Incontro di aggiornamento sui disordini linfoproliferativi
e sui protocolli della Fondazione Italiana Linfomi
Torino, 24 novembre 2017

Nuove prospettive nella terapia di prima linea

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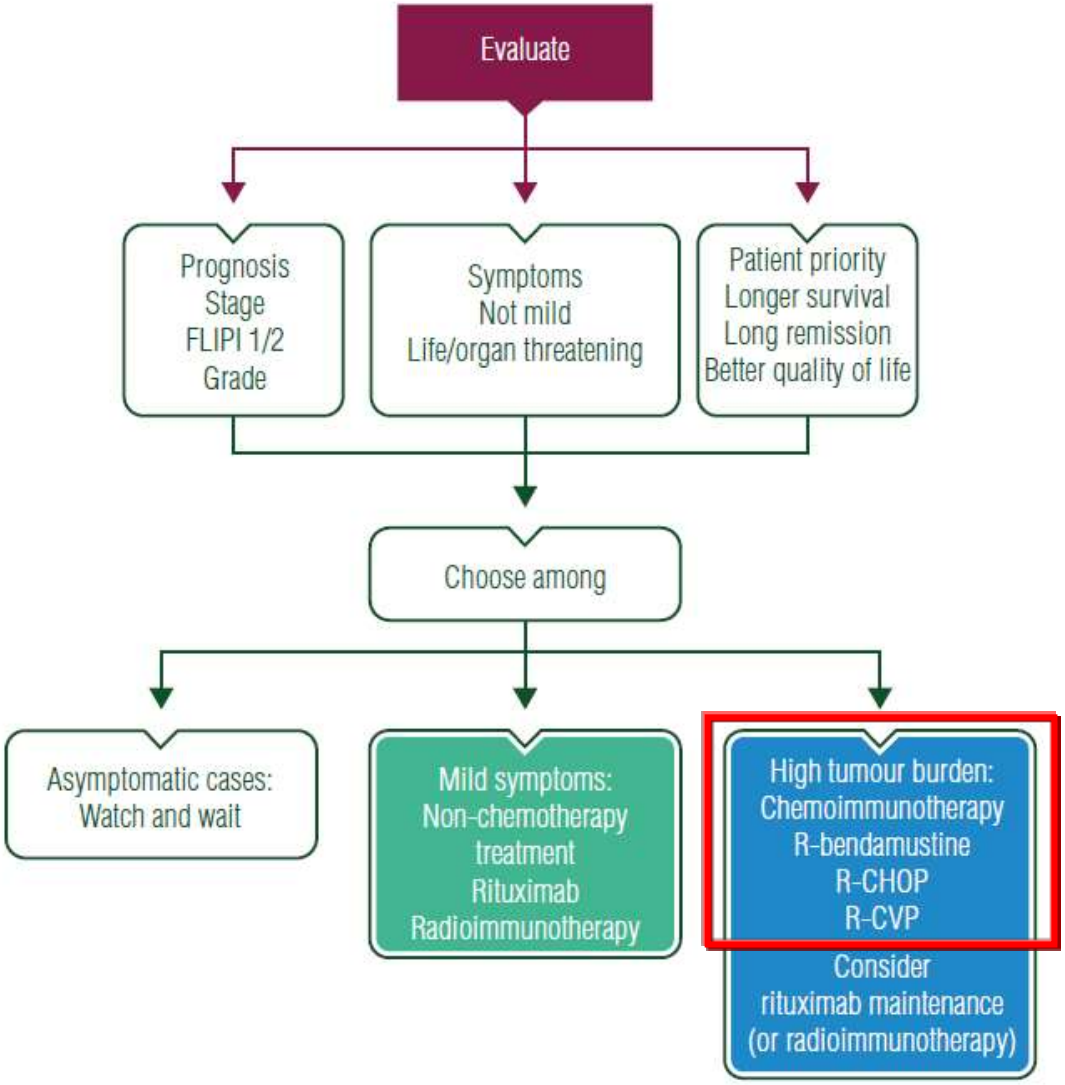
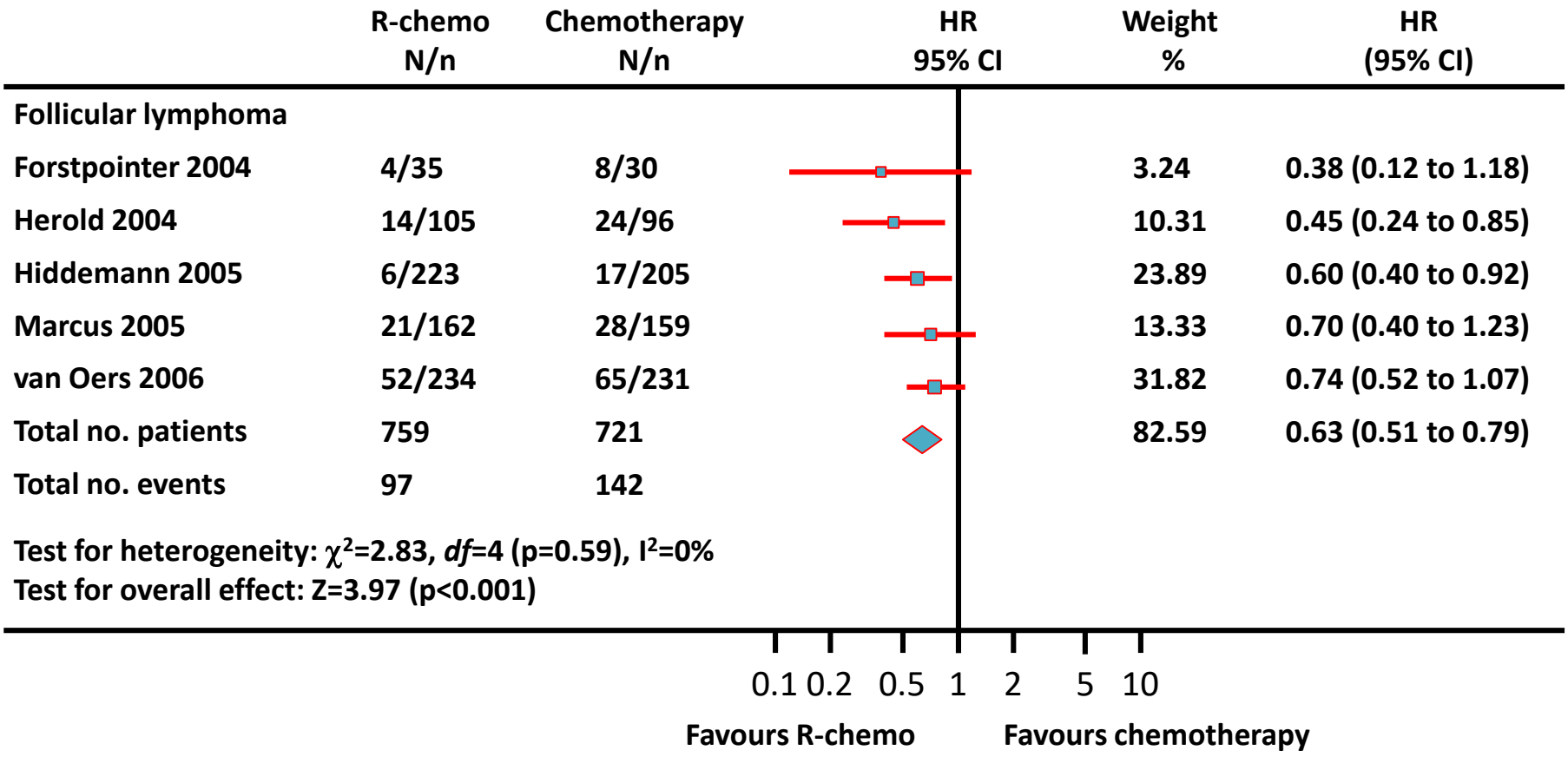
First line treatment in FL
Therapeutic algorithm



Dreyling, ESMO CR FL 2016

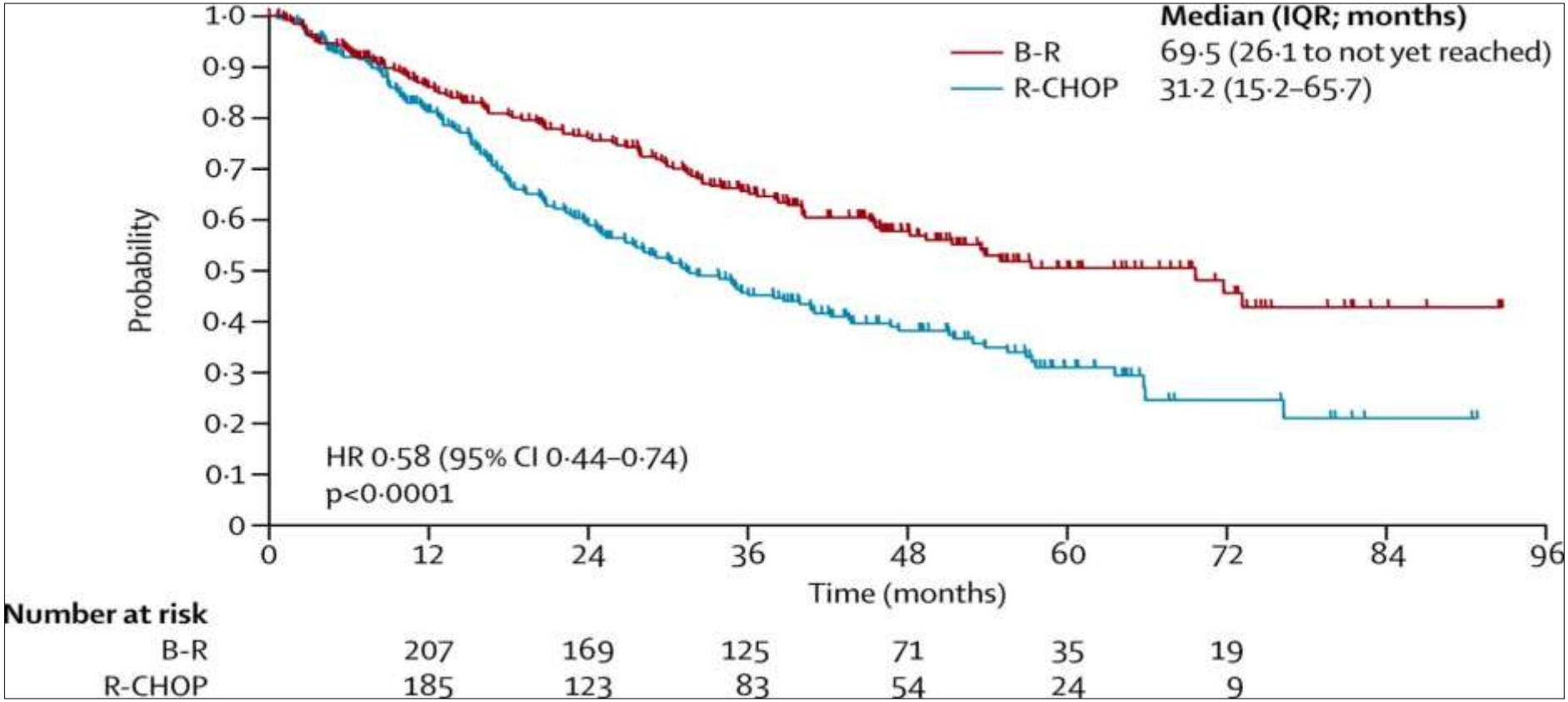
Immunochemotherapy in high tumor burden patients

