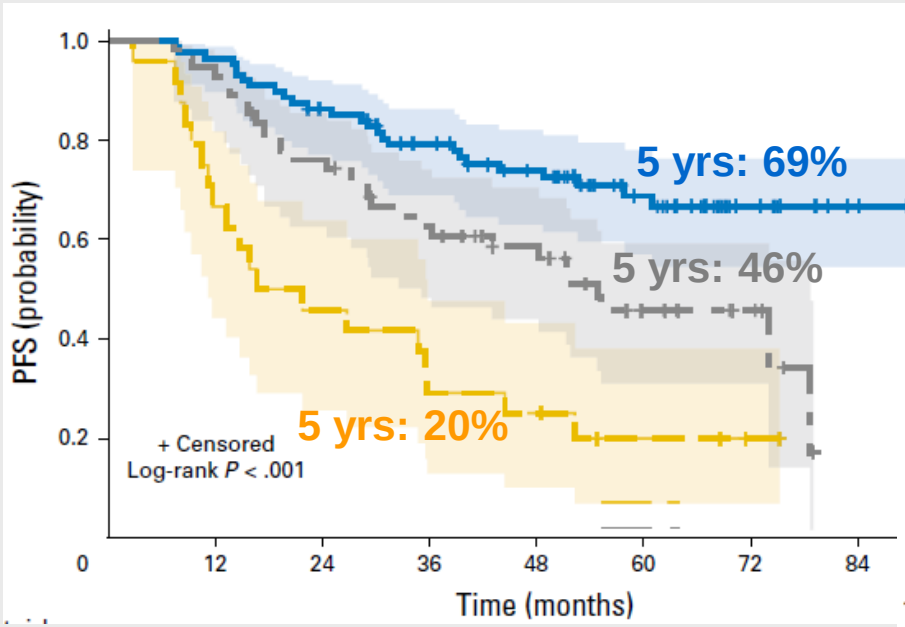
Median PFS for pts with high: <3 years

Median PFS for pts with low TMTV: >6 years

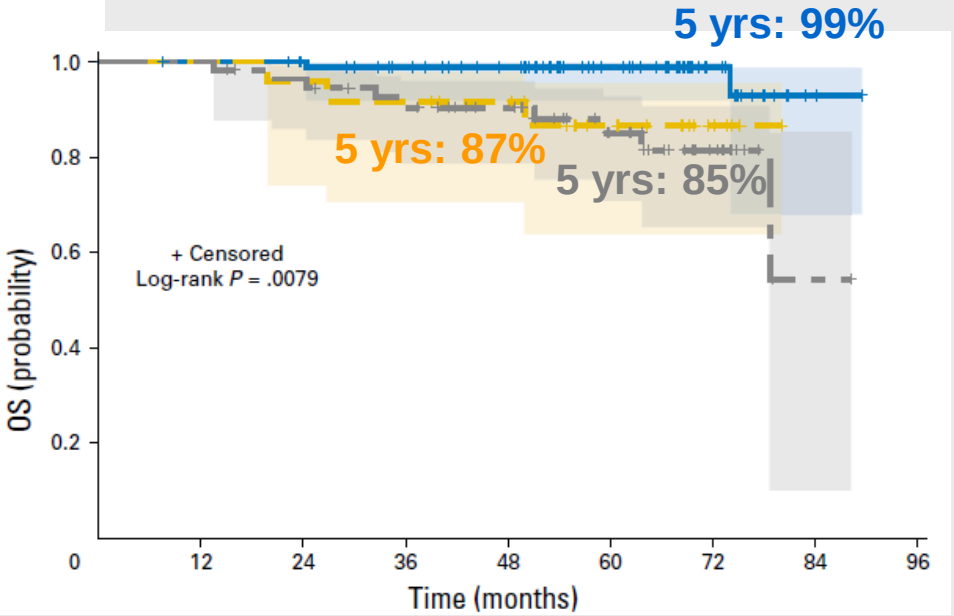


Meignan M, et al; JCO 2016

Baseline Metabolic Tumor Volume Predicts Outcome in High–Tumor-Burden Follicular Lymphoma: A Pooled Analysis of Three Multicenter Studies



