LOW GRADE LYMPHOMAS
MODERN TREATMENT STRATEGIES IN FOLLICULAR LYMPHOMA

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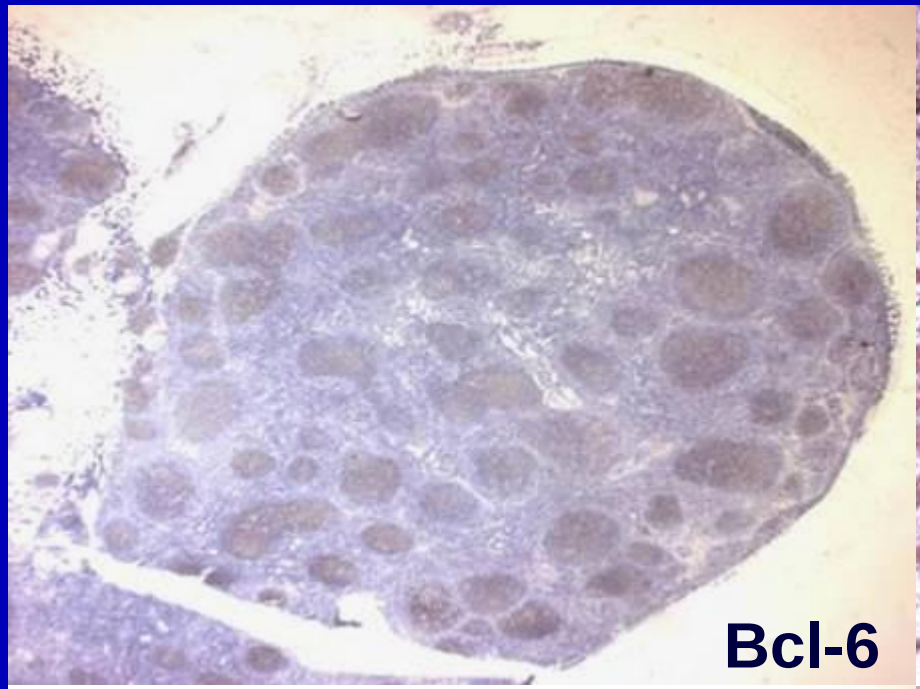
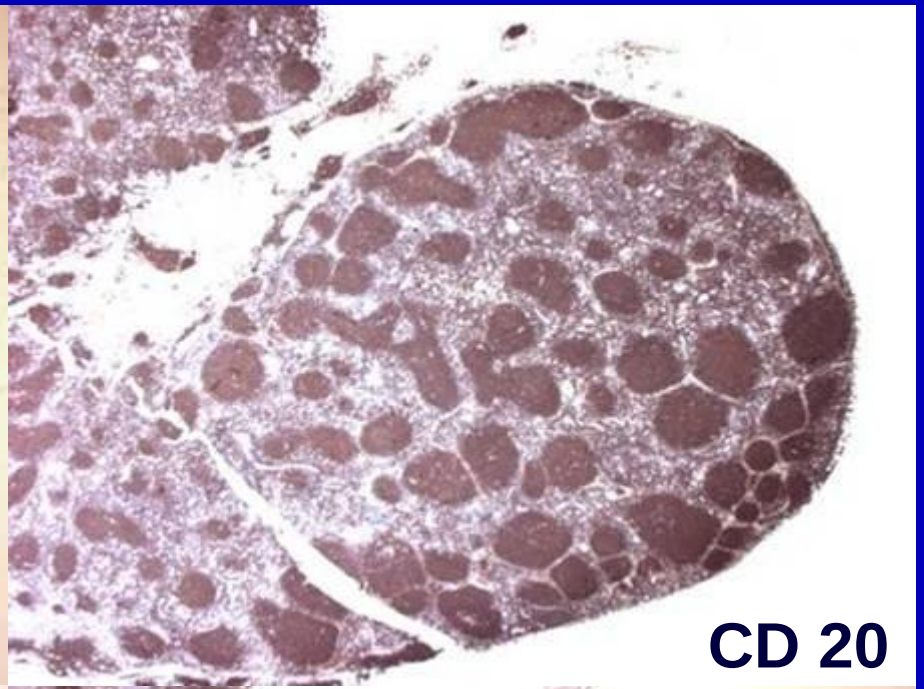
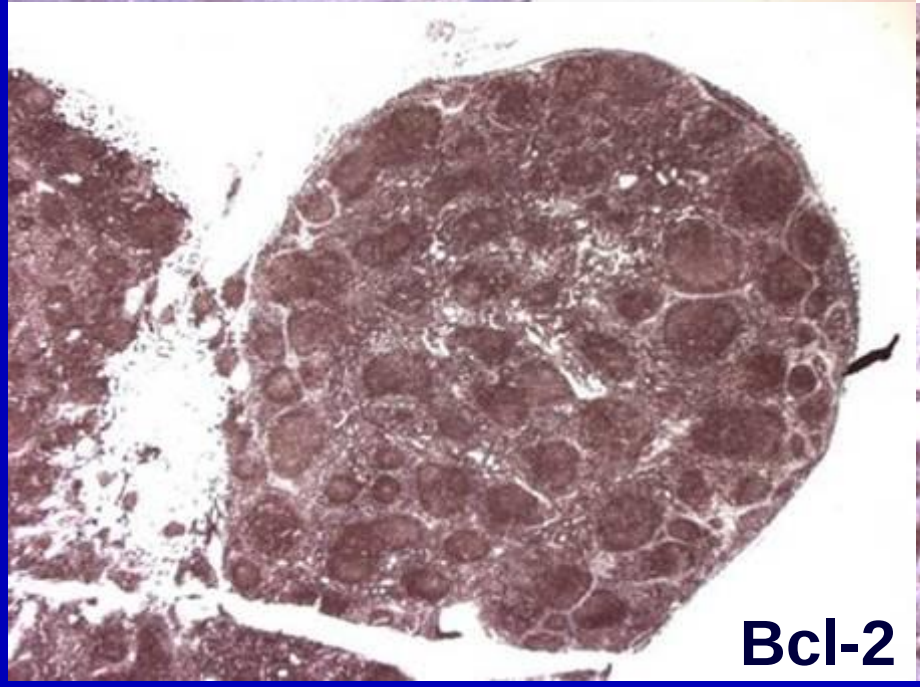
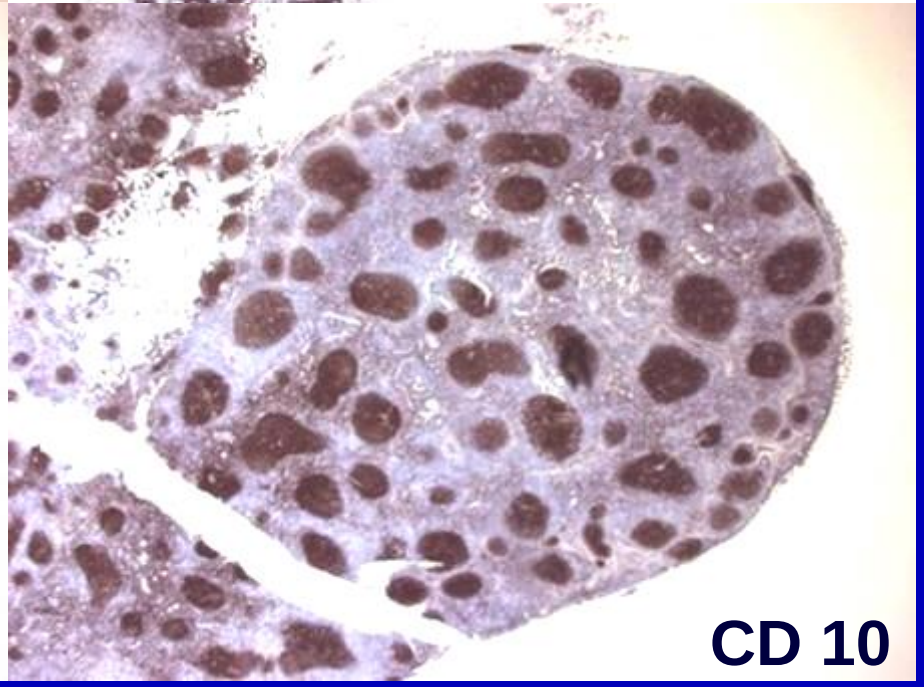
DISCLOSURES ANTON HAGENBEEK