Meta-analysis of chemotherapy vs R-chemotherapy
Overall survival



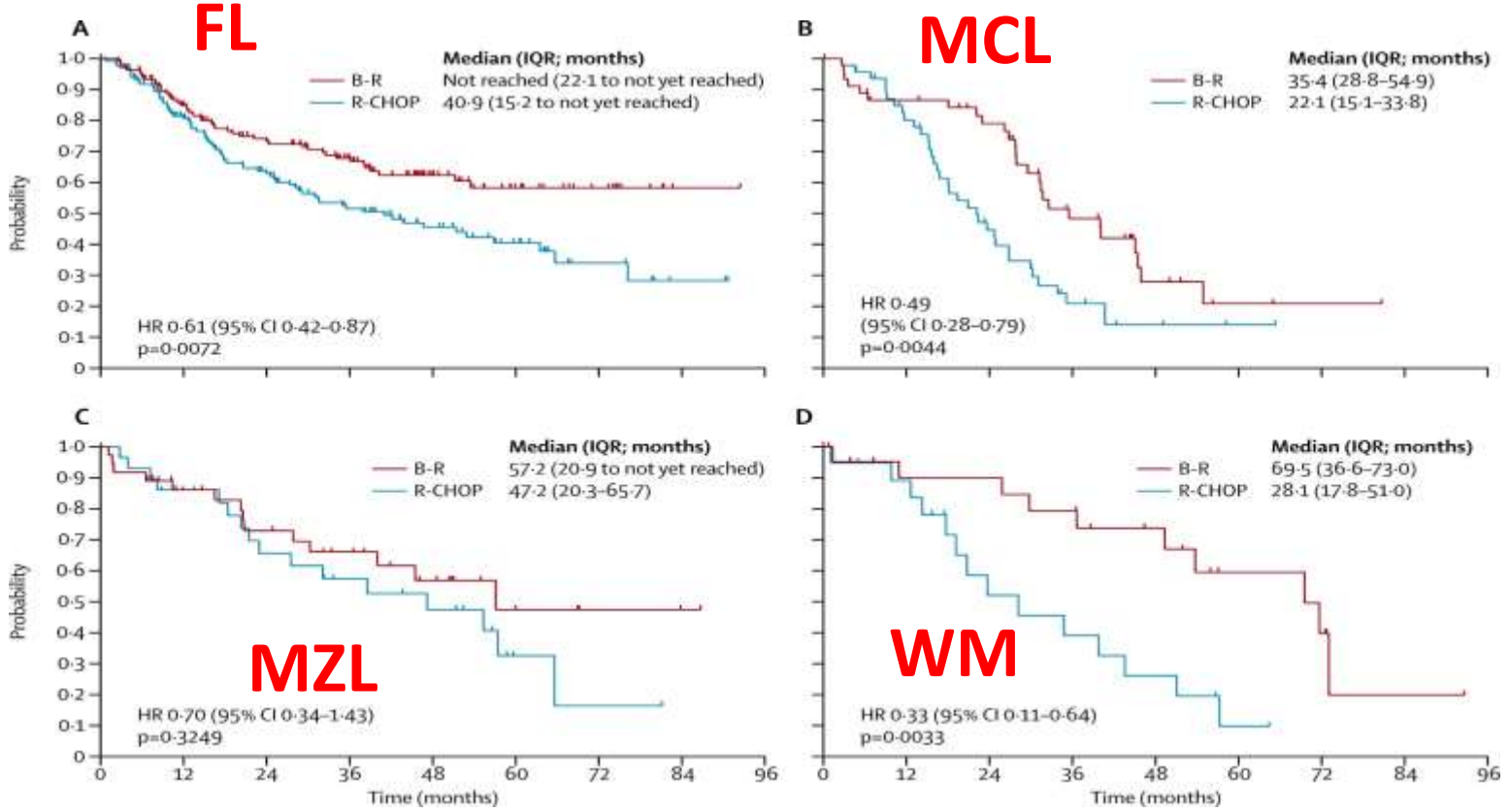
Schulz et al. J Natl Cancer Inst 2007

Stil study: PFS



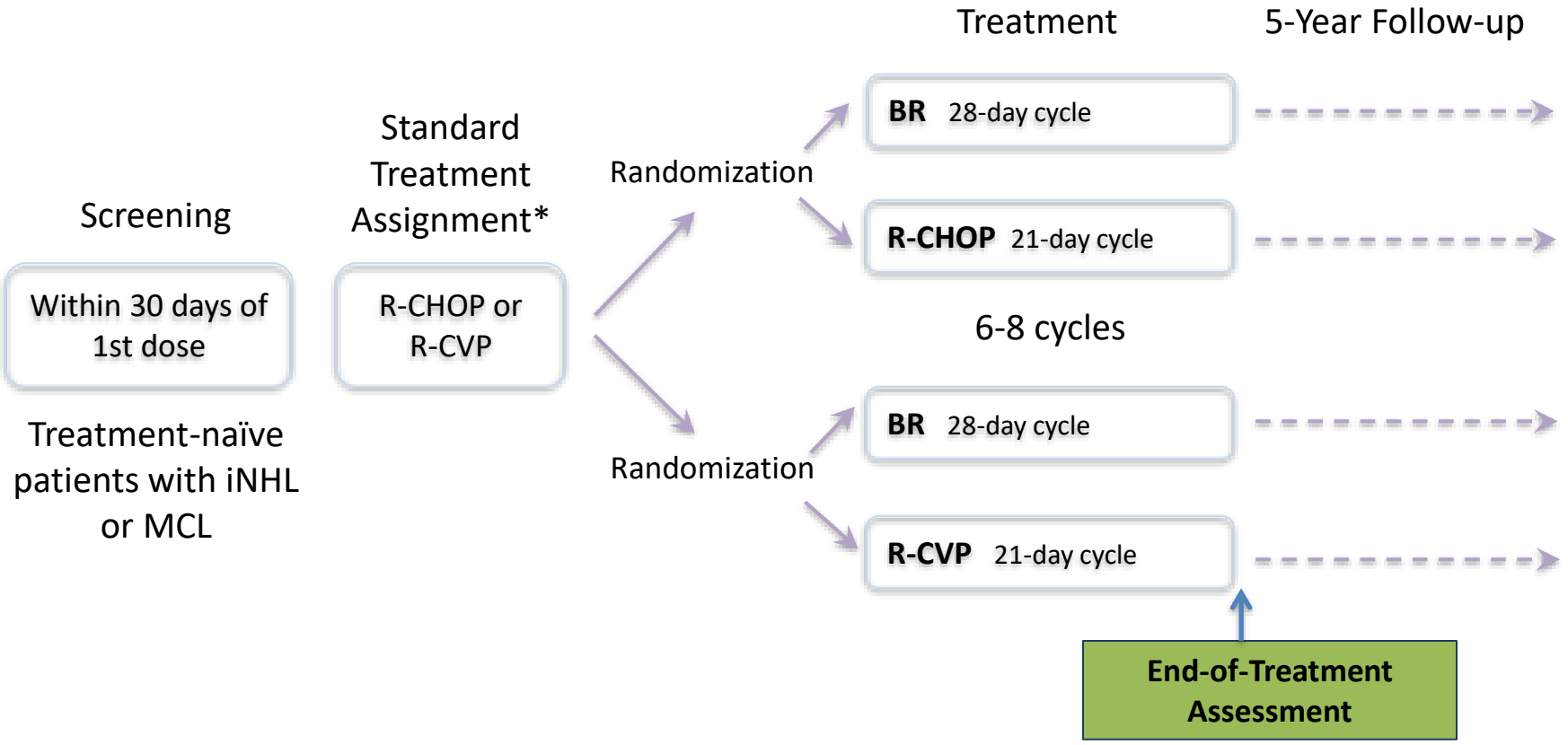
Rummel et al Lancet 2013

PFS for histotype



Rummel et al Lancet 2013

BRIGHT Study Design



*Based on investigator decision.

B: bendamustine; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: cyclophosphamide, vincristine, and prednisone; iNHL: indolent non-Hodgkin lymphoma; MCL: mantle cell lymphoma; R: rituximab.

Background

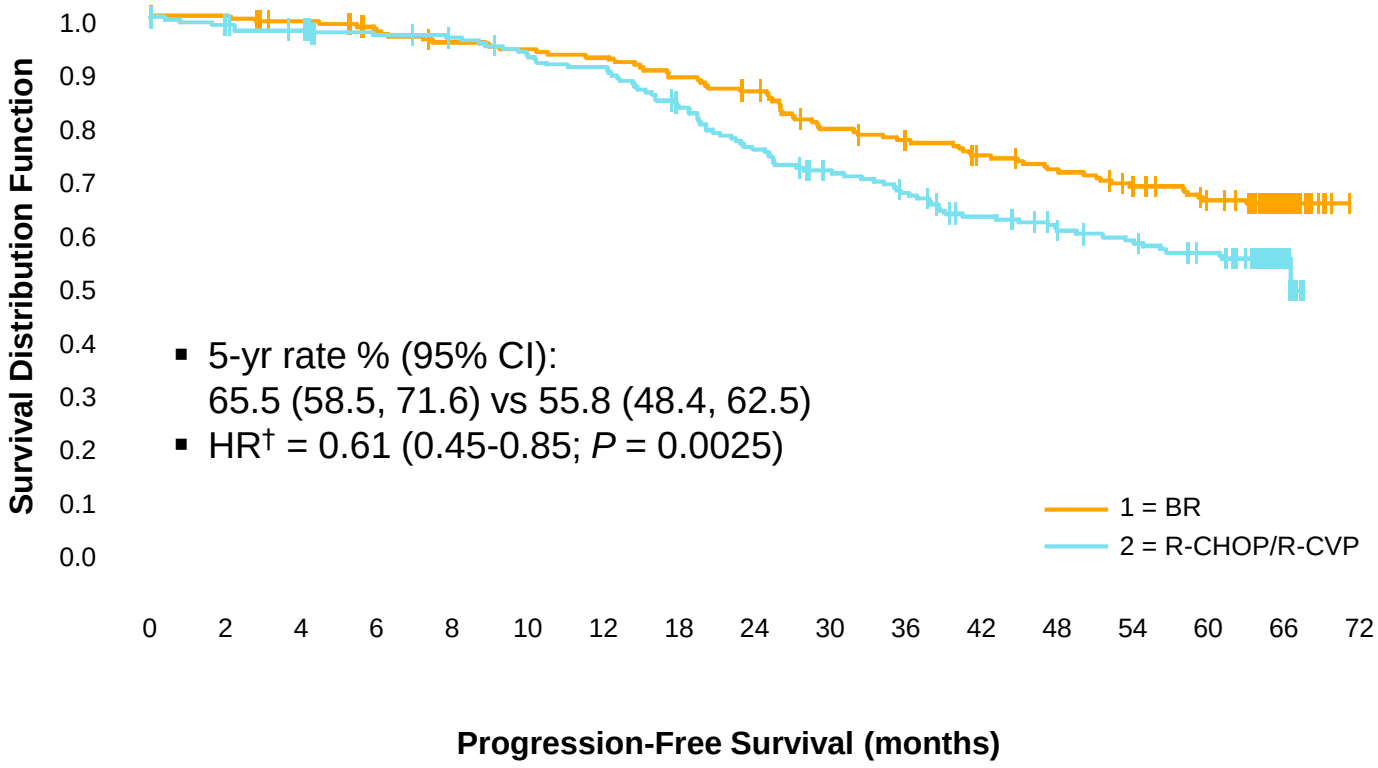
- Initial study results
  - Primary endpoint*
    - CR: **31%** BR vs **25%** R-CHOP/R-CVP
    - CR rate ratio 1.26; *P* = 0.0225 for non-inferiority
  - Safety*
    - BR: ↑ hypersensitivity, vomiting and nausea, lymphocytopenia
    - R-CHOP/R-CVP: ↑ peripheral neuropathy, alopecia, neutropenia
  - Quality of life†
    - Improved for BR patients vs R-CHOP/R-CVP in the domains of QLQ-C30 which include Cognitive, Physical, Social, and Emotional Functioning, and GHS as well as reduction in dyspnea, constipation, and fatigue

**Blood*. 2014;123(19):2944-2952; powered for non-inferiority of CR ratio.
†*Clin Lymphoma Myeloma Leuk*. 2016;16(4):182-190.

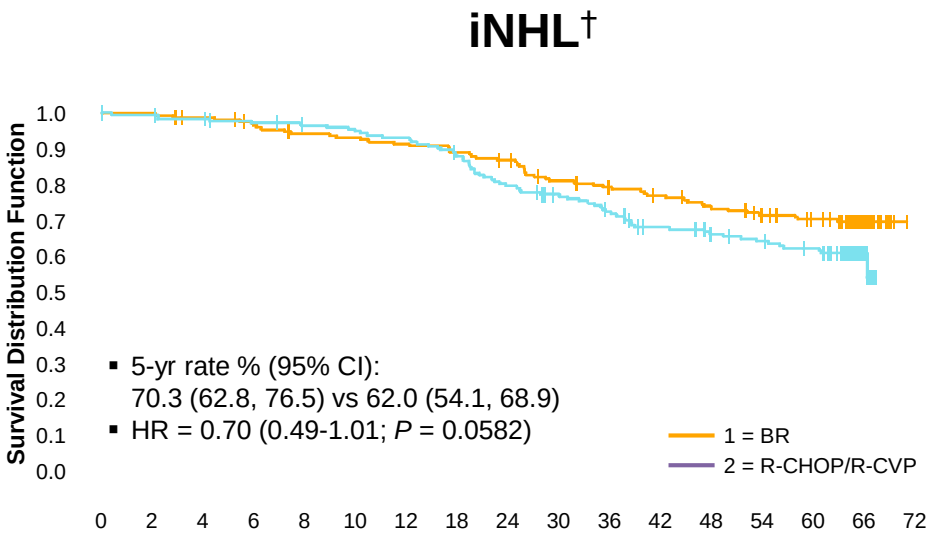
CR: complete response; GHS: global health status;
QLQ-C30: 30-question quality-of-life questionnaire.