- Both TMTV and FLIPI2 were independent predictors of PFS and gave added predictive value in combination

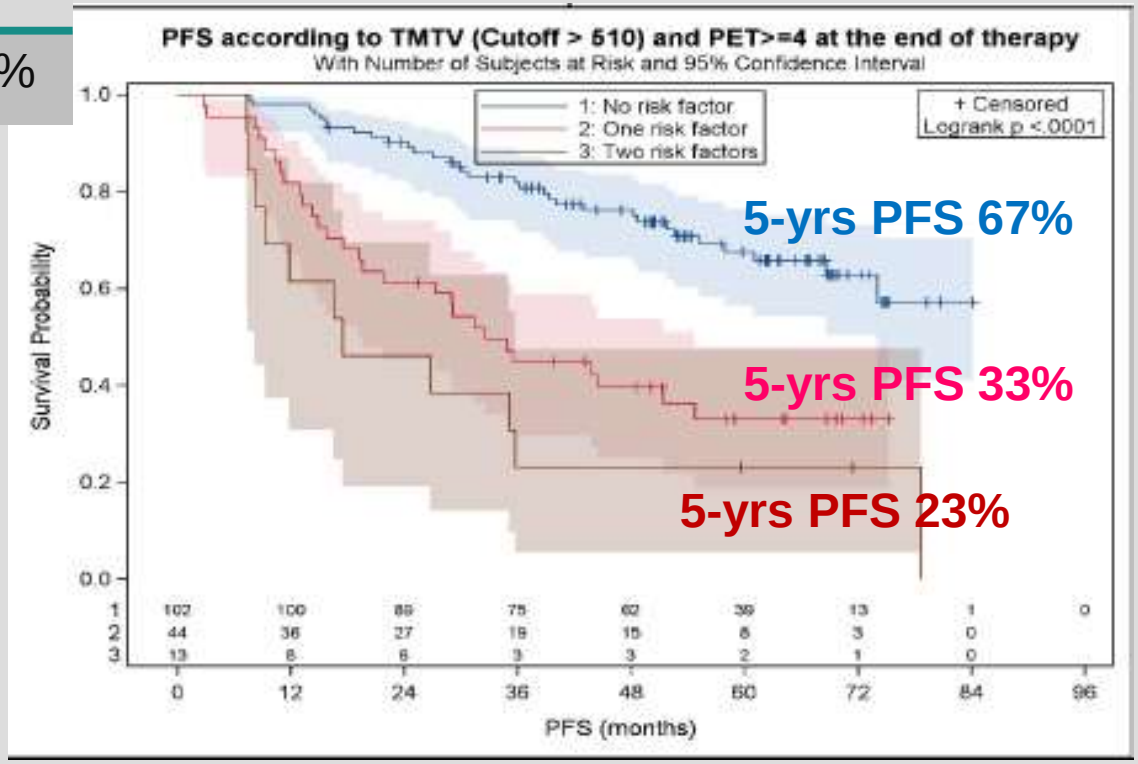


- **MTMV >510 cm^3**
- **FLIPI2 score of 3-5**
  - Group 1: neither
  - Group 2: either 1 factor
  - Group 3: both