None





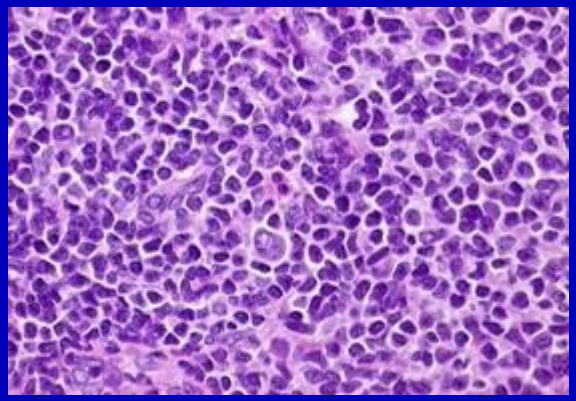




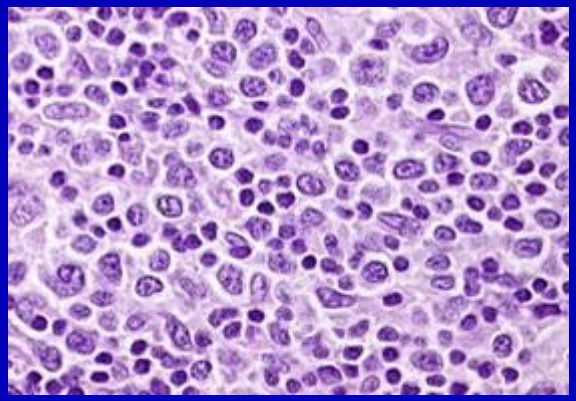
Piris, Valencia, 2006

Follicular Lymphoma : Grading

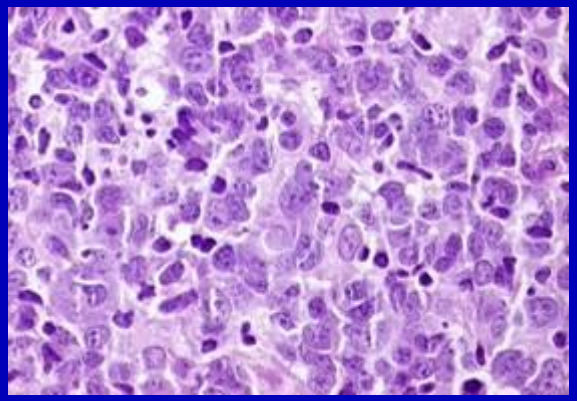
Grade 1



Grade 2



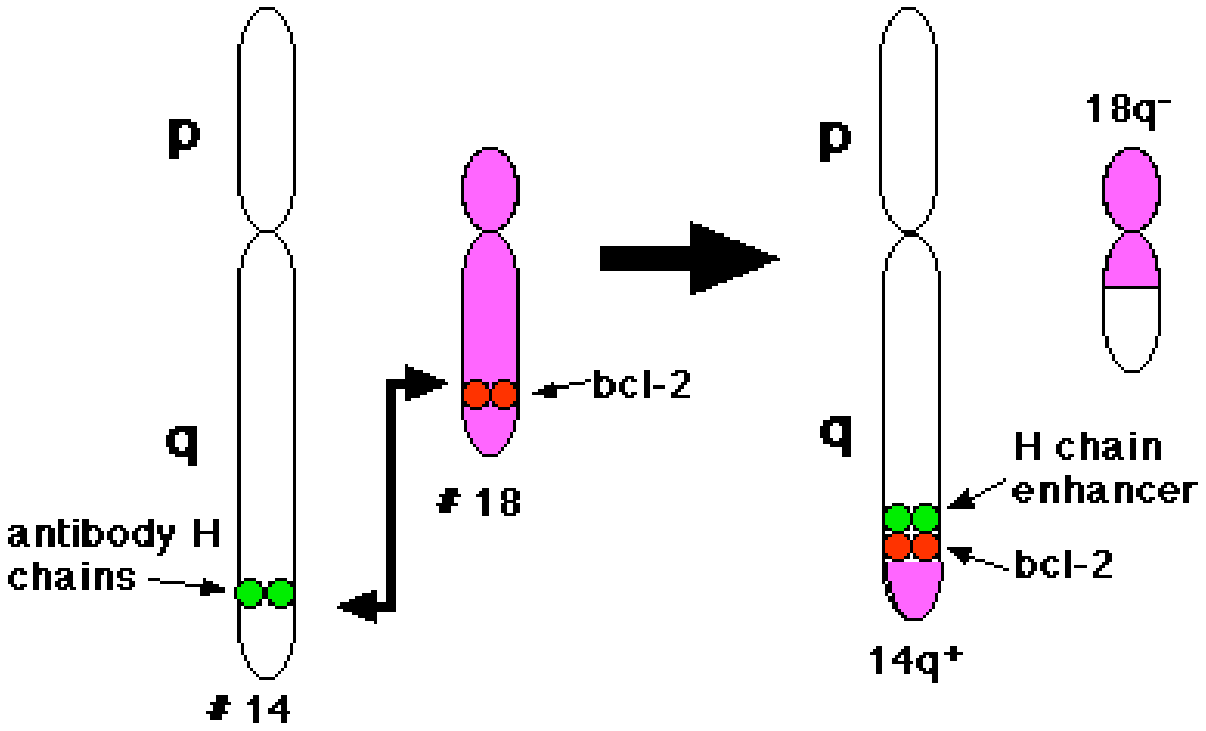
Grade 3



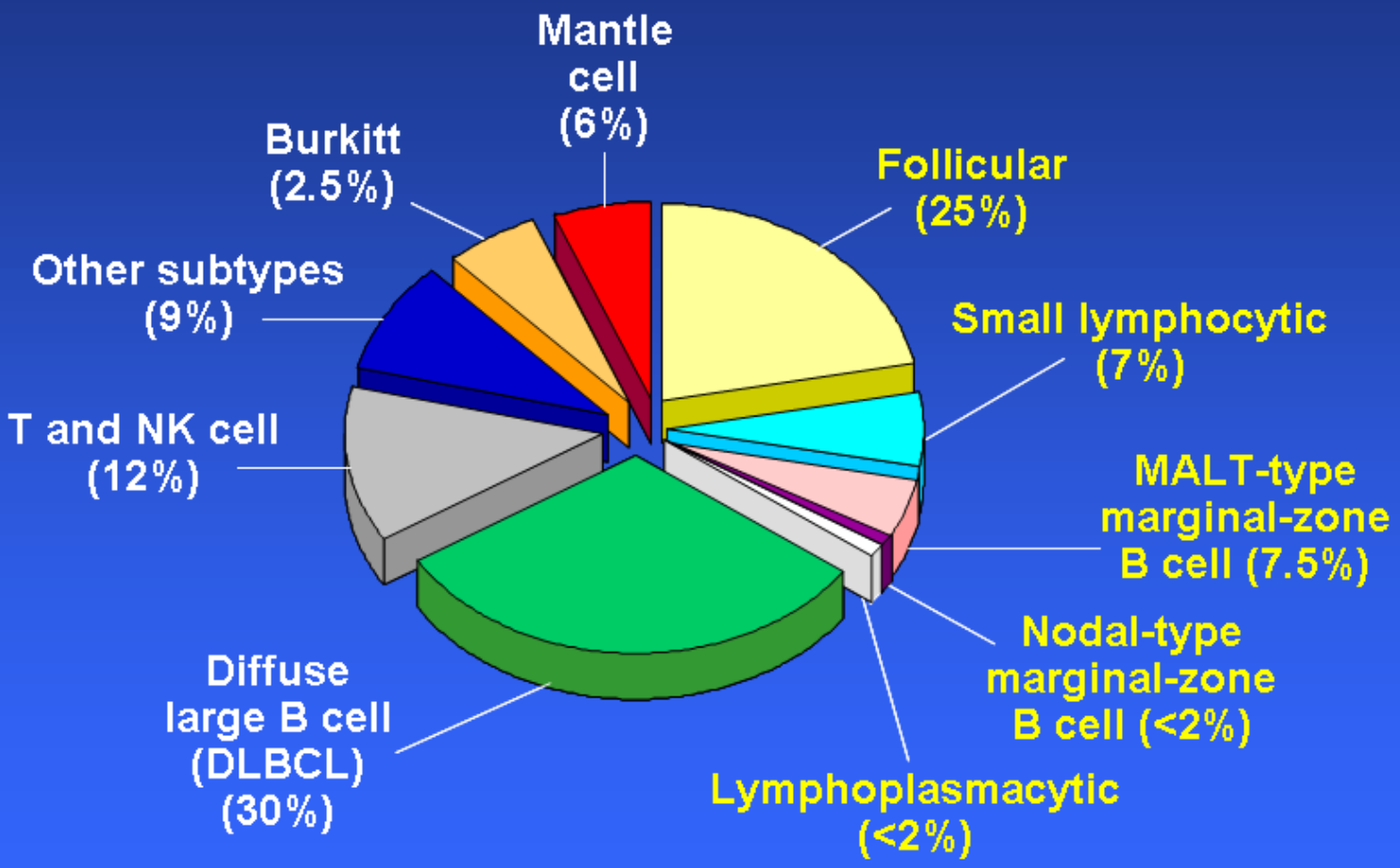
Histological subtype	Number of centroblasts/HPF
Grade I	0–5
Grade II	6–15
Grade III	> 15
Grade IIIa	centrocytes still present
Grade IIIb	centroblasts form solid sheets with no residual centrocytes