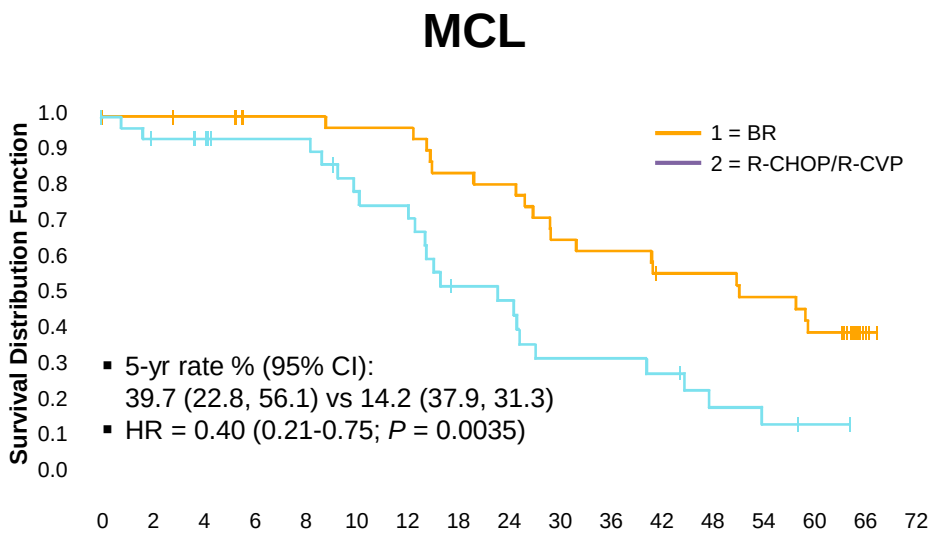
Hawkins et al ICML 2017

Progression-Free Survival by Treatment Group*



Progression-Free Survival by Lymphoma Type*

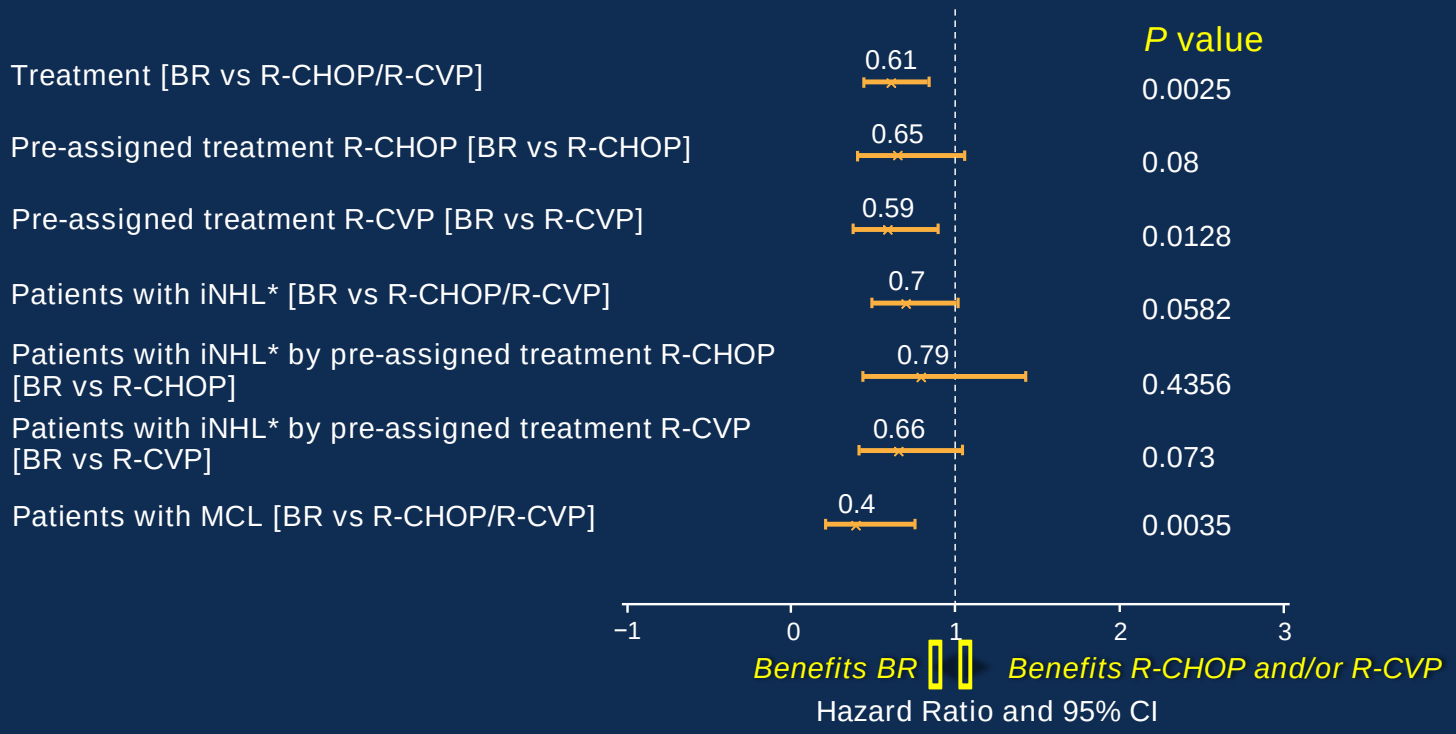




Progression-Free Survival (months)

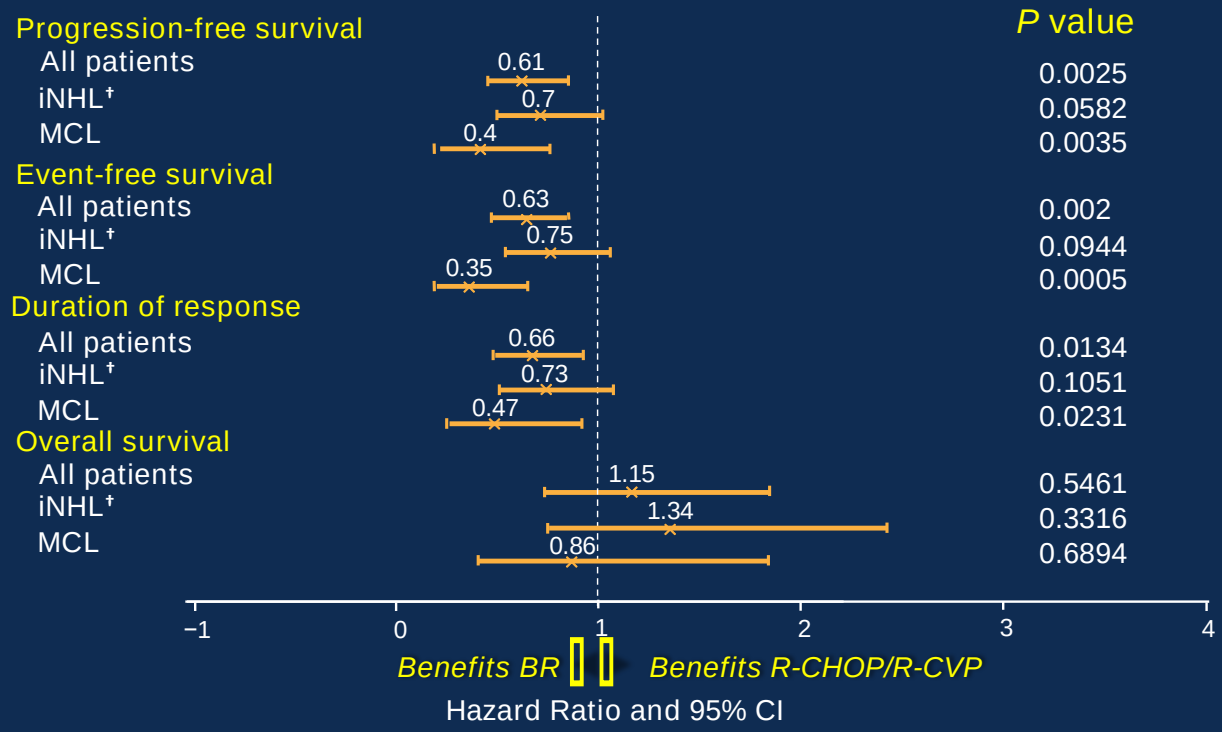
*BR vs R-CHOP/R-CVP.
†Not including MCL.

Forest Plot of PFS Subgroup Analyses



*Not including MCL.

Forest Plot of Time-to-Event Variables*



*BR vs R-CHOP/R-CVP.
†Not including MCL.

Patient Mortality

Reported Causality	BR (n = 224)	R-CHOP/R-CVP (n = 223)
Disease progression	16	17
Other* and reason not reported	3	6
Cardiovascular	7	2
Respiratory	3	1
Infection	6	3
Secondary malignancy *(excluding transformed NHL)*	5	3
All causes[†]	40	32
Deaths up to 100 days of last dose	pneumonia (2) cardiac arrest (1) respiratory failure (1)	septic shock (1) disease progression (2)

*Complications of stem cell transplant.
[†]Not statistically significant.

Secondary Malignancy*

	BR (n = 221)	R-CHOP/R-CVP (n = 215)	
Transformed NHL/DLBCL	5	7	
Basal cell carcinoma	9	4	
Squamous carcinoma of the skin	12	2	
Melanoma	2	1	
MDS	1	1	
Other solid malignancy	19	11	
Patients with secondary malignancy	42 (19%)	24 (11%)	*P* = 0.022
Excluding NHL and non-melanoma skin cancer	22 (10%)	13 (6%)	*P* = 0.133

*Exploratory analysis; histology not collected.

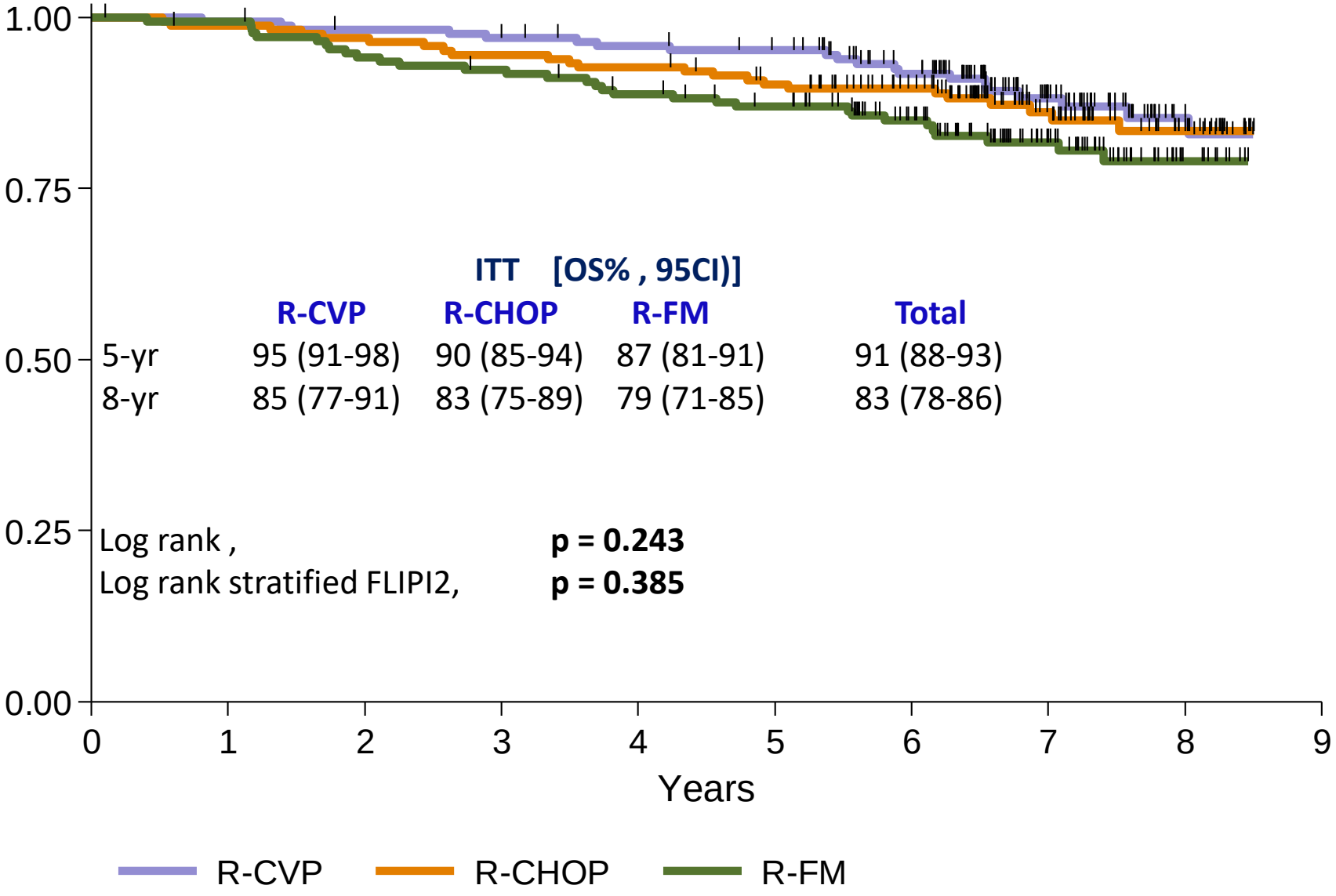
DLBCL: diffuse large B-cell lymphoma; MDS: myelodysplastic syndrome.

Bright study

- PFS, EFS, and DOR were significantly in favor of BR vs R-CHOP/R-CVP regimen
  - Greater benefit vs R-CVP
  - Strongest benefit in MCL subgroup
- No difference in OS
- Overall safety profile was as previously reported, with the exception of a higher incidence of secondary malignancies in the BR treatment group