Meignan M, et al; JCO 2016

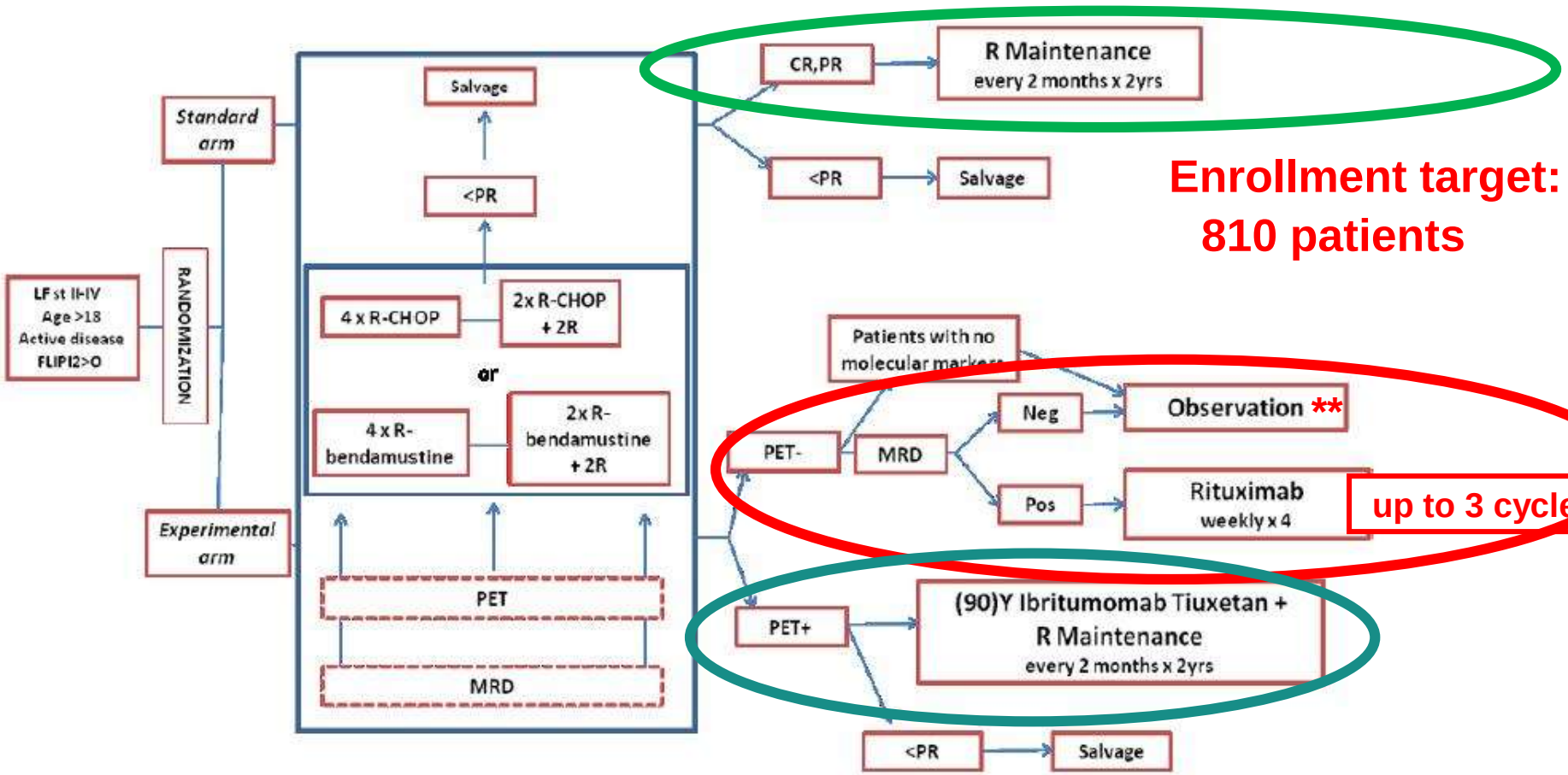
Prognostic model for high tumor burden follicular lymphoma integrating baseline and end induction PET: a LYSA/FIL study

PFS	2-yrs	5-yrs
NO risk factor	90%	67%
ONE risk factor	61%	33%
TWO risk factors	46%	23%



Cottereau AS, et al : Blood 2018

FOLL12 study: A phase 3 multicenter, randomized study comparing standard treatment with Rituximab maintenance vs response adapted post-induction treatment as first line treatment in advanced FL