Piris, Valencia, 2006

Follicular lymphoma is characterized by t(14;18)



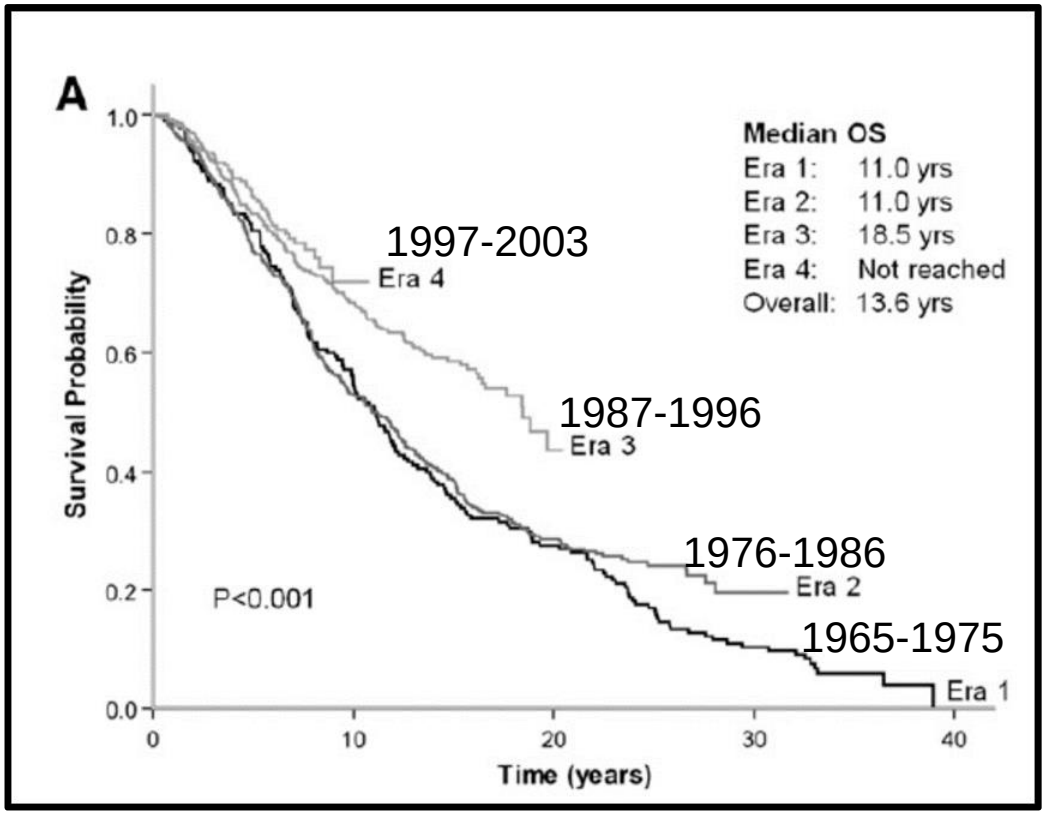
WHO CLASSIFICATION



Natural History of Follicular Lymphoma and Improved Overall Survival

- **Median age 65**
  - 5-10% of patients are younger than 40 years
- **Advanced disease at diagnosis**
  - 20% have early stage disease
- **Median overall survival** ~20 years :

  chronic disease !



Stanford University Experience

Tan et al. Blood 122:981-987, 2013; Casulo et al. Ann Onc 11: 2311-2317, 2015

TREATMENT OF ADVANCED STAGE FOLLICULAR NHL

- Wait-and-see strategy
- Remission - induction treatment
- Maintenance treatment

TREATMENT OF ADVANCED STAGE FOLLICULAR NHL - FIRST LINE

- Wait-and-see strategy
- Remission - induction treatment
- Maintenance treatment

Is the “Wait-and-See” strategy in advanced stage follicular lymphoma still valid?

- Several prospective , randomized phase III clinical trials showed no difference in Overall Survival between “Wait and See” and immediate treatment with Chemo or Rituximab

ABANDON WAIT-AND-SEE POLICY ?
Anno 2019 : NO !

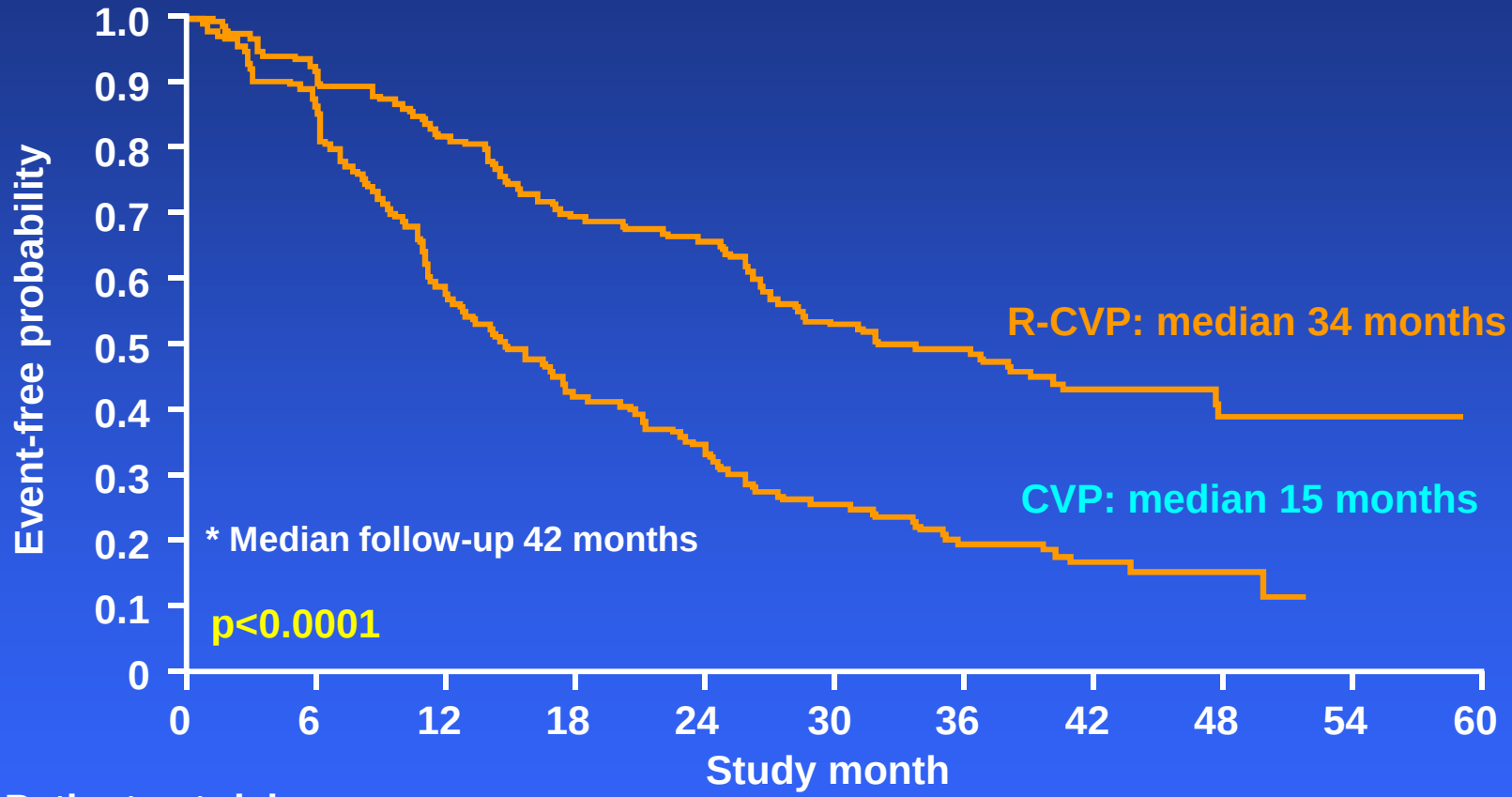
Not until:

- **Immediate treatment = curative**
- **Better overall survival (clinical trials!)**
- **Better quality of life**
- **Better prognostic indices**
  - **Clinical (FLIPI ; FLIPI-2 = still valid in R-chemo era)**
  - **Biological (gene expression profiling, tissue microarrays, etc.)**

TREATMENT OF ADVANCED STAGE FOLLICULAR NHL

- Wait-and-see strategy
- Remission - induction treatment
- Maintenance treatment

R-CVP MORE THAN DOUBLES TIME TO PROGRESSION , RELAPSE OR DEATH



Patients at risk:

CVP	159	129	87	64	51	39	29	14	5	0	0
R-CVP	162	144	132	112	105	84	73	40	16	5	0

Solal-Celigny P, et al. Blood 2005;106:106a (Abstract 350)

Rituximab combined with chemotherapy (R-chemo) has improved Overall Survival (OS) in patients with advanced FL

Study name and author	Follow-up, years	OS, %		p-value
		Control	R-chemo	
M3902: Marcus *et al.* (2008)[1]	**4**	**77**	**83**	✓
GLSG: Buske *et al.* (2008)[2]	**5**	**84**	**90**	✓
M39023: Herold *et al.* (2007)[3]	**4**	**74**	**87**	✓
FL2000: Salles *et al.* (2008)[4]	**5**	**79**	**84**	✓ (high-risk pts)

Cochrane analysis:
HR 0.63 (95% CI: 0.51, 0.79)[5]

1. Marcus R, et al. J Clin Oncol 2008;26:4579–86
2. Buske C, et al. ASH 2008 presentation (Abstract 2599)
3. Herold M, J Clin Oncol 2007;25:1986–92
4. Salles G, et al. Blood 2008;112:4824–31
5. Schulz H, et al. Cochrane Database Syst Rev 2007;(4):CD003805

SPECIFIC QUESTIONS IN FIRST LINE

- Which chemo is preferred ?
- Choice of anti-CD20 antibody ?
- Chemo-free regimens ?

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R-CVP VS R-CHOP VS R-FM IN NEWLY DIAGNOSED ADVANCED STAGE FOLLICULAR NHL

(Federico et al., Lugano 2011)

534 patients were randomized

	3 yrs TTF (%)	3 yrs OS (%)
8x R-CVP[1]	47	97
6x R-CHOP + 2x R	57	96
6x R-FM + 2x R[3]	60	92

TTF : 1-2: p=0.026; 1-3: p=0.023; 2-3: p=0.979

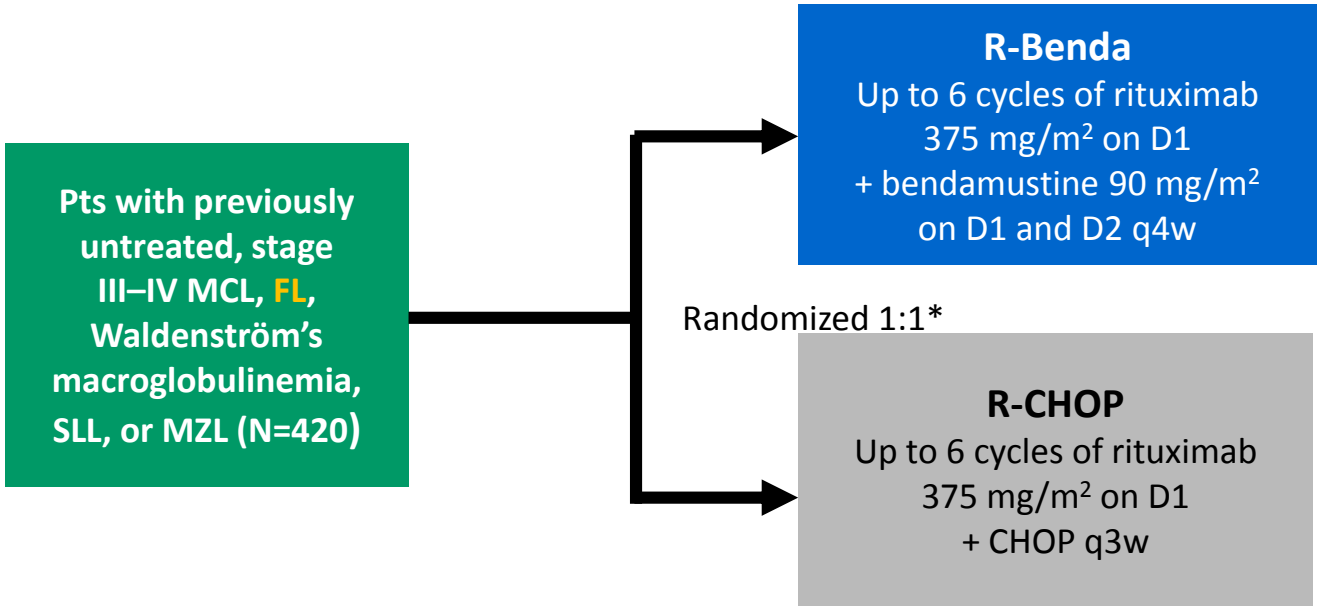
NB: Neutropenia after R-FM > R-CHOP : OR 1.96; p=0.004

Conclusion : R-CHOP standard of care ….. (FLIPI 3-5 ?)