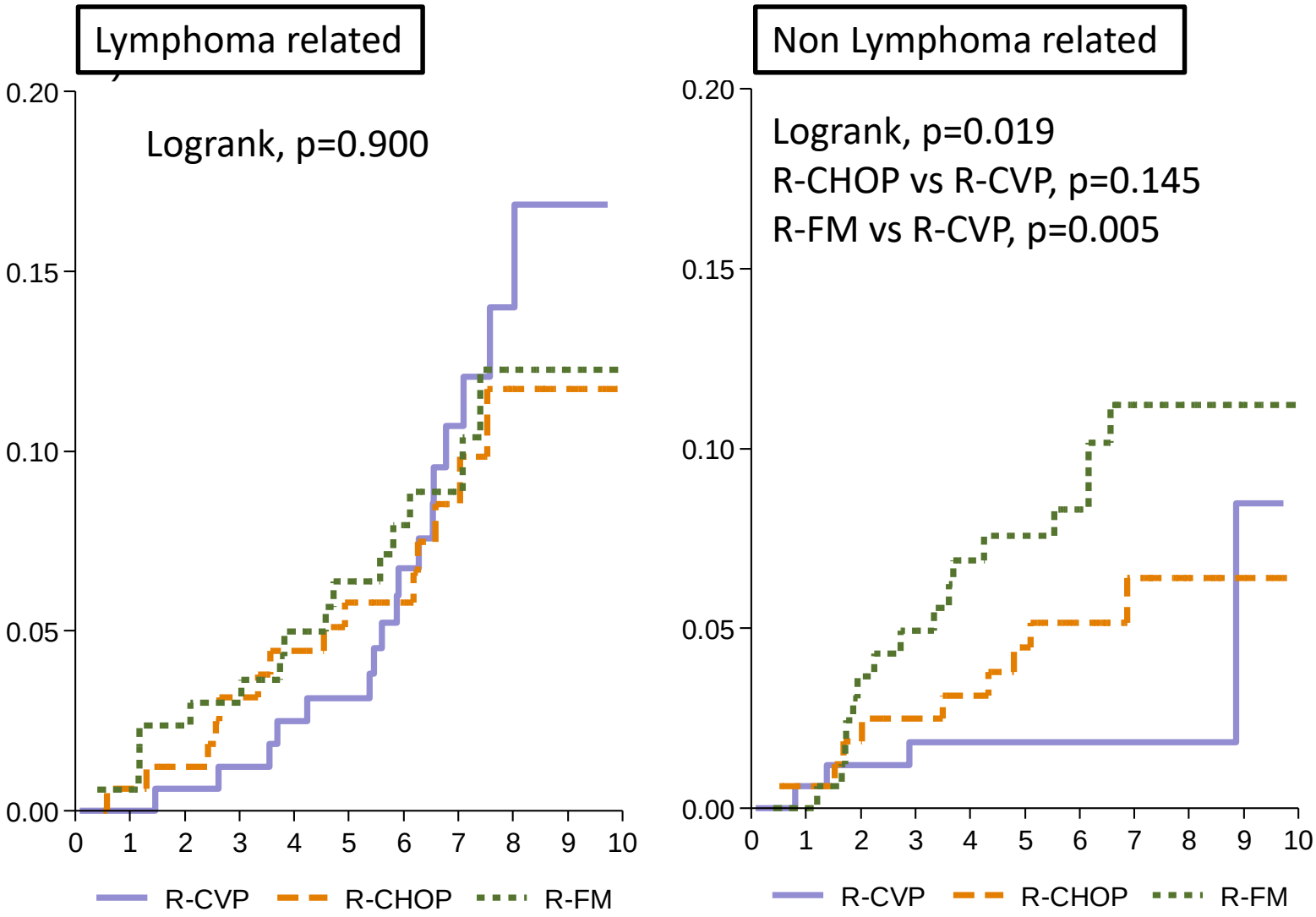
Hawkins et al ICML 2017

FOLL05 Study Update: OS



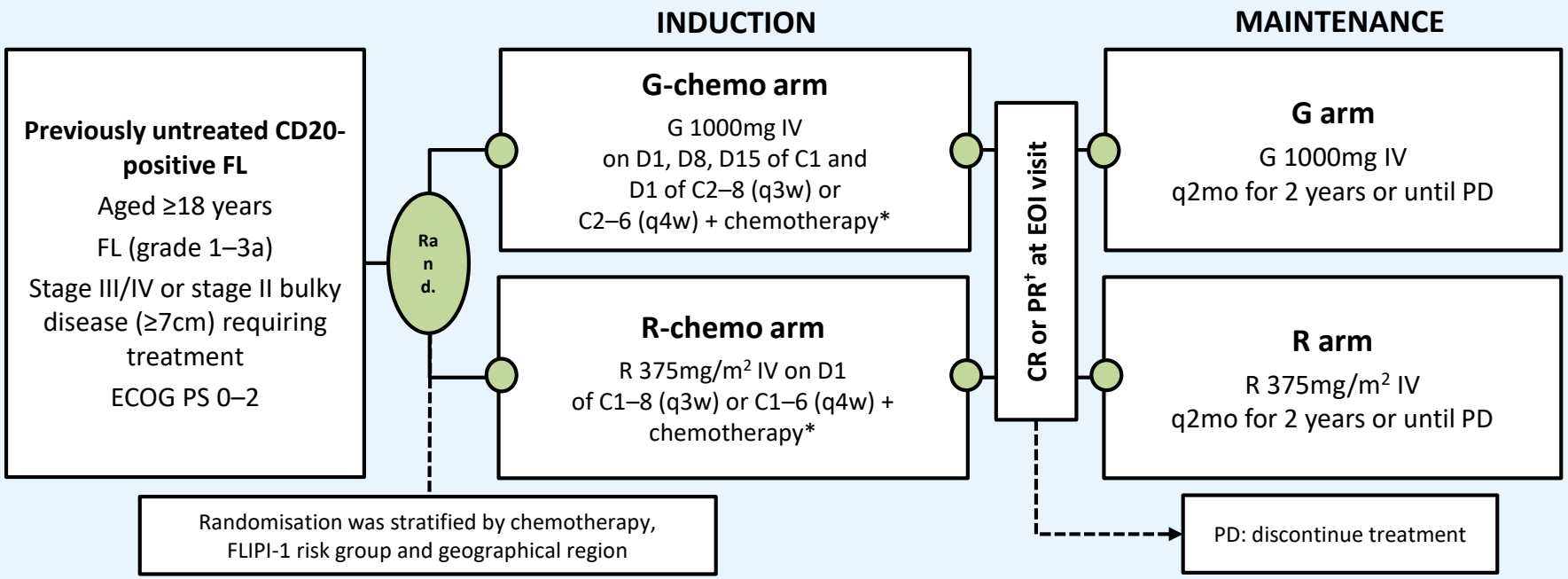
Luminari et al JCO 2017

FOLL05 Study Update: Cause-specific mortality



GALLIUM study design (FL)

International, open-label, randomised Phase III study in 1L pts (NCT01332968)



Primary endpoint

- PFS (INV-assessed)

Secondary endpoints

- PFS (IRC-assessed)
- OS, EFS, DFS, DoR, TTNALT
- ORR/CR at EOI (+/– FDG-PET)
- Safety
- PROs

*CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles; chemo regimen chosen by site prior to initiation and received by all FL pts at site; †patients with SD at EOI entered observation for up to 2 years or until PD if earlier

Hiddemann et ICML 2017

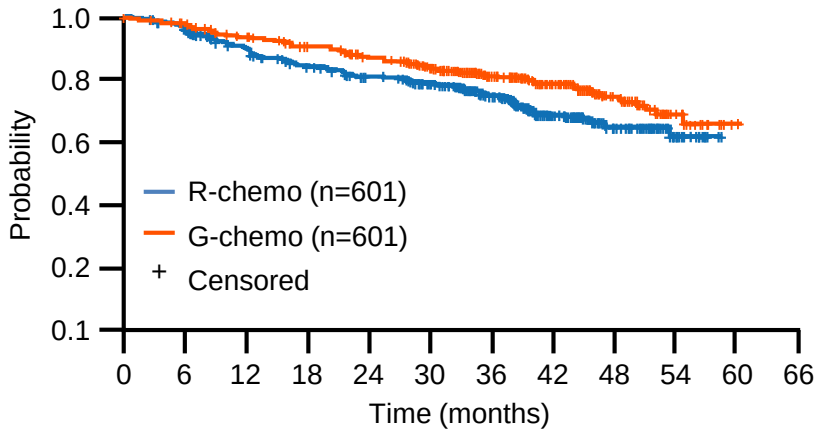
Baseline characteristics*

n (%)	*R-chemo, n=601*	*G-chemo, n=601*
Median age, years (range)	58.0 (23–85)	60.0 (26–88)
Male	280 (46.6)	283 (47.1)
Ann Arbor stage at diagnosis		
I	8 (1.3)†	10 (1.7)‡
II	44 (7.4)†	41 (6.9)‡
III	208 (34.8)†	209 (34.9)‡
IV	337 (56.4)†	338 (56.5)‡
FLIPI risk group		
Low (0–1)	125 (20.8)	127 (21.1)
Intermediate (2)	223 (37.1)	225 (37.4)
High (≥3)	**253 (42.1)**	**249 (41.4)**
Bone marrow involvement	295 (49.3)‡	318 (53.7)§
Extranodal involvement	396 (65.9)	392 (65.2)
Bulky disease (≥7cm)	**271 (45.2)¶**	**255 (42.5)¶**
Median t from dg to random, mo (range)	**1.4 (0–168.1)‡**	**1.5 (0.1–121.6)‡**

*ITT population; †n=597; ‡n= 598; § n=592; ¶n=600

PFS after 41.1 mo median f-up*

INV-assessed PFS

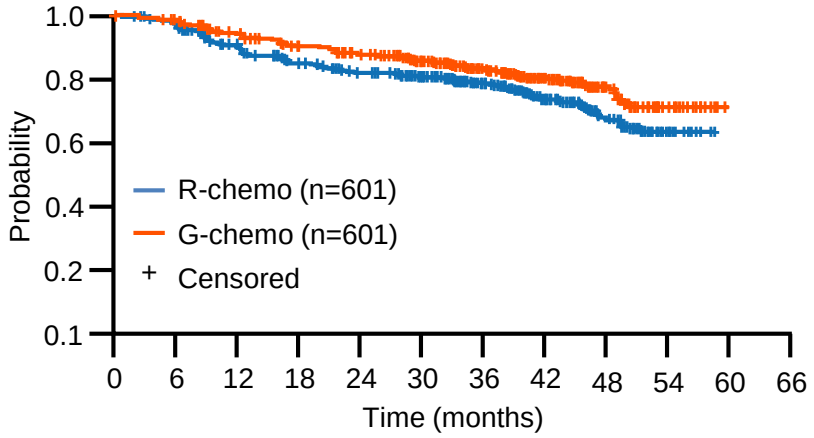


No. of patients at risk

G-chemo	601	561	505	464	438	396	267	149	77	18	
R-chemo	601	569	535	505	478	420	291	176	85	25	1

	R-chemo, n=601	*G-chemo, n=601*
3-yr PFS, % (95% CI)	75.0 (71.0, 78.5)	81.5 (77.9, 84.6)
HR (95% CI), p-value†	0.68 (0.54, 0.87), **p=0.0016**	

IRC-assessed PFS



No. of patients at risk

G-chemo	601	563	502	463	438	394	271	151	73	16
R-chemo	601	571	532	497	476	414	287	179	79	22

	R-chemo, n=601	*G-chemo, n=601*
3-yr PFS, % (95% CI)	78.9 (75.2, 82.1)	83.4 (79.9, 86.3)
HR (95% CI), p-value†	0.72 (0.56, 0.93), **p=0.0118**	

*ITT population; †stratified analysis; stratification factors = FLIPI, chemotherapy regimen

Adverse events*

n (%) of pts reporting ≥1 one event	*R-chemo, n=597*	*G-chemo, n=595*
Any AE	585 (98.0)	593 (99.7)
Grade 3–5 AEs	409 (68.5)	**449 (75.5)**
SAE	246 (41.2)	**281 (47.2)**
Grade 5 (fatal) AE	21 (3.5)	24 (4.0)
AE leading to treatment discontinuation	88 (14.7)	98 (16.5)

- All-cause deaths in each arm: R-chemo, 52 (8.7%); G-chemo, 42 (7.1%)

*Safety population

Selected grade 3–5 AEs of particular interest (frequency >2%)*

n (%) of pts reporting ≥1 one event	*R-chemo, n=597*	*G-chemo, n=595*
Neutropenia	236 (39.5)	**278 (46.7)**
Infections†	98 (16.4)	**121 (20.3)**
Infusion-related reactions‡	40 (6.7)	**74 (12.4)**
Thrombocytopenia	16 (2.7)	**36 (6.1)**
Second malignancies (SMQ)§	21 (3.5)	29 (4.9)
Cardiac events	17 (2.8)	23 (3.9)

*AEPIs occurring in >2% of patients in safety population, in either treatment arm
†System Organ Class 'Infections and Infestations'
‡Related to study treatment and occurring during or in the 24 hours after infusion
§ Standardised MedDRA query, i.e. malignant or unspecified tumours occurring >6 mo after study drug intake

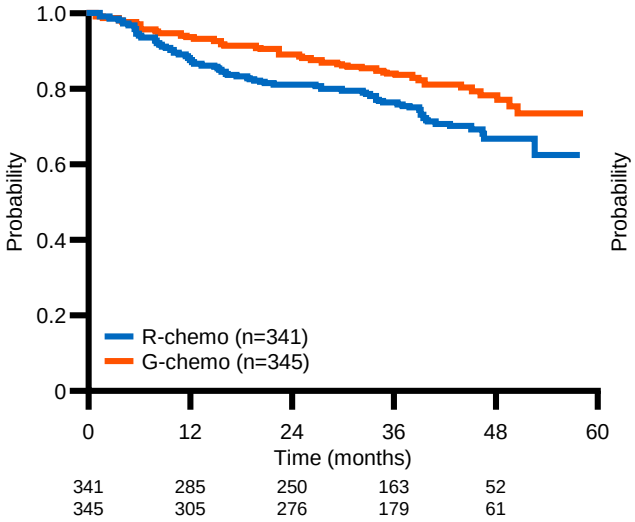
Baseline characteristics by chemo*

n (%)	*Benda, n=686*	*CHOP, n=399*	*CVP, n=117*
Median age, years (range)	59 (23–88)	58 (31–85)	59 (32–85)
Age ≥80 years	**23 (3.4)**	3 (0.8)	**4 (3.4)**
Male	332 (48.4)	177 (44.4)	54 (46.2)
Charlson Comorbidity Index score ≥1†	**163 (23.8)**	69 (17.3)	22 (18.8)
ECOG PS 2	24 (3.5)	8 (2.0)	6 (5.1)
FLIPI high risk (≥3)	274 (39.9)	**187 (46.9)**	41 (35.0)
Bulky disease (≥7cm)	274 (39.9)	**206 (51.6)**	46 (39.3)

*ITT population; †scored retrospectively based on conditions reported on medical history page of CRF

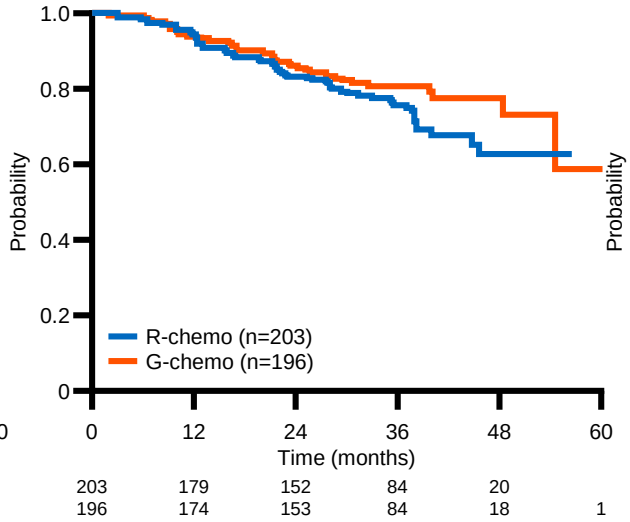
INV-assessed PFS by chemo*

Benda



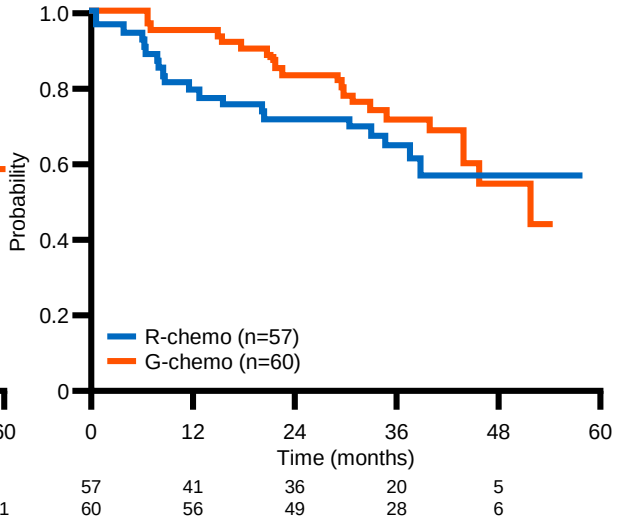
HR (95% CI)†	0.63 (0.46, 0.88)
3-yr PFS	84.1% G-B vs 76.4% R-B