Enrollment target: 810 patients

****If PCR- →+ Rituximab weekly x 4 doses up to 3 cycles**

Ideal therapy for elderly patients

- In the last decade FIL has achieved good experience in treating elderly FL patients with brief chemoimmunotherapy strategy

- An ideal and specifically devised therapy for elderly patients must be well tolerated, highly effective with low toxicity, feasible in an out-patient setting and brief lasting

- Retrospective analysis to compare two FIL trials specifically devised for elderly advanced stage FL requiring therapy

C. Boccomini, et al; SIE 2017

FLE09 treatment scheme

Sep 2009 – Nov 2011:
76 eligible pts

R-BM x 4 once a month
Rituximab 375 mg/m^2 day 0 or 1 (day 8 on cycle 1)
Mitoxantrone 8 mg/m^2 iv day 1
Bendamustine 90 mg/m^2 iv days 1-2

Rituximab x 4 once a week

29 CENTRES

Clinical and molecular follow-up
(6, 12, 18, 24 months)

Mundipharma provided Rituximab and Bendamustine free and partially supported the study

C. Boccomini, et al; SIE 2017

ML17638 treatment scheme

Roche provided Rituximab free and partially supported the study

33 CENTRES

R-FND x 4 once a month

Rituximab 375 mg/m^2 g 1 (d 8 on cycle 1)
Fludarabine 25 mg/m^2 dd 2-4
Mitoxantrone 10 mg/m^2 d 2
Dexamethasone 10 mg dd 2-4