StiL NHL 1-2003 study design : R-Bendamustine versus R-CHOP in previously untreated indolent NHL or MCL

- **10-year update**

Non-inferiority trial : Primary endpoint PFS



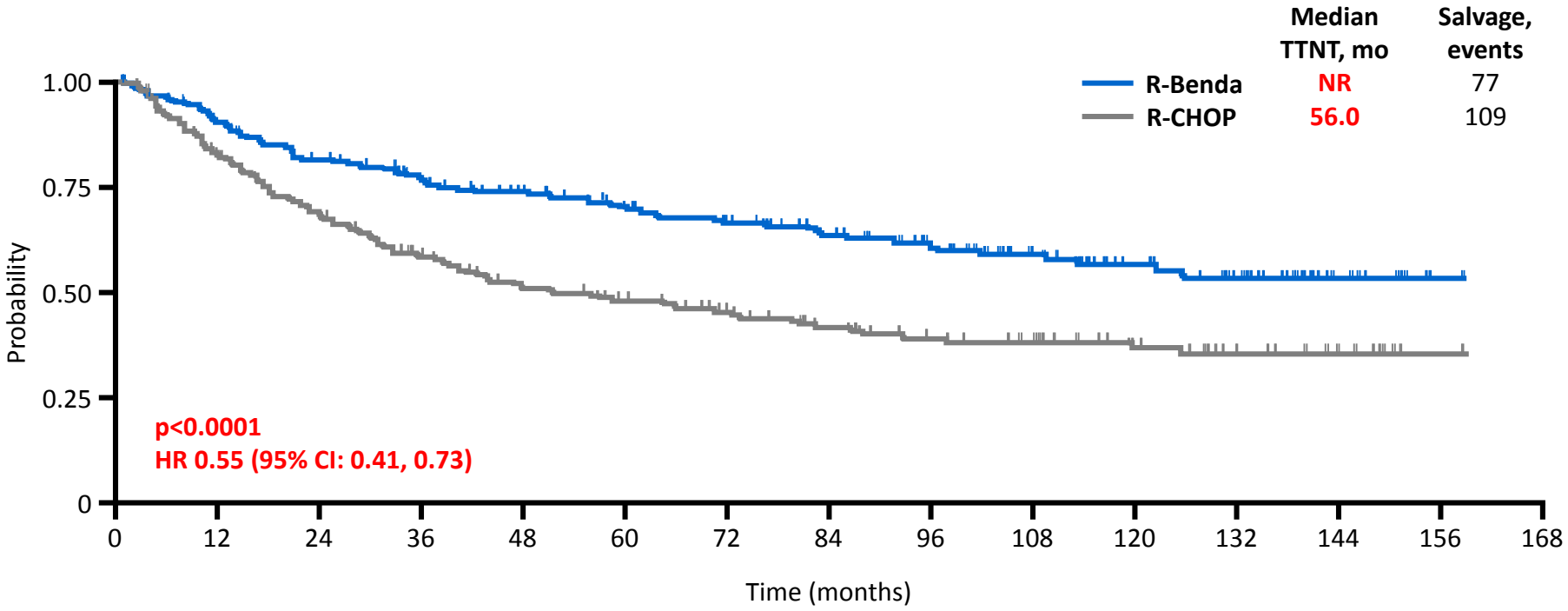
Rummel M, et al. ASCO presentation 2017 (Abstract 7501)
Rummel M, et al. Lancet 2013;381:1203–10

B-R VS CHOP-R : TOXICITIES (ALL CTC-GRADES)

	B-R (n=260) no. of pts	CHOP-R (n=253) no. of pts	*P* value
Alopecia	-	+++	< 0.0001
Paresthesias	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Skin (erythema)	42	23	= 0.0122
Allergic reaction (skin)	40	15	= 0.0003
Infectious complications	96	127	= 0.0025
- Sepsis	1	8	= 0.0190

StiL NHL 1-2003 : 10-year update confirmed superiority of R-Bendamustine over R-CHOP in previously untreated iNHL or MCL (median follow-up : 117 months)

TTNT (as surrogate for PFS)



Rummel M, et al. ASCO presentation 2017 (Abstract 7501)

No difference in OS

DOES IT REALLY MATTER IN WHICH SEQUENCE THE DIFFERENT EFFECTIVE CHEMO-IMMUNOTHERAPY REGIMENS ARE GIVEN?

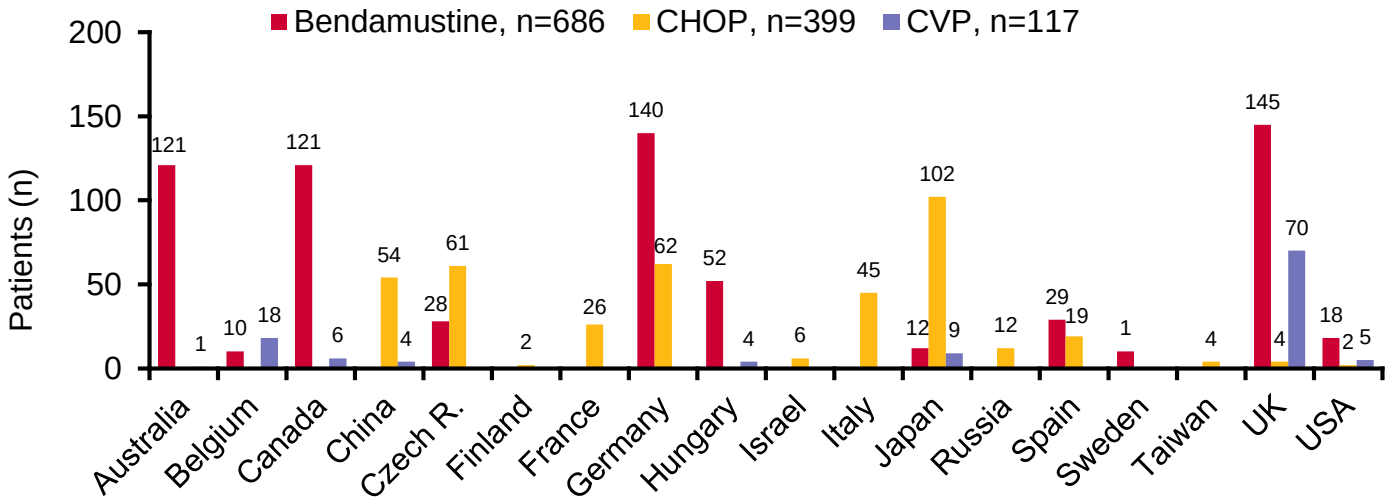
- **Patients may receive between 1 and 10 (?) regimens during the course of their disease ….**

R-Chlorambucil
R-CVP
R-CHOP
R-FM
R-FCM
R-FND
R-Bendamustine
R-etcetera **+/- Rituximab maintenance**

NB: Not a single regimen yields cures !

Worldwide choice of 1st line treatment in follicular lymphoma

R-CHOP or R-Bendamustine
or R-CVP (shorter PFS) ? : no clearcut advice…



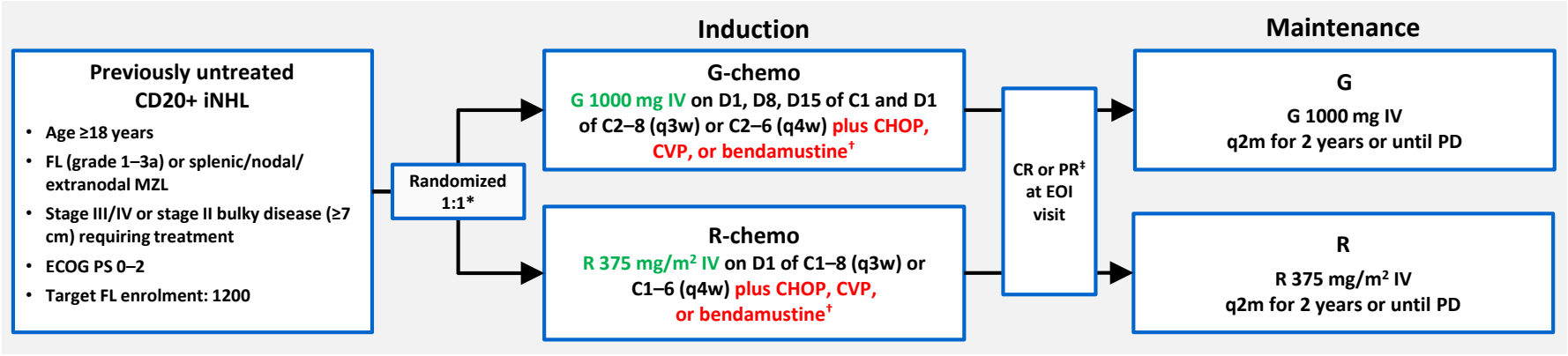
Hiddemann et al., ICML 2017

SPECIFIC QUESTIONS IN FIRST LINE

- Which chemo is preferred ?
- Choice of anti-CD20 antibody ?
- Chemo-free regimens ?