CHOP



HR (95% CI)†	0.72 (0.48, 1.10)
3-yr PFS	80.6% G-CHOP vs 75.6% R-CHOP

CVP



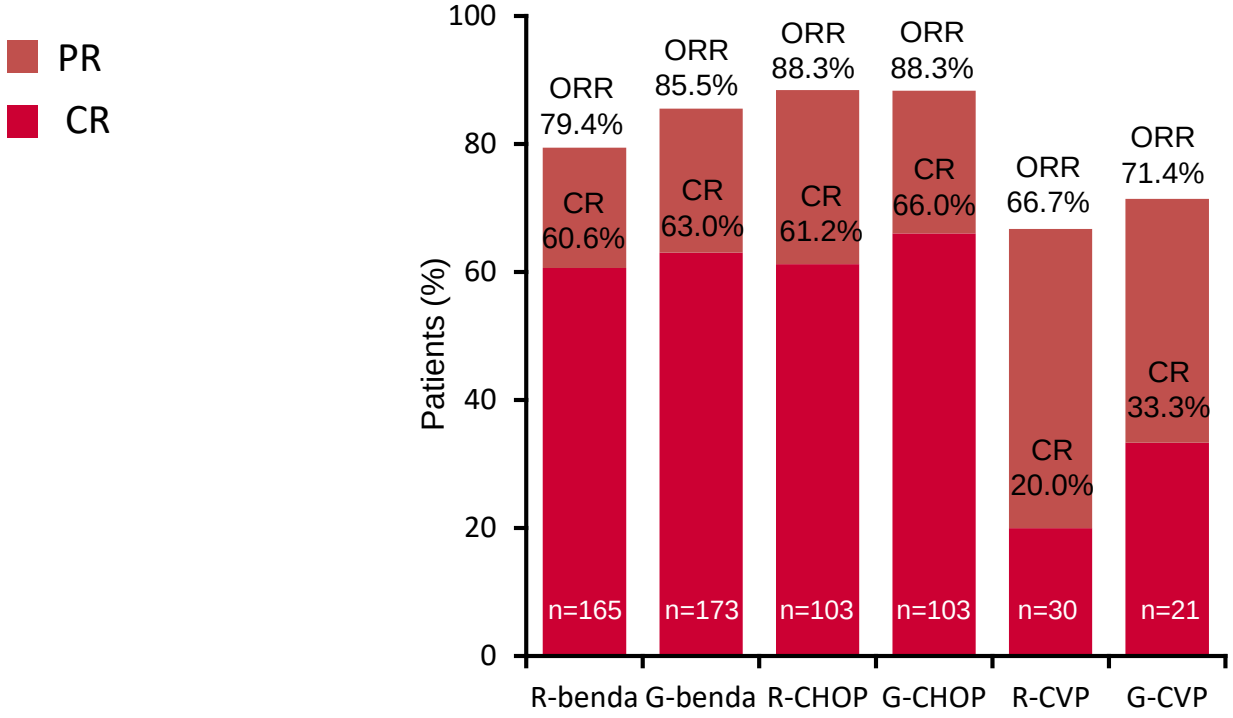
HR (95% CI)†	0.79 (0.42, 1.47)
3-yr PFS	71.3% G-CVP vs 64.2% R-CVP

- By chemo analysis not powered to demonstrate statistically significant differences between treatment arms

- *ITT population; †analysis stratified by FLIPI (as well as chemotherapy regimen)

INV-assessed response at end of induction

*CT- and PET-based**†



*PET ITT population i.e. all randomised FL pts who had PET-avid lesions representing lymphoma at baseline

†assessed acording to Cheson 2007 criteria

AEs by treatment arm*

n (%) of pts reporting ≥1 event	*R-benda, n=338*	*G-benda, n=338*	*R-CHOP, n=203*	*G-CHOP, n=193*	*R-CVP, n=56*	*G-CVP, n=61*
Any AE	331 (97.9)	338 (100)	201 (99.0)	191 (99.0)	56 (100)	61 (100)
Grade 3–5 AE	228 (67.5)	233 (68.9)	**151 (74.4)**	**171 (88.6)**	**30 (53.6)**	**42 (68.9)**
SAE	160 (47.3)	176 (52.1)	**67 (33.0)**	**76 (39.4)**	**19 (33.9)**	**26 (42.6)**
Grade 5 (fatal) AE	16 (4.7)	20 (5.9)	4 (2.0)	3 (1.6)	1 (1.8)	1 (1.6)
AE leading to treatment discontinuation	48 (14.2)	52 (15.4)	31 (15.3)	32 (16.6)	9 (16.1)	11 (18.0)

- Difference between treatment arms in grade 3–5 AEs and SAEs was more pronounced in patients treated with CHOP and CVP
- Comparisons confounded by imbalances in baseline patient and disease characteristics between chemo groups

*Safety population, i.e. all randomised FL pts who received at least one dose of study drug

AEs by chemo*

n (%) of pts reporting ≥1 event	*R-benda, n=338*	*G-benda, n=338*	*R-CHOP, n=203*	*G-CHOP, n=193*	*R-CVP, n=56*	*G-CVP, n=61*
Any AE	331 (97.9)	338 (100)	201 (99.0)	191 (99.0)	56 (100)	61 (100)
Grade 3–5 AE	228 (67.5)	233 (68.9)	**151 (74.4)**	**171 (88.6)**	30 (53.6)	42 (68.9)
SAE	**160 (47.3)**	**176 (52.1)**	67 (33.0)	76 (39.4)	19 (33.9)	26 (42.6)
Grade 5 (fatal) AE†	**16 (4.7)**	**20 (5.9)**	4 (2.0)	3 (1.6)	1 (1.8)	1 (1.6)
AE leading to treatment discontinuation	48 (14.2)	52 (15.4)	31 (15.3)	32 (16.6)	9 (16.1)	11 (18.0)

- Grade 3–5 AEs most frequent with CHOP (neutropenia, leukopenia, febrile neutropenia, IRRs); SAEs and fatal AEs most frequent with benda
- Frequency of grade 5 AEs similar to R-CHOP arms in SABRINA (5.7%, i.v.; 3.6%, s.c.)

*Safety population, i.e. all randomised FL pts who received at least one dose of study drug; †includes 6 pts with fatal AEs that occurred after start of new anti-cancer therapy (G-benda, 4; R-benda, 2)

Grade 5 (fatal) AEs excluding six pts who started new anti-cancer treatment*†

SOC	*R-benda, n=338*	*G-benda, n=338*	*R-CHOP, n=203*	*G-CHOP, n=193*	*R-CVP, n=56*	*G-CVP, n=61*
Infections and infestations	1 (0.3)	4 (1.2)	0	1 (0.5)	0	0
Cardiac disorders	2 (0.6)	2 (0.6)	0	0	0	0
Gastrointestinal disorders	0	1 (0.3)	0	0	0	1 (1.6)
General disorders and administration site conditions	2 (0.6)	1 (0.3)	0	1 (0.5)	1 (1.8)	0
Metabolism and nutrition disorders	1 (0.3)	1 (0.3)	0	0	0	0
Neoplasms benign, malignant and unspecified	3 (0.9)	4 (1.1)	2 (1.0)	1 (0.5)	0	0
Nervous system disorders	4 (1.2)	0	2 (1.0)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.3)	3 (0.9)	0	0	0	0
Total (all SOCs)	**14 (4.1%)**	**16 (4.7%)**	4 (2.0%)	3 (1.6%)	1 (1.8%)	1(1.6%)

- Many pts with fatal AEs had adverse risk factors, e.g. aged ≥80 years (benda, 6; CVP, 1), ECOG PS grade 2 (benda, 4; CVP, 1), and CCI ≥1 (benda, 11; CHOP, 1; CVP, 1)

*Safety population; †fatal AEs in 5 G-benda and 1 R-benda pts that occurred after new systemic anti-cancer treatment had started were not included (PD, 4 pts; new malignancies, 2 pts); CCI, Charlson Comorbidity Index

Selected grade 3–5 AEs of particular interest by chemo*

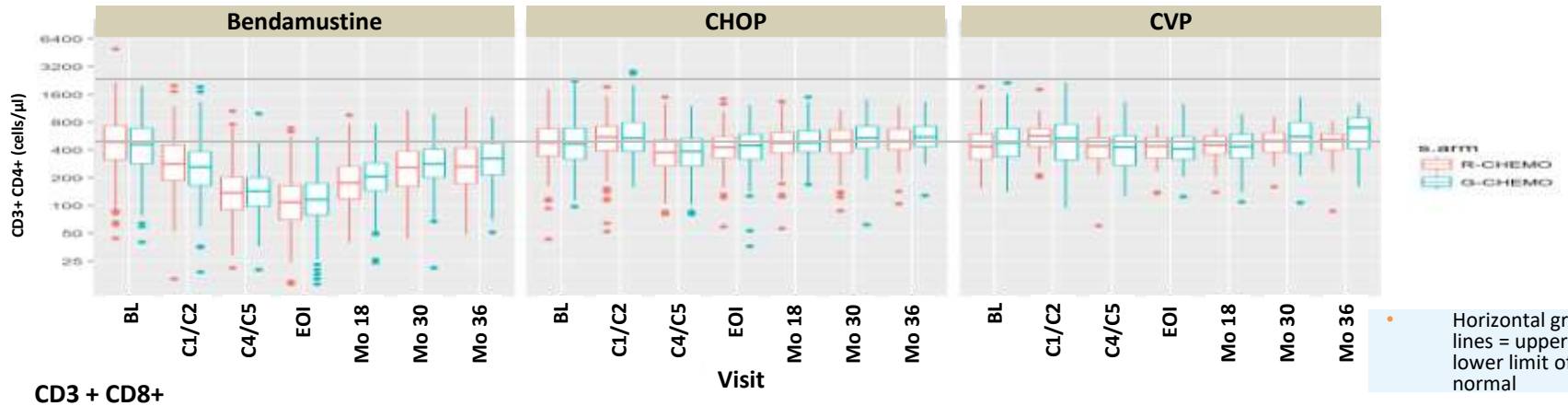
n (%) of pts reporting ≥1 event	*R-benda, n=338*	*G-benda, n=338*	*R-CHOP, n=203*	*G-CHOP, n=193*	*R-CVP, n=56*	*G-CVP, n=61*
Cardiac events	12 (3.6)	13 (3.8)	5 (2.5)	6 (3.1)	0 (0.0)	4 (6.6)
Neutropenia	107 (31.7)	107 (31.7)	**115 (56.7)**	**142 (73.6)**	14 (25.0)	29 (47.5)
Febrile neutropenia	13 (3.8)	18 (5.3)	**14 (6.9)**	**22 (11.4)**	2 (3.6)	2 (3.3)
Second malignancies†	**12 (3.6)**	**21 (6.2)**	7 (3.4)	7 (3.6)	2 (3.6)	1 (1.6)
Other solid tumours	9 (2.7)	11 (3.3)	7 (3.4)	4 (2.1)	2 (3.6)	0
Hematological tumours‡	0	3 (0.9)	0	3 (1.6)	0	0
Non-melanoma skin cancer	**3 (0.9)**	**7 (2.1)**	0	0	0	1 (1.6)
Infections	**66 (19.5)**	**89 (26.3)**	25 (12.3)	23 (11.9)	7 (12.5)	8 (13.1)
Opportunistic infections§	6 (1.8)	10 (3.0)	2 (1.0)	5 (2.6)	0	0

- Frequency of grade 3–5 second malignancy and infections similar in G and R arms for CHOP and CVP groups but not for benda
- Comparisons confounded by imbalances in baseline patient and disease characteristics between chemo groups

*Safety population; †standardised MedDRA query = malignant or unspecified tumours occurring >6 months after first study drug intake; ‡Hodgkin disease (n=3), AML (n=2), and ALL (n=1); § including fungal infections, cytomegalovirus, herpes zoster and pneumocystis jirovecii pneumonia

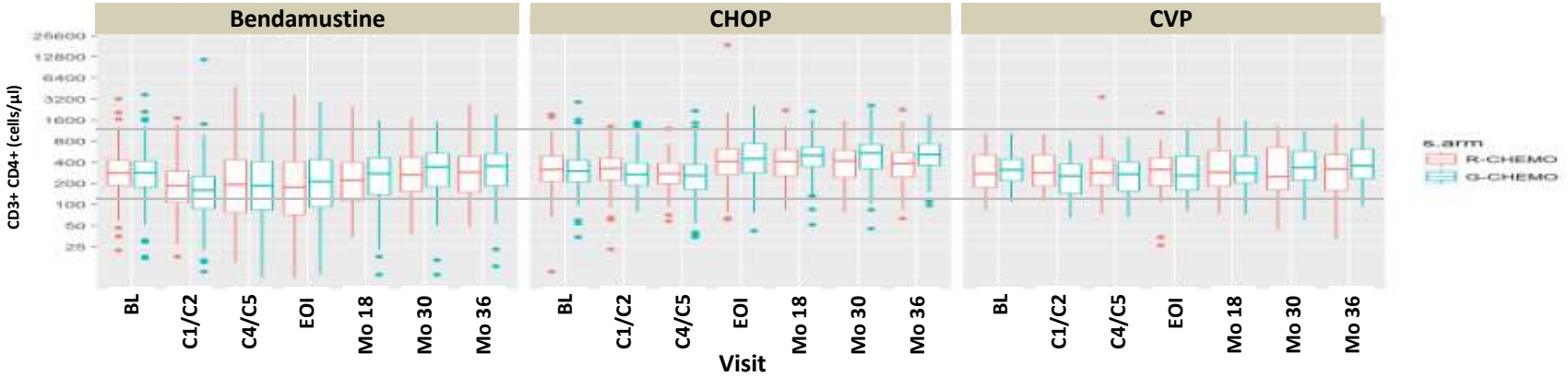
T-cell counts over time

CD3 + CD4+



- Horizontal grey lines = upper and lower limit of normal

CD3 + CD8+



Low T-cell count at baseline	*R-benda, n=341*	*G-benda, n=345*	*R-CHOP, n=203*	*G-CHOP, n=196*	*R-CVP, n=57*	*G-CVP, n=60*
CD3+/CD4+ cell count of ≤200/mm^3	36 (12.5%)	36 (11.4%)	12 (7.2%)	9 (5.1%)	2 (4.4%)	4 (7.4%)