Rituximab x 4 once a week

32 pts
Not Randomized

Jan 2004 – Dec 2007:
242 screened pts
234 eligible pts

CR/PCR+/- or PR
RANDOM: 202 pts

101 pts

Rituxima[illegible]aintenance x 4
at mo[illegible], 11, 13, 15

101 pts

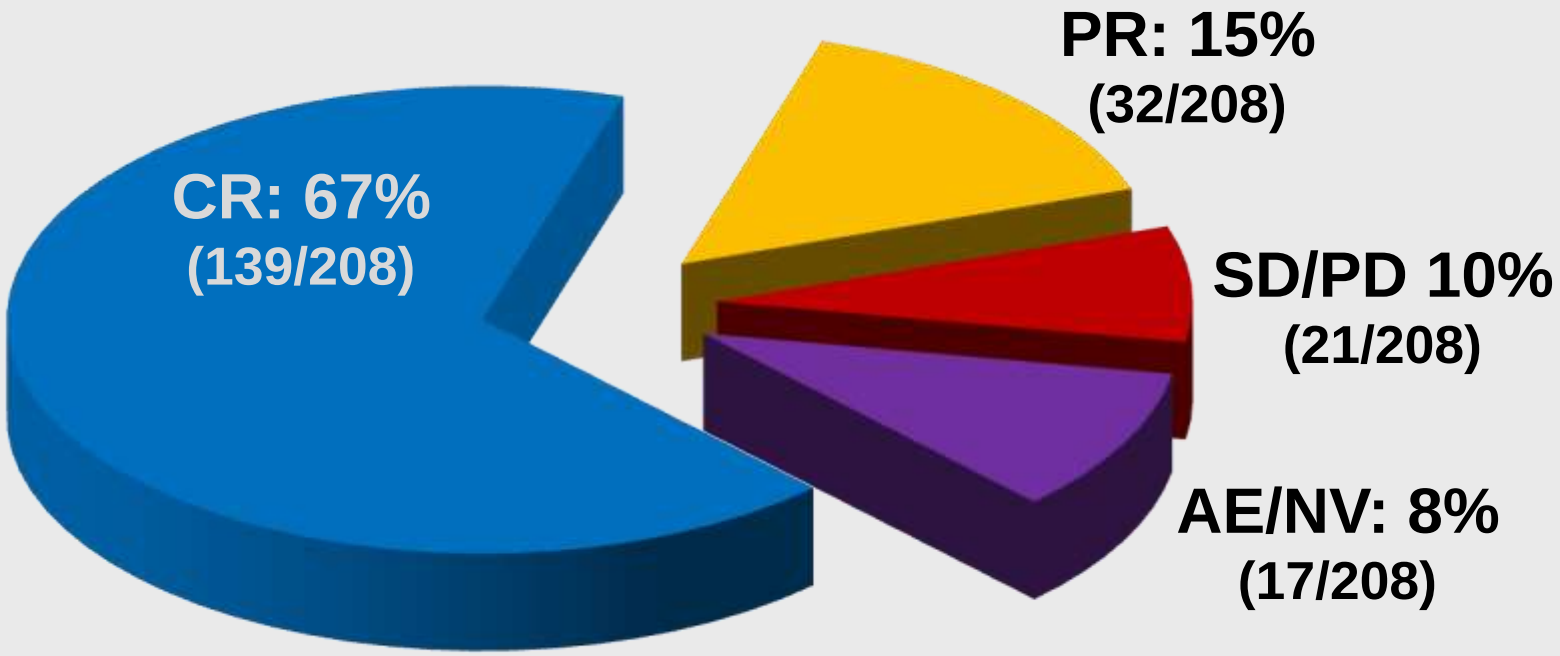
Observation

133 pts

C. Boccomini, et al; SIE 2017

Response to treatment: 208 evaluable pts