GALLIUM study design: Obinutuzumab (G)-chemo versus Rituximab (R)-chemo plus G/R maintenance in patients with previously untreated, CD20+ iNHL

International, open-label, randomized phase III study in 1202 patients



Primary endpoint

- **PFS (INV-assessed in FL)**

Secondary and other endpoints

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

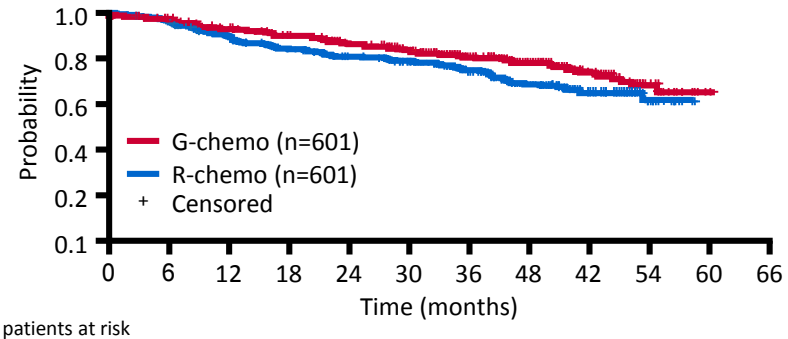
▼ authorities in your country according to your national requirements

Marcus R, et al. N Engl J Med 2017;377:1331–44

GALLIUM : PFS was significantly improved with G-chemo versus R-chemo

PFS after 41.1 months median follow up

INV-assessed PFS

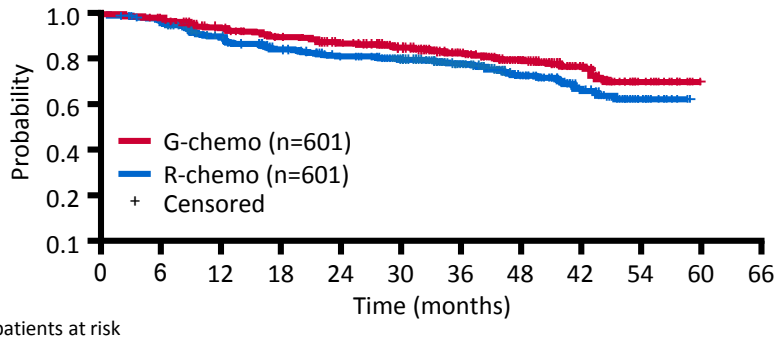


No. of patients at risk

G-chemo	601	561	505	464	438	396	267	149	77	18	0	0
R-chemo	601	569	535	505	478	420	291	176	85	25	1	0

	R-chemo (n=601)	G-chemo (n=601)
3-year PFS, % (95% CI)	**75** (71, 78)	**82** (78, 85)
HR (95% CI), p-value†	**0.68 (0.54, 0.87), p=0.0016**	

IRC-assessed PFS



No. of patients at risk

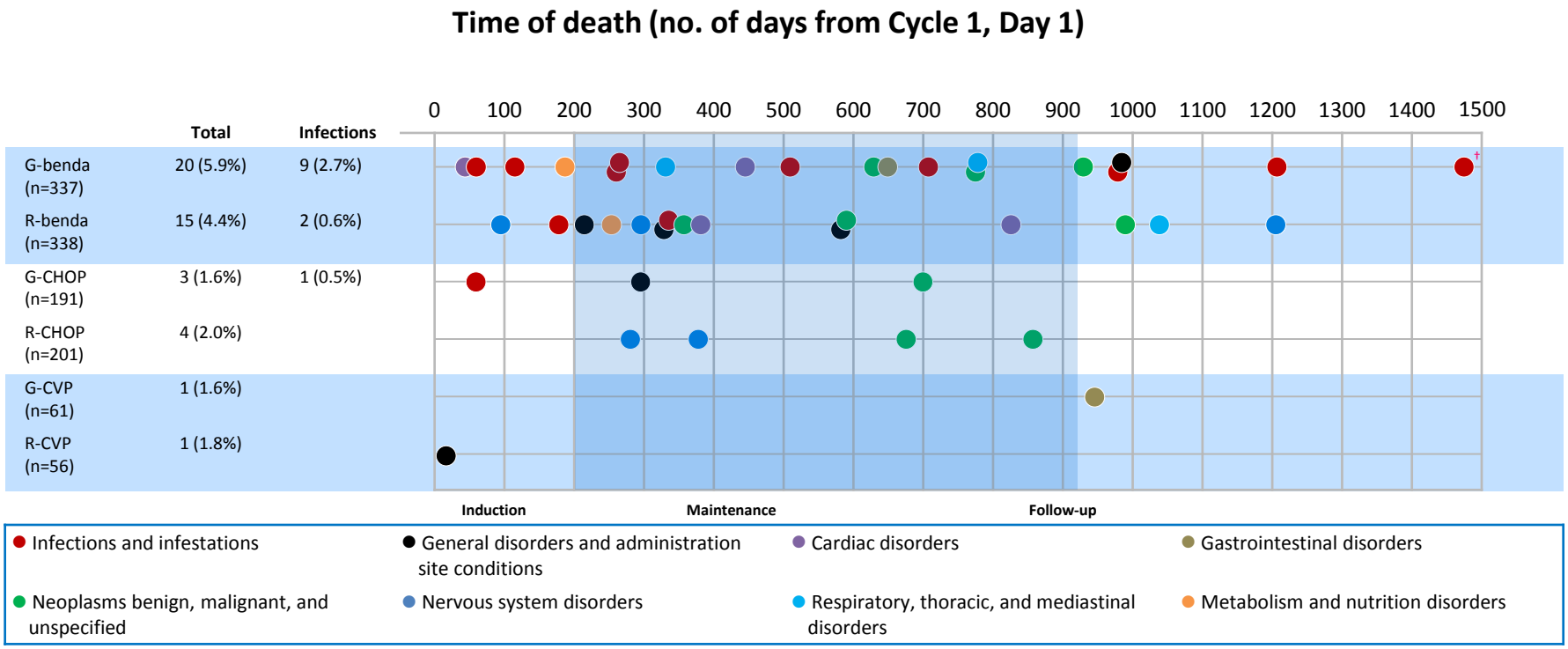
G-chemo	601	563	502	463	438	394	271	151	73	16	0	0
R-chemo	601	571	532	497	476	414	287	179	79	22	0	0

	R-chemo (n=601)	G-chemo (n=601)
3-year PFS, % (95% CI)	79 (75, 82)	83 (80, 86)
HR (95% CI), p-value†	**0.72 (0.56, 0.93), p=0.012**	

1. Hiddemann W, et al. J Clin Oncol 2018 [Epub ahead of print)

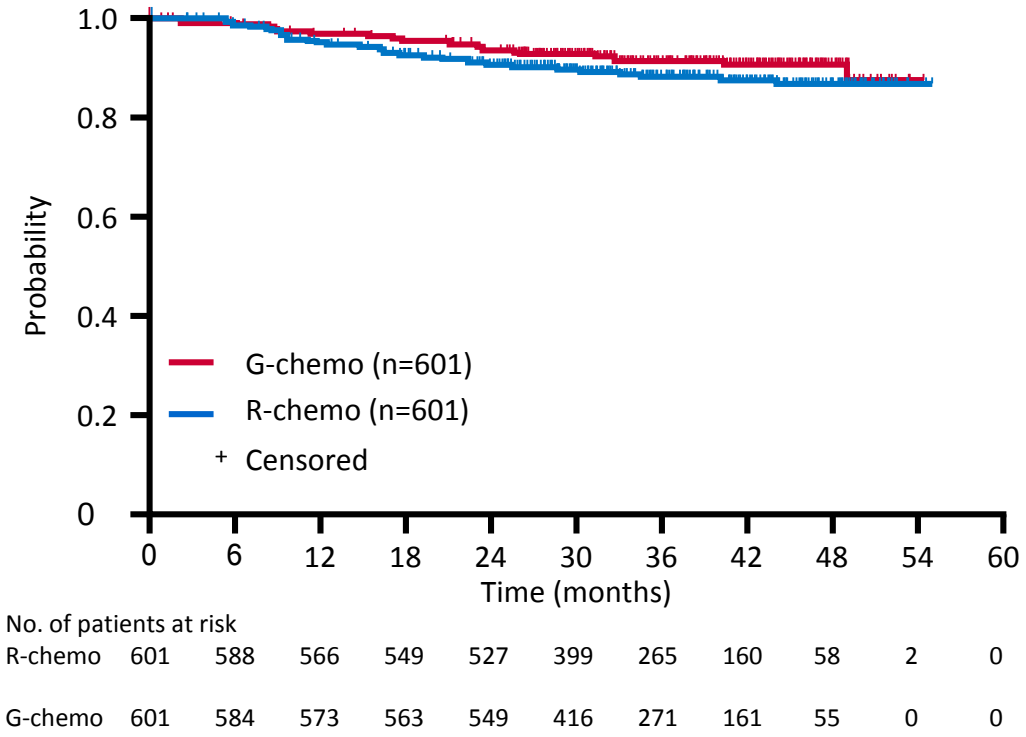
2. Marcus R, et al. N Engl J Med 2017;377:1331–44