Grade 3–5 infections by chemo and by phase

n (%) of pts reporting ≥1 event	*R-benda, n=338*	*G-benda, n=338*	*R-CHOP, n=203*	*G-CHOP, n=193*	*R-CVP, n=56*	*G-CVP, n=61*
All study periods	66 (19.5)	89 (26.3)	25 (12.3)	23 (11.9)	7 (12.5)	8 (13.1)
Induction	26 (7.7)	27 (8.0)	13 (6.4)	14 (7.3)	4 (7.1)	3 (4.9)
Maintenance	**39 (13.0)**	**51 (16.7)**	11 (5.9)	7 (3.9)	1 (2.5)	5 (8.8)
Observation	12 (3.8)	28 (8.8)	6 (3.1)	3 (1.6)	3 (5.7)	1 (1.7)
N (%) of pts receiving G-CSF prophylaxis	48 (14.2)	54 (16.0)	108 (53.2)	112 (58.0)	13 (23.2)	10 (16.4)

Comparisons confounded by imbalances in baseline patient and disease characteristics between chemo groups

*Safety population

Lenalidomide produces responses in patients with R/R FL

Lenalidomide monotherapy

- 22 with FL Grade 1/2[1]
- Median (range) prior systemic therapies: 3 (1–17)[1]

ORR: 27% in Grade 1/2 FL[1]

Lenalidomide combinations

- Subsequent studies focused on lenalidomide and rituximab combinations in relapsed and resistant disease[2,3]

ORR: 65–77%[2,3]

1. Witzig TE, et al. J Clin Oncol 2009
2. Chong EA, et al. Clin Cancer Res 2015;
3. Tuscano JM, et al. Br J Haematol 2014

R2 in first-line FL

	MDACC[1]	CALGB[2]
N (enrolled)	50	66
Lenalidomide	20 mg $d_{1\text{-}21}$ x 6	20 mg $d_{1\text{-}21}$ x 12
Rituximab	375 mg/m^2 QD 4 wks x 6	375 mg/m^2 weekly x 4 + Cycle 4, 6, 8, 10
Median age[a]	58	53
FLIPI ≥2[a] (%)	78	69
RR (%)	98	93
CR (%)	87	72
2-year PFS (%)	89	–

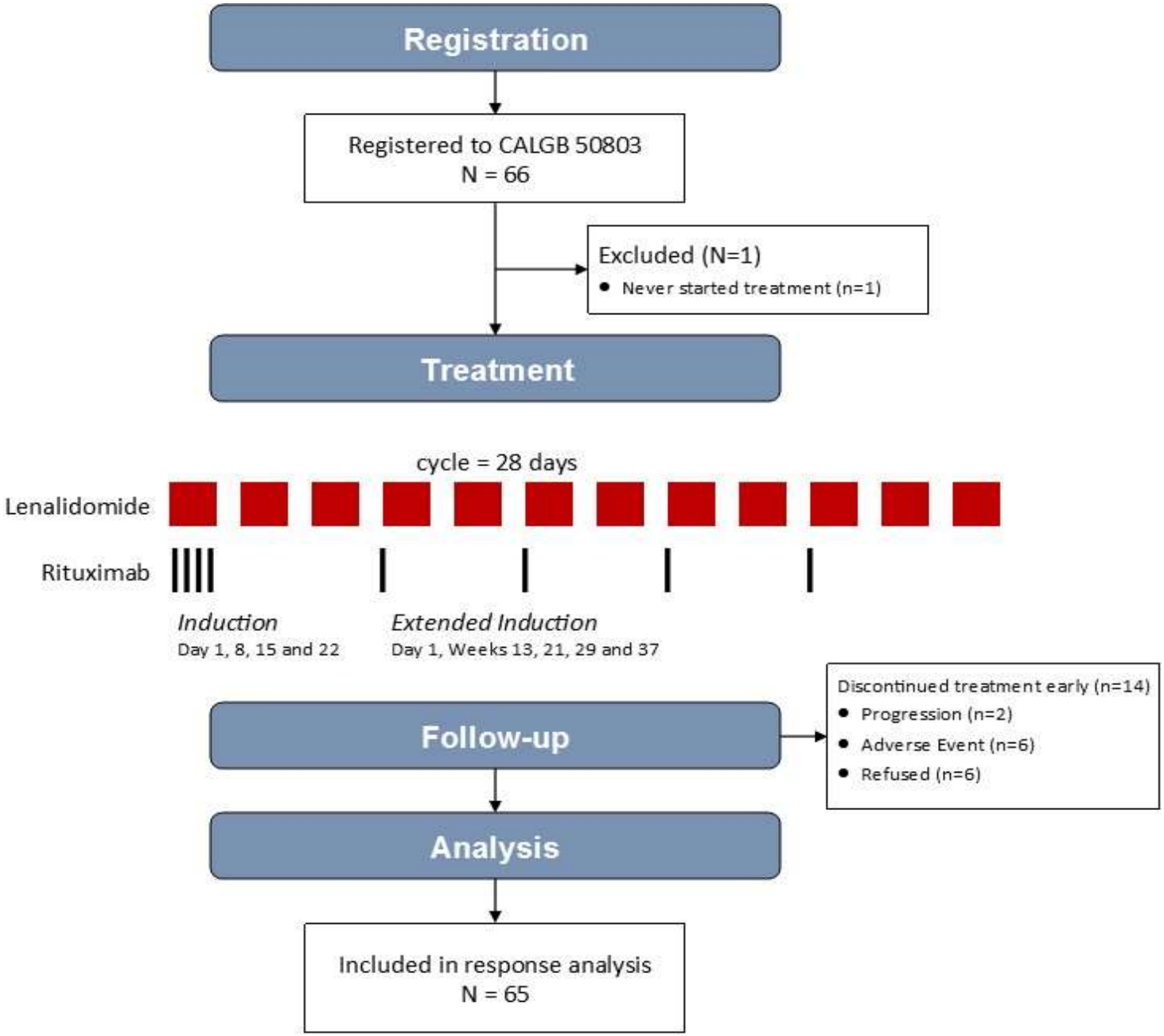
Is R^2 as active as R-chemo?

Alliance study

- Untreated Follicular lymphoma
  - Grade 1-3a
  - Stage 2 bulky, 3, 4
  - FLIPI 0-2 risk factors
- No CNS involvement

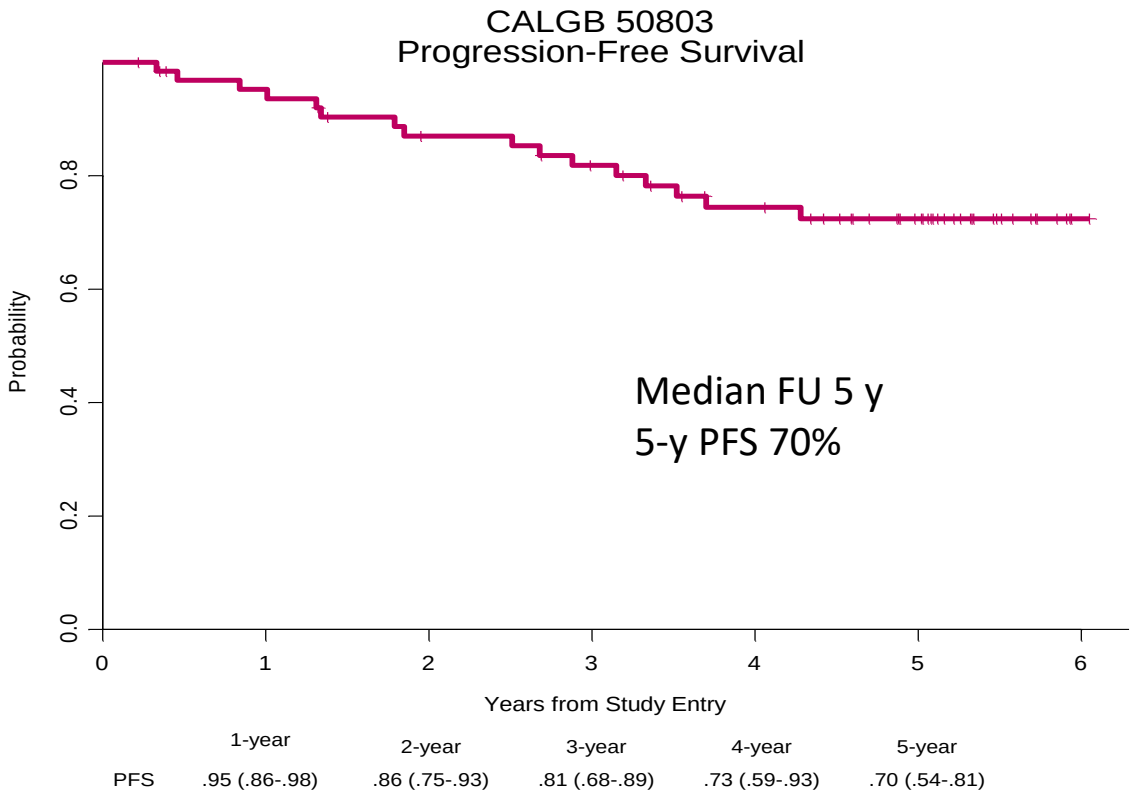
- ANC $\geq$ 1,000/μL
- Plts $\geq$ 75,000/μL
- CrCl $\geq$ 30 mL/min
- T bili $\leq$ 2 x ULN
- No HBV, HCV

Characteristics	N = 66
Age	53 years (32-79)
Sex M vs. F	32 vs. 34
FLIPI 0-1 vs. 2 vs. 3	21 vs. 43 vs. 2
Grade 1 vs. 2. vs 3a	39 vs. 21 vs. 4
Non-bulky vs. bulky	50 vs. 15
FCGR3A 158F vs. 158F/V vs 158V	22 vs. 27 vs. 10
FCGR2A 131H vs. 131R/H vs 131R	18 vs. 28 vs. 13

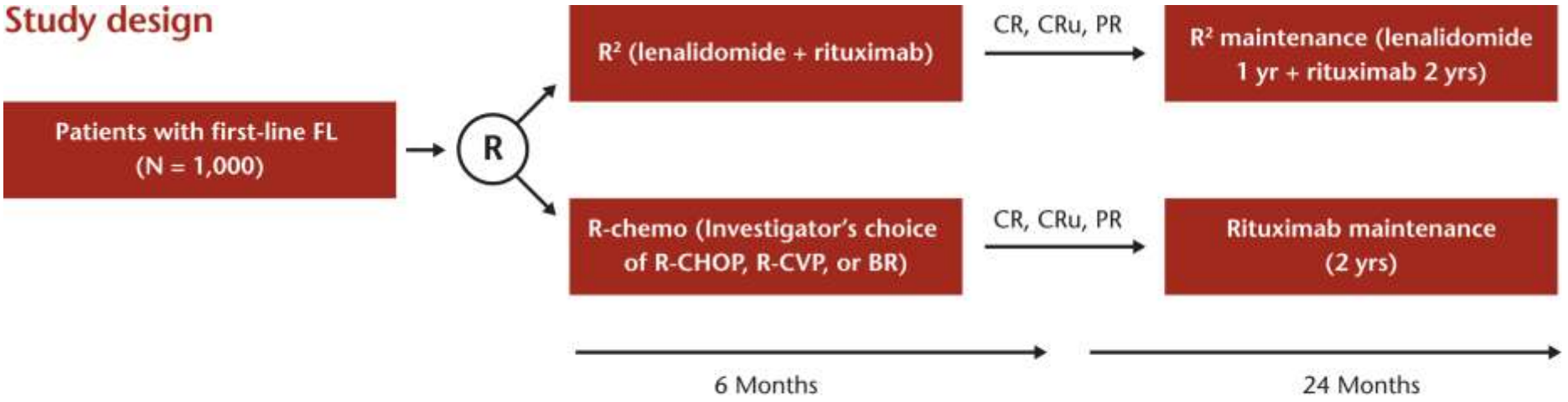

Registration
Registered to CALGB 50803
N = 66
Excluded (N=1)
Never started treatment (n=1)
Treatment
cycle = 28 days
Lenalidomide
Rituximab
Induction
Day 1, 8, 15 and 22
Extended Induction
Day 1, Weeks 13, 21, 29 and 37
Follow-up
Discontinued treatment early (n=14)
Progression (n=2)
Adverse Event (n=6)
Refused (n=6)
Analysis
Included in response analysis
N = 65

Efficacy

Best Response	FLIPI 0-1, N=21	FLIPI 2-3, N=44*	Overall (N=65)
ORR	94%	96%	95%
CR	15 (71%)	32 (73%)	47 (72%)
PR	5 (23%)	10 (23%)	15 (23%)
Stable	0	1 (2%)	1 (2 %)
Not evaluated – AE	1 (5%)	1 (2%)	1 (2%)