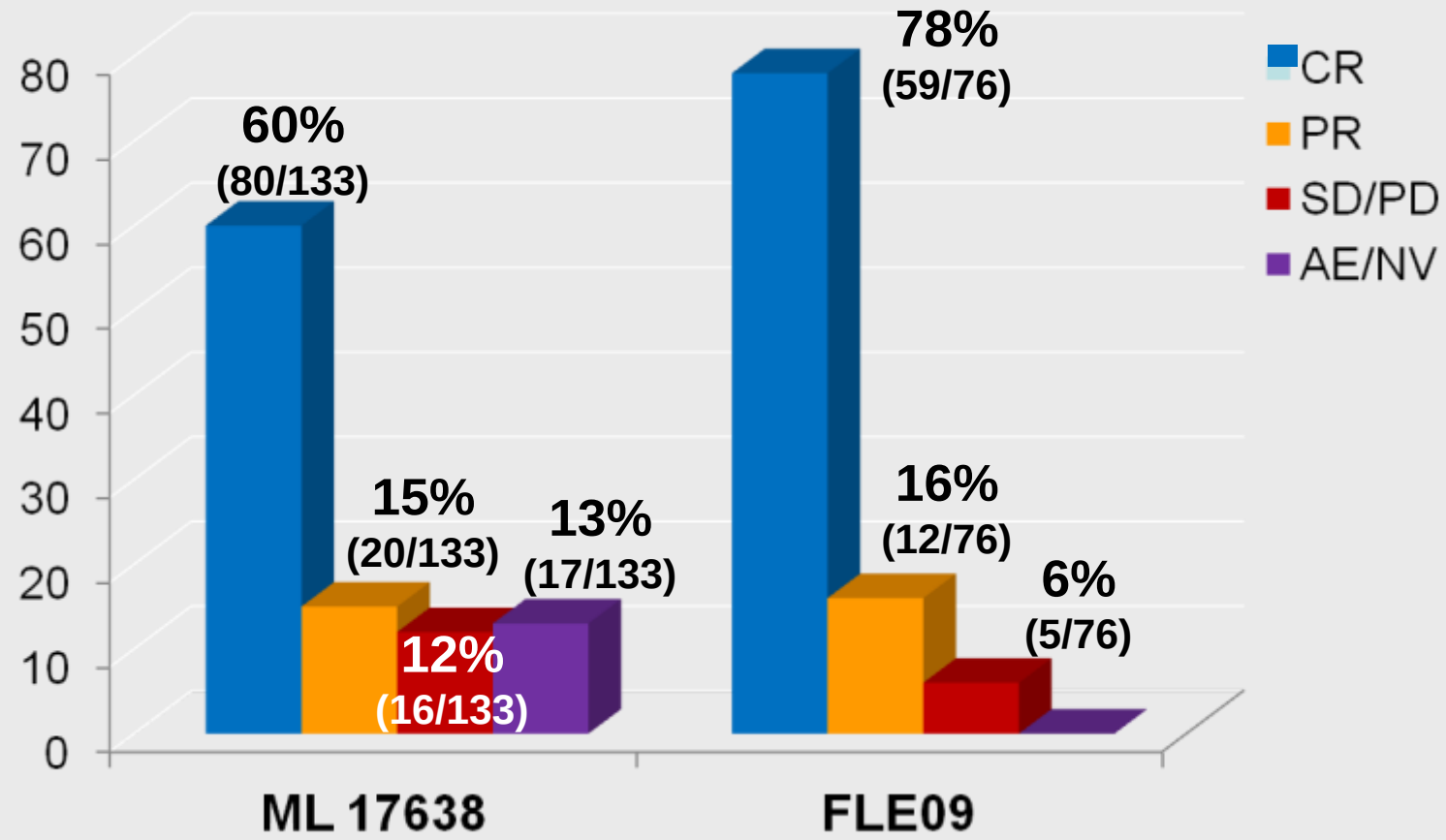
OVERALL RESPONSE RATE: 82%



C. Boccomini, et al; SIE 2017

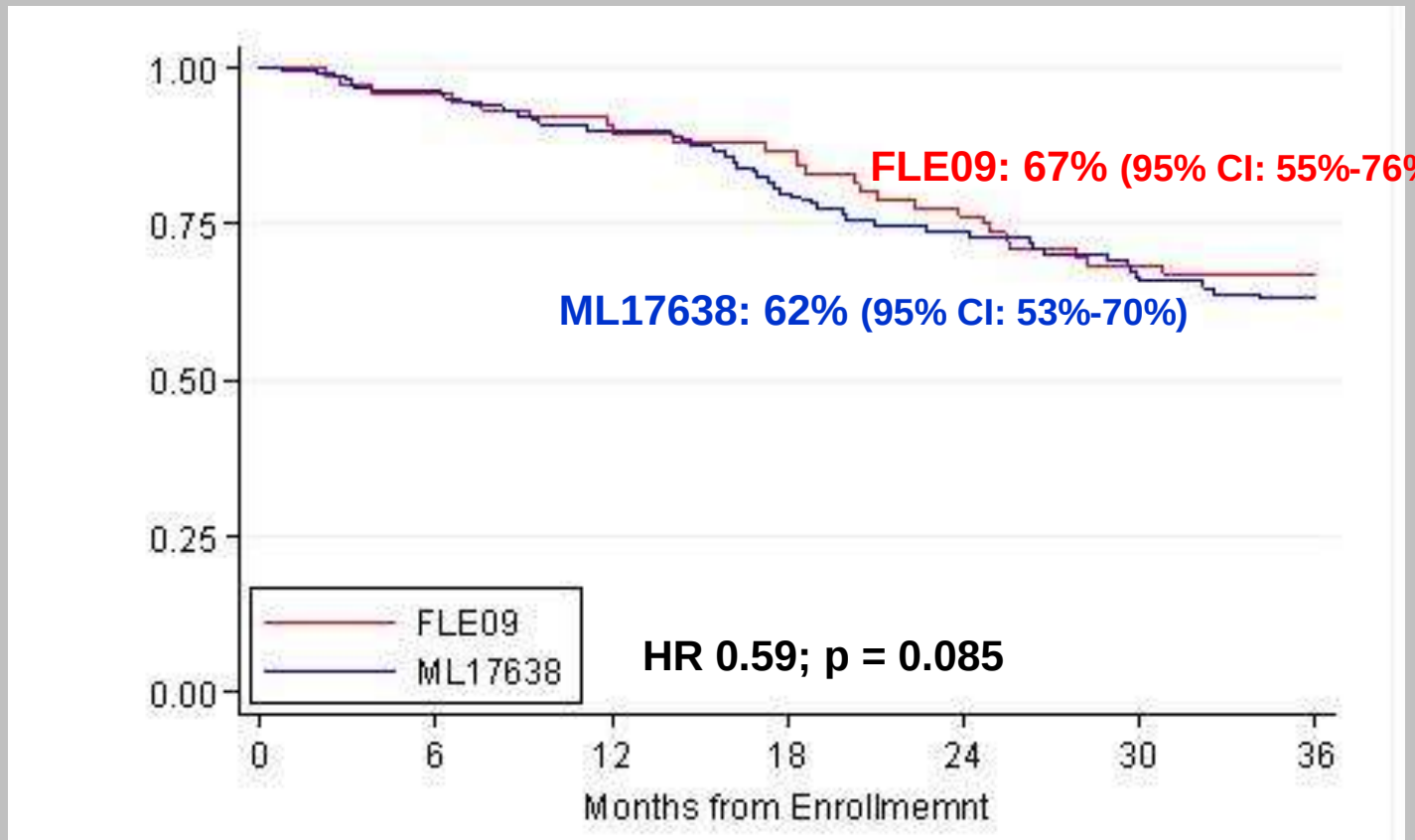
Response to treatment: 208 evaluable pts