GALLIUM : Incidence, nature, and timing of grade 5 (fatal) AE's by treatment received



Marcus R, et al. N Engl J Med 2017;377:1331–44

GALLIUM :
OS was similar with G-chemo and R-chemo



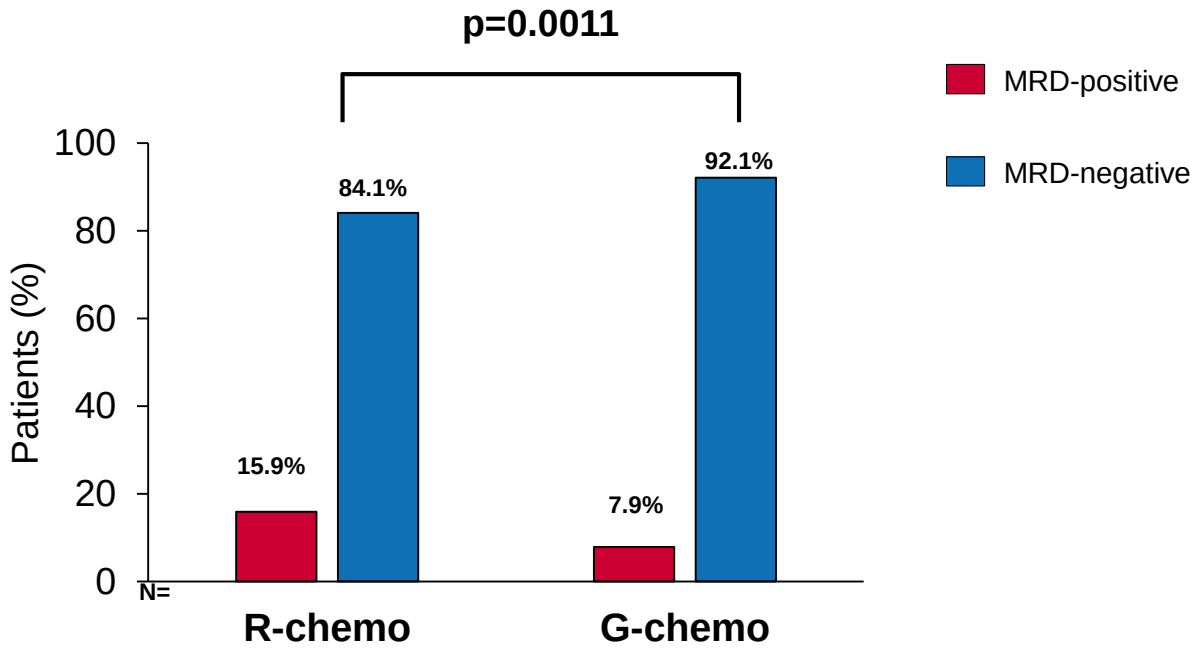
	R-chemo (n=601)	G-chemo (n=601)
Patients with event, n (%)	46 (7.7)	35 (5.8)
3-year OS, % (95% CI)	**92.1** (89.5, 94.1)	**94.0** (91.6, 95.7)
HR (95% CI), p-value*	0.75 (0.49, 1.17), p=0.21	

Median follow-up: 34.5 months

Marcus R, et al. N Engl J Med 2017;377:1331–44

MRD status by treatment arm at EOI (in PB/BM)

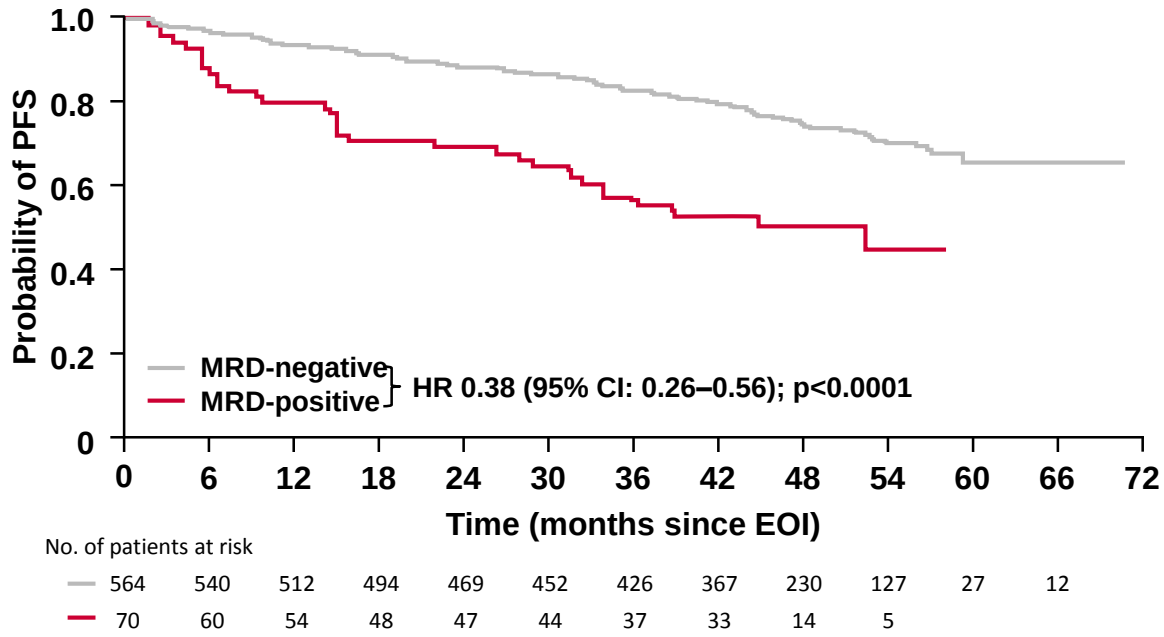
Christiane Pott et al. , ASH 2018



- **In pooled PB/BM, more patients treated with G-chemo versus R-chemo achieved an MRD response at EOI**

).

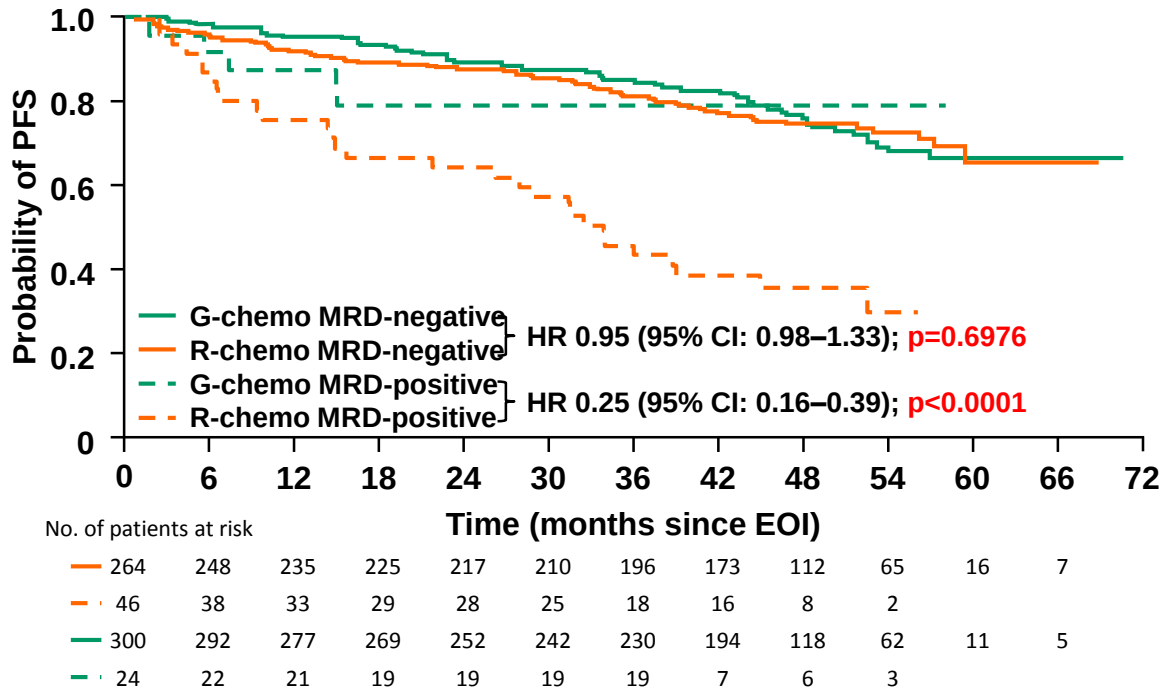
PFS by MRD status at EOI*



- **PFS was improved in patients who were MRD-negative versus those who were MRD-positive**

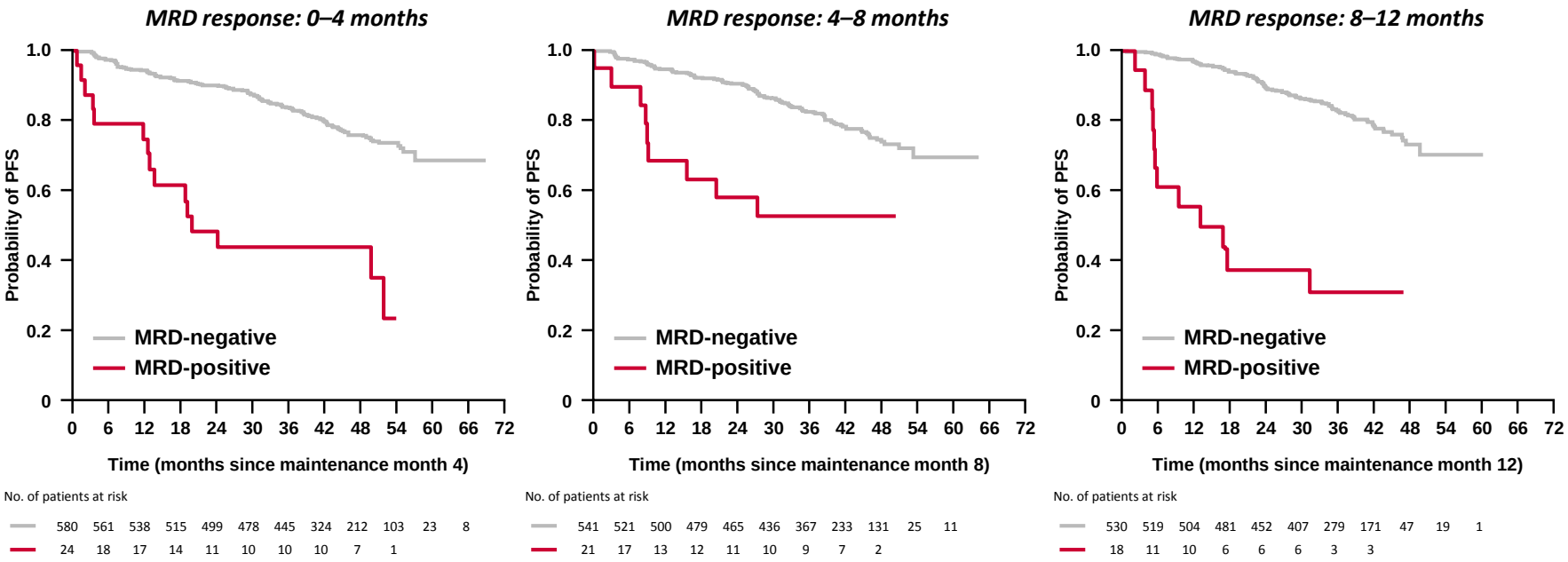
*Combined results for all patients treated with G and R

PFS by MRD status at EOI and treatment arm



- **PFS was similar in patients achieving MRD negativity independent of treatment arm**
  - **MRD positive patients treated with R-chemo appear to have worse outcomes**

Landmark PFS analysis by MRD status*



- **MRD status during maintenance is closely associated with clinical relapse and achievement of MRD negativity is of high prognostic relevance**

*Patients were included if no PFS event had occurred by the specific time points.

COMMENTS TO THE RESULTS OF THE GALLIUM STUDY

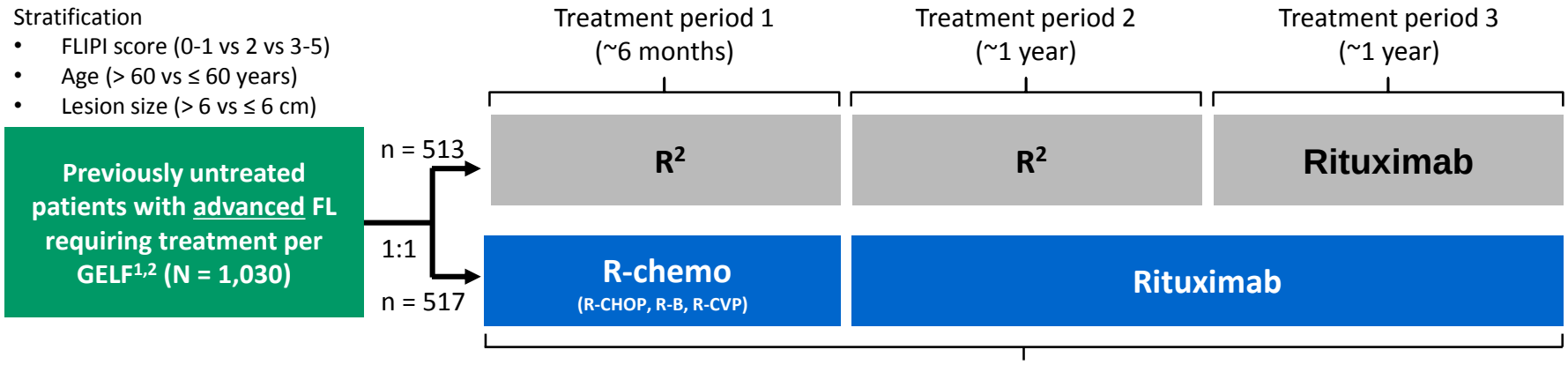
- Significantly more antibody given in the G-chemo arm (1.5 times more)
- More cytopenias,infections and infusion-related reactions in the G-chemo arm
- With only 7% increase in PFS and no difference in OS : G-chemo new standard of care ?
- NB. Toxicity with G-Bendamustine (T cell depletion in Bendamustine arm)

SPECIFIC QUESTIONS IN FIRST LINE

- Which chemo is preferred ?
- Choice of anti-CD20 antibody ?
- Chemo-free regimens ?

RELEVANCE study design : R + Lenalidomide (R^2) versus R-chemo, followed by R maintenance

International, multicenter, randomized study



- **R-chemo**
  - **Investigator choice of R-CHOP, R-CVP, or R-Benda**
- **R^2**
  - **Lenalidomide 20 mg D2–22 x 6 ; 28