THE RELEVANCE TRIAL

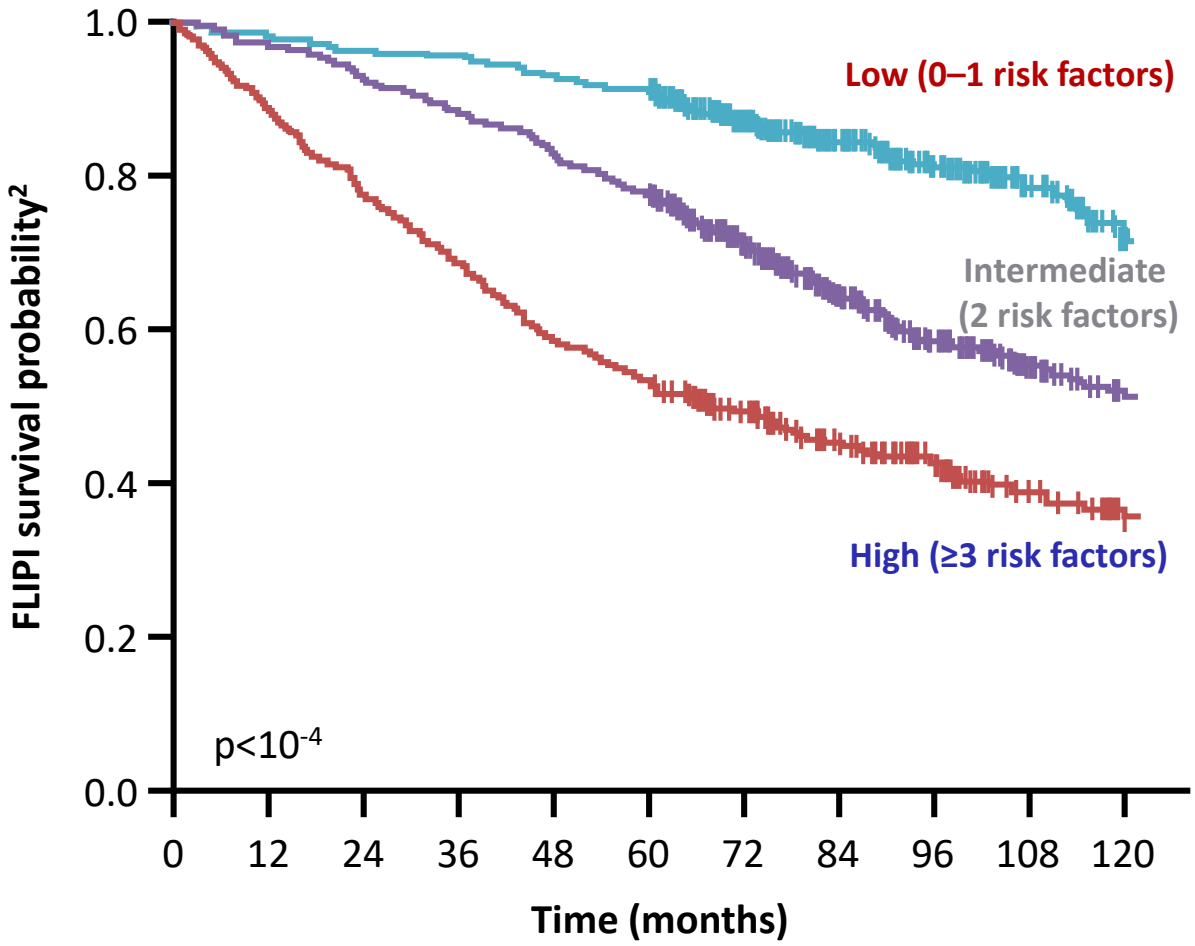


BR = bendamustine, rituximab; CR = complete response; CRu = complete response, unconfirmed; FL = follicular lymphoma; PR = partial response; R = randomize; R² = lenalidomide, rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone

Lysa
THE LYMPHOMA STUDY ASSOCIATION

Prognostic assessment

FLIPI



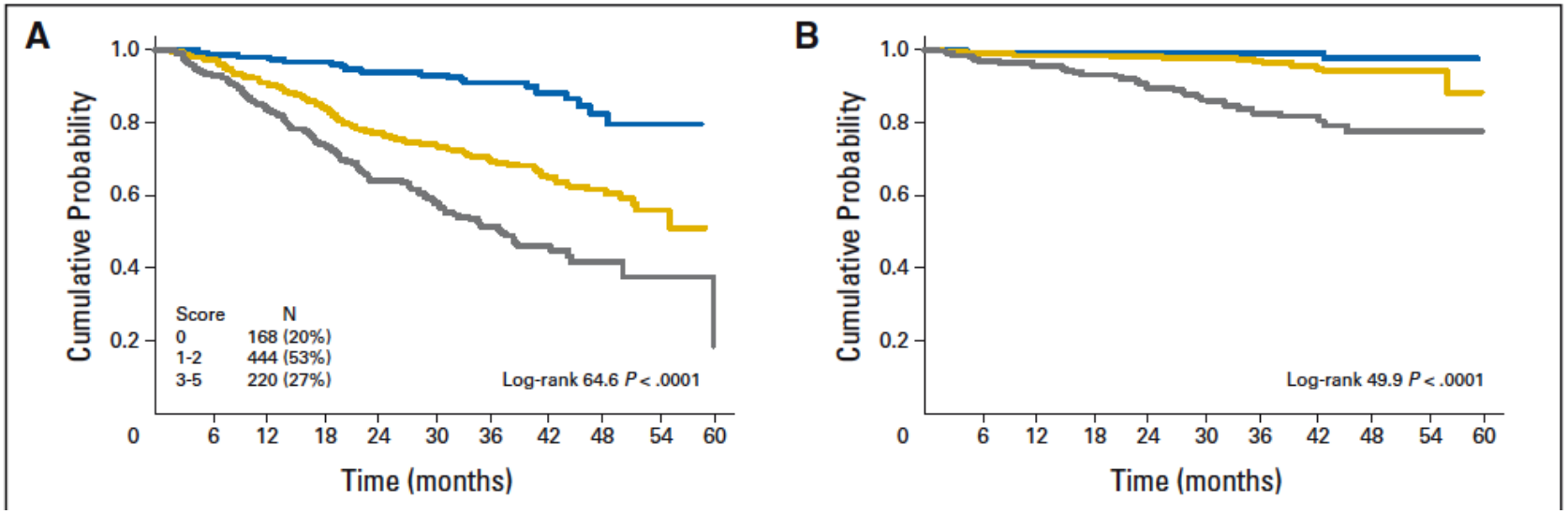
Distribution of patients	5-year OS	10-year OS
36%	90.6%	70.7%
37%	77.6%	50.9%
27%	52.5%	35.5%

Risk factors: age (≥60 vs <60 years), Ann Arbor stage (III–IV vs I–II), number of nodal areas involved (>4 vs ≤4), lactate dehydrogenase serum level (above normal vs normal or below)
FLIPI: Follicular Lymphoma International Prognostic Index; OS: overall survival

1. Smith SM, *et al. Hem Am Soc Hematol Educ Program* 2013; 2013;561–567.
2. Solal-Céligny P, *et al. Blood* 2004;104:1258–1265.

FLIPI2 – multivariate analysis of PFS

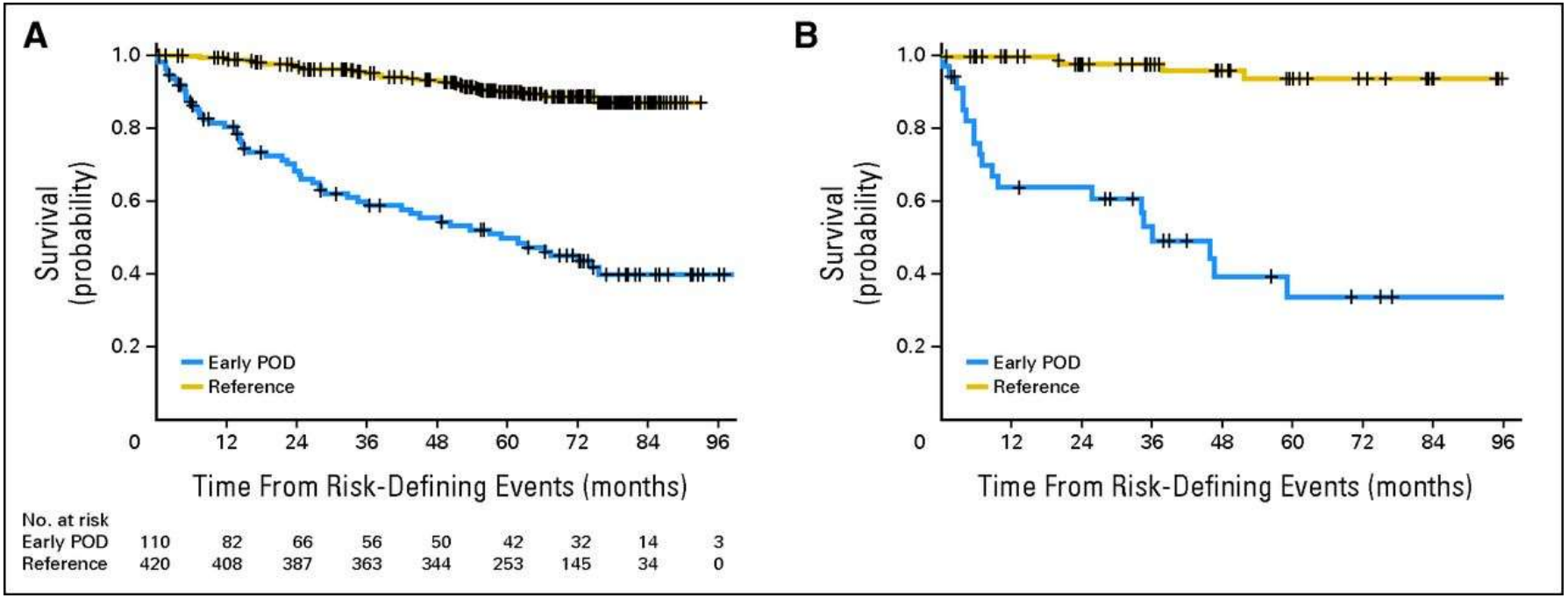
	HR	*P*
B2M	1.47	0.004
Hb	1.55	0.003
Age	1.43	0.005
BM	1.56	0.001
LoDLIN[a]	1.43	0.007



[a]LoDLIN: longest diameter of largest lymph node (≥6 cm).

Federico M, et al. *J Clin Oncol.* 2009;27(27):4555-4562.

(A) Overall survival (OS) from a risk-defining event after diagnosis in patients who received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the National LymphoCare Study group.



Casulo et al. JCO 2014

M-7 FLIPI

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

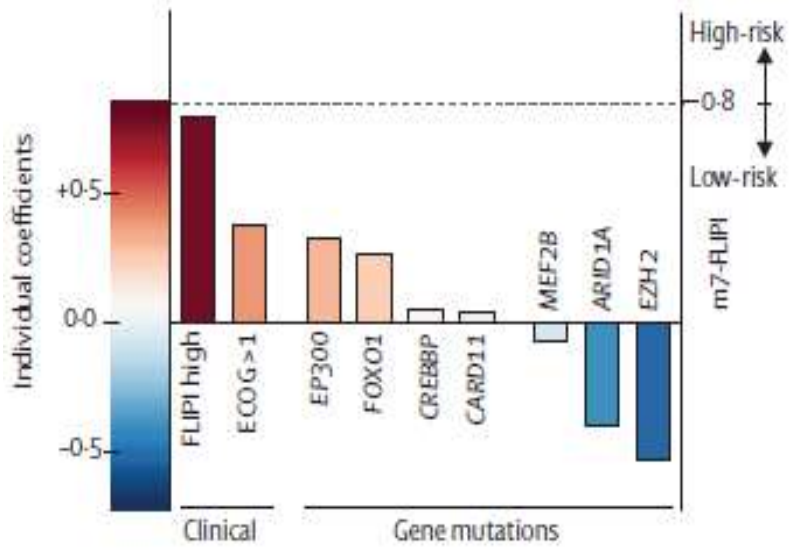
Alessandro Pastore*, Vindi Jurinovic*, Robert Kridel*, Eva Hoster*, Annette M Staiger, Monika Szczepanowski, Christiane Pott, Nadja Kopp, Mark Murakami, Heike Horn, Ellen Leich, Alden A Moccia, Anja Mottok, Ashwini Sunkavalli, Paul Van Hummelen, Matthew Ducar, Daisuke Ennishi, Hennady P Shulha, Christoffer Hother, Joseph M Connors, Laurie H Sehn, Martin Dreyling, Donna Neuberg, Peter Möller, Alfred C Feller, Martin L Hansmann, Harald Stein, Andreas Rosenwald, German Ott, Wolfram Klapper, Michael Unterhalt, Wolfgang Hiddemann, Randy D Gascoyne*, David M Weinstock*, Oliver Weigert*

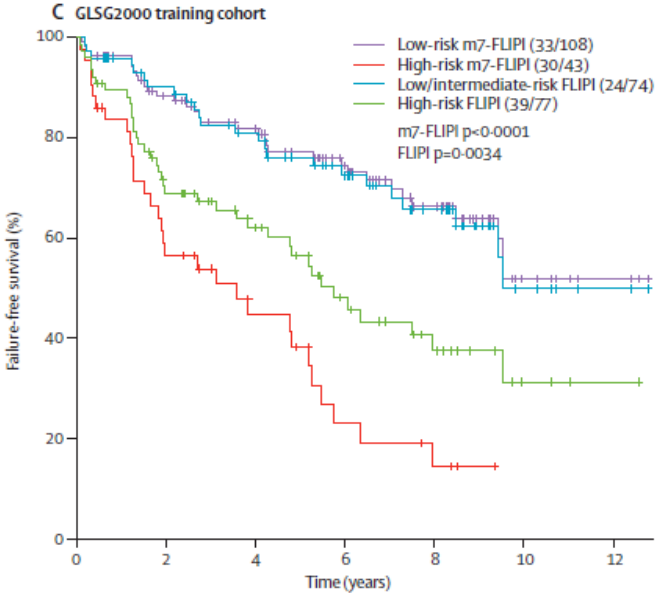
Lancet Oncol. 2015; 16(9):1111-1122.