RESPONSE ACCORDING TO TREATMENT



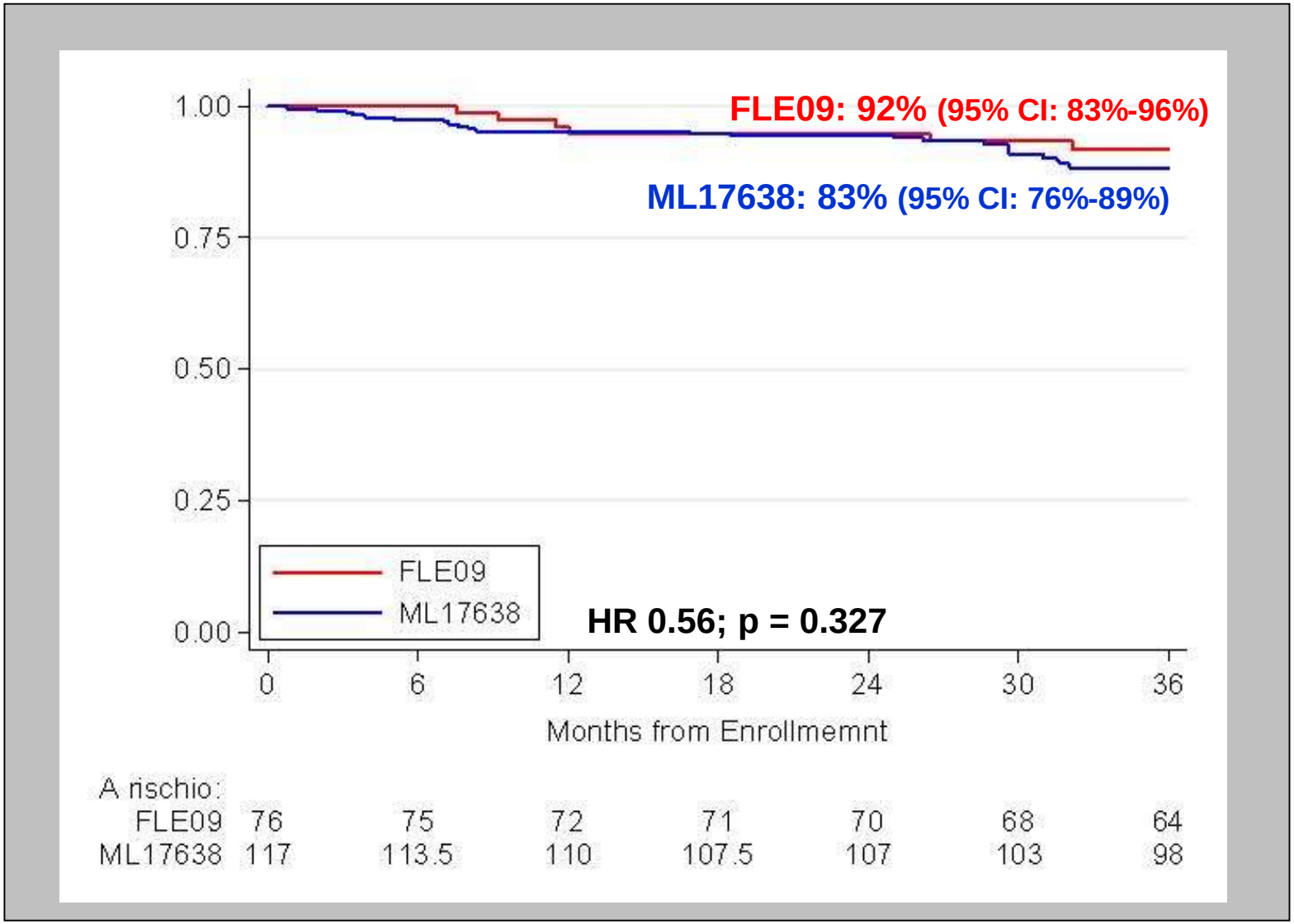
C. Boccomini, et al; SIE 2017

3-yrs PFS according to trial



C. Boccomini, et al; SIE 2017

3-yrs OS according to trail



C. Boccomini, et al; SIE 2017

Conclusions

- A brief chemoimmunotherapy strategy can induce high CR rate and prolonged PFS in elderly untreated advanced stage FL patients
- Both regimen are effective and safe but
- **R-BM regimen seems to induce higher CR rate and better PFS with reduced toxicity**
- Substitution of Fludarabine with Bendamustine allows curative approach to an older patient cohort
- Overall, brief chemoimmunotherapy strategy confirms its effective and safety profile in comparison to standard approach in elderly patients

	R-BM x 4	R-FND x 4	B-R x 6(1)	R-CVP/R-CHOP x6-8(2)
Median age	71 (65-79)	65 (62-69)	60 (51-67)	73/70 (65-80)
ORR (CR)	94% (78%)	75% (60%)	93% (40%)*	88%/94%
2-yrs PFS	76%	73%	75%	71%/79%
2-yrs PFS for FLIPI≥3	76%	n.a.	n.a.	60%/79%
Neutropenia (grade 3-4)	57%	61%	29%	n.a.
Neutropenic fever	9%	3%	n.a.	n.a.
Infections (all grade)	13%	22%	37%	n.a.

** Data on all histological subgroups*

(1) Rummel MJ, Lancet 2013

(2) Unpublished data by courtesy of Friedberg J on the behalf of National Lymphocare Study (NLCS)

Conclusions

- A brief chemoimmunotherapy strategy can induce high CR rate and prolonged PFS in elderly untreated advanced stage FL patients
- Both regimen are effective and safe but
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- Overall, brief chemoimmunotherapy strategy confirms its effective and safety profile in comparison to standard approach in elderly patients

	R-BM x 4	R-FND x 4	FIL FOLL05		
			R-CVP x8 n=29	R-CHOP x 6 + 2R n=31	R-FM x 6 +2 R n=37
Age	71 (65-79)	65 (62-69)	>65	>65	>65
3-yrs PFS	67%	62%	55%	61%	59%

C. Boccomini, et al; SIE 2017

CONCLUSIONS

- Excellent results with standard chemoimmunotherapy followed by Rituximab maintenance
- Clinical significant heterogeneity of Follicular Lymphoma patients
- Find a tool for identification of high risk patients is an unmet need
- A new generation of clinical trials for 1st line Follicular Lymphoma is warranted:
  - Low risk: excellent efficacy; the goal is not to harm
  - High risk: efficacy should be improved (new drugs in first line)

THANK YOU FOR YOUR ATTENTION