m7-FLIPI as a clinicogenetic risk model, that included:

- **the mutation status of seven genes (*EZH2*, *ARID1A*, *MEF2B*, *EP300*, *FOXO1*, *CREBBP*, *CARD11*)**
- **FLIPI score**
- **ECOG PS**

DNA deep sequencing to retrospectively analyse the mutation status of 74 genes in 151 follicular lymphoma biopsy specimens

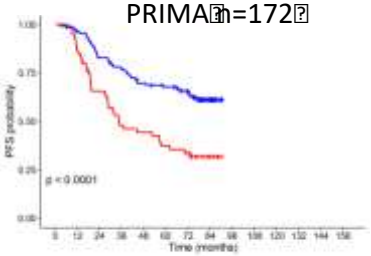




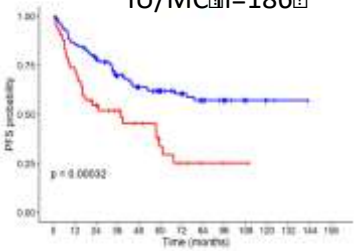
Gene-Expression Profiling Predicts Disease Progression in Follicular Lymphoma

Validation Cohorts - Results

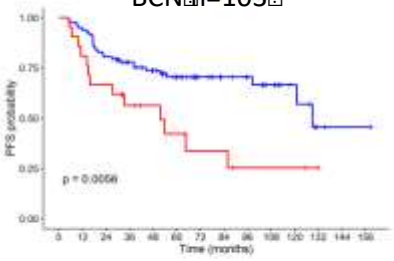
PRIMA (n=172)



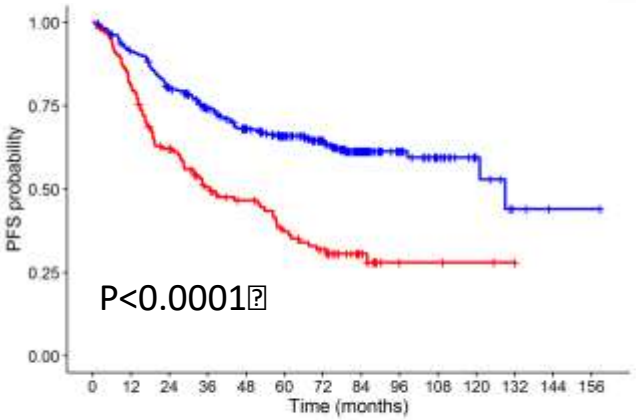
IU/MC (n=186)



BCN (n=103)



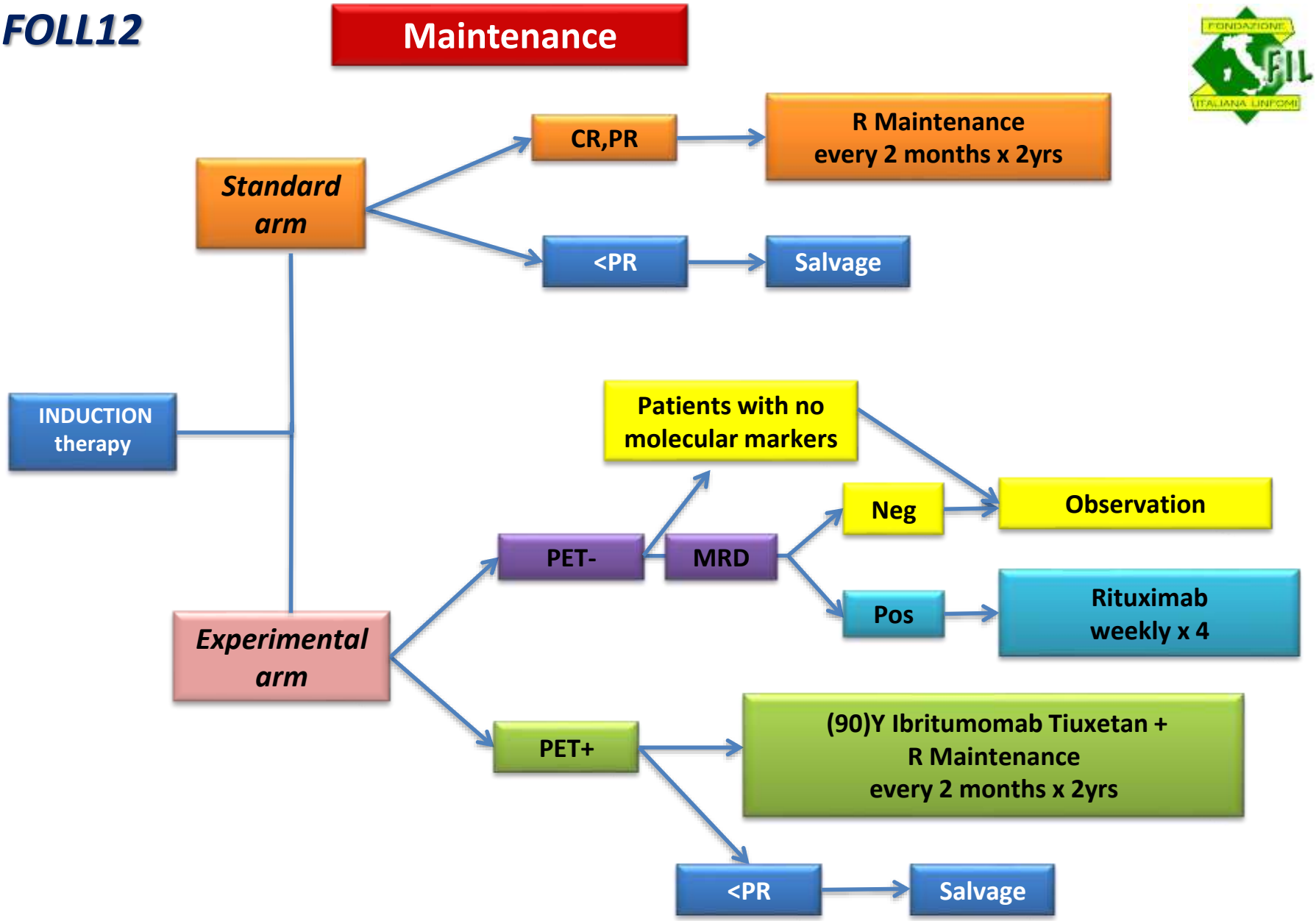
All validation cohorts (n=461)



- HR=2.30 (1.72-3.08)
- C-index: 0.628
- Median time to progression: 3.1 vs 10.8 years
- POD24 : 38% (high score) vs 19% (low score)
- Multivariate analysis: the predictor score was independent of FLIPI and maintenance

Huet et ICML 2017

FOLL12

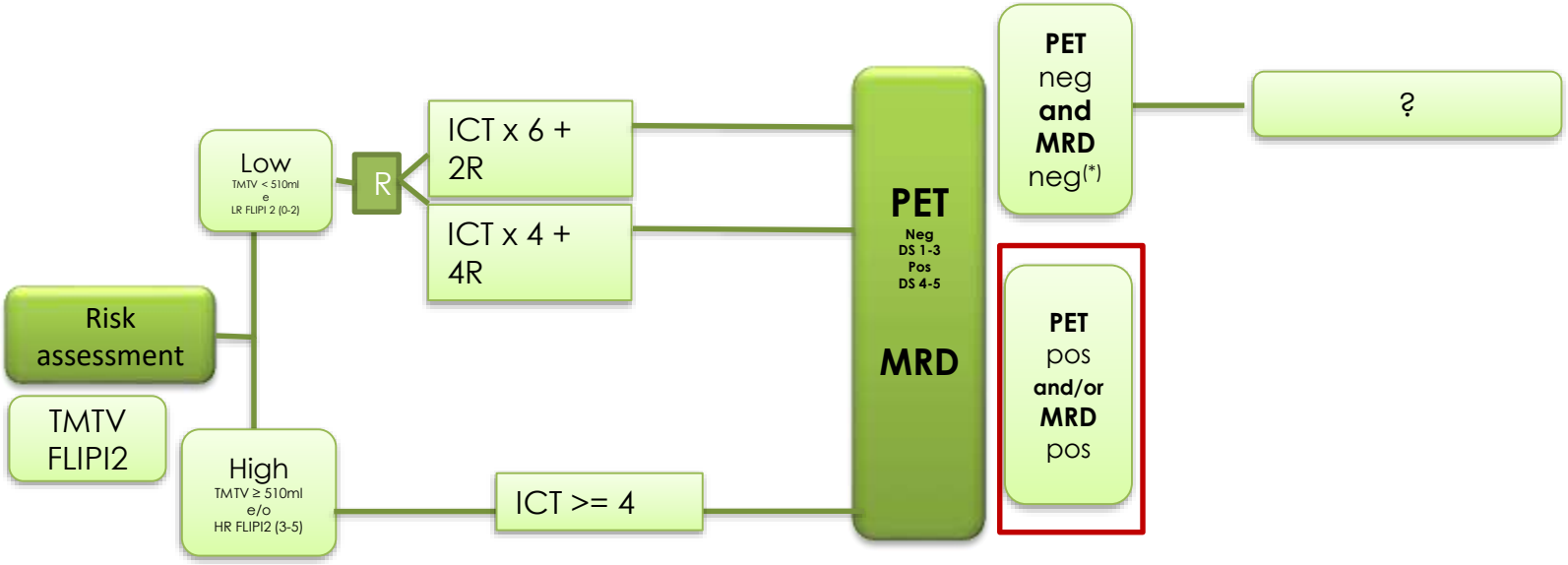

Maintenance
Standard arm
CR,PR
R Maintenance every 2 months x 2yrs
<PR
Salvage
INDUCTION therapy
Experimental arm
Patients with no molecular markers
PET-
MRD
Neg
Observation
Pos
Rituximab weekly x 4
PET+
(90)Y Ibritumomab Tiuxetan + R Maintenance every 2 months x 2yrs
<PR
Salvage

Prognostic factors in FL

- Baseline
  - FLIPI and/or FLIPI2
  - m7FLIPI
- Post-induction
  - MRD
  - PET response
  - TMTV

Prognostic factors in FL

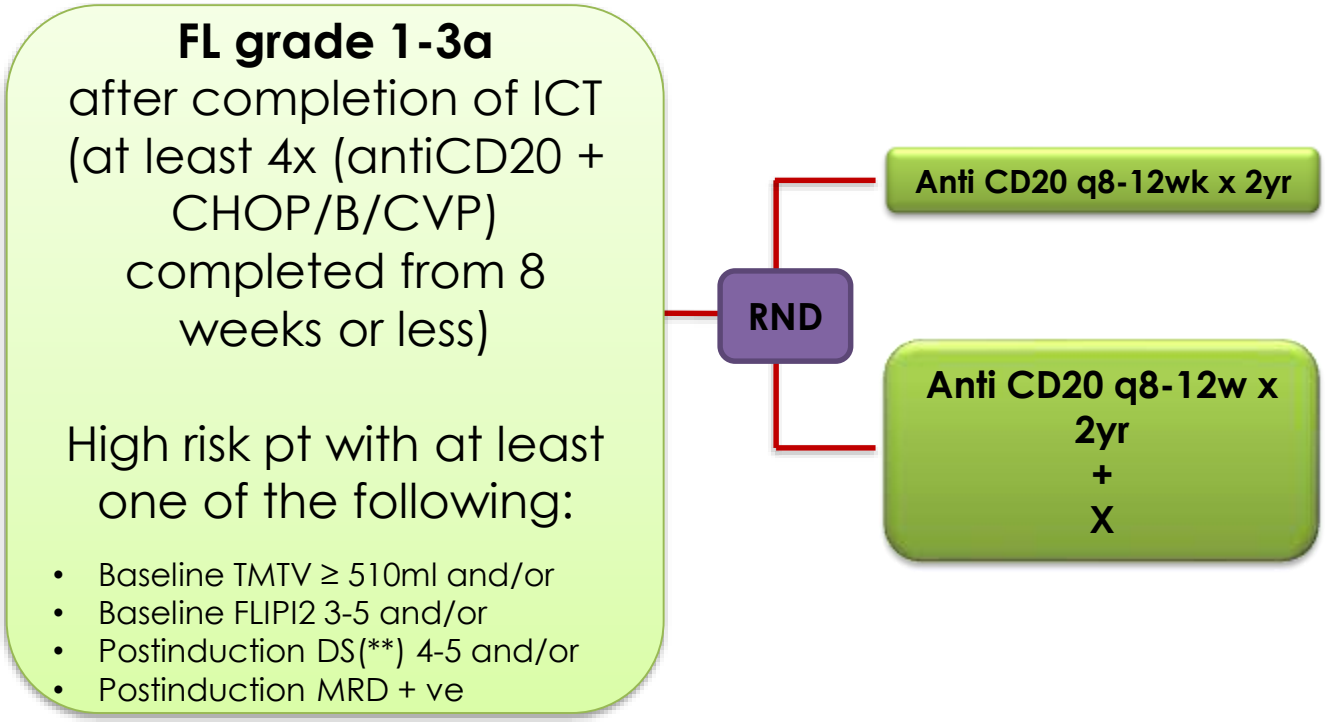
- Baseline
  - FLIPI and FLIPI2
  - ~~m7FLIPI~~
- Post-induction
  - MRD
  - PET response
  - TMTV



ICT: AntiCD20 + CHOP or Benda or CVP

* Include pz senza marcatore molecolare

Trial Outline: X-R vs R as postinduction therapy in high risk FL responding to induction CT



Legend to figure: FL: Follicular lymphoma; TMTV Total Metabolic Tumor volume (Meignan et al JCO 2016); FLIPI2 Follicula Lymphoma Internationale Prognostic Index 2 (Federico et al JCO 2009) MRD Minimal Residual Disease; DS Deauville score (Meignan et al Leuk Lymph 2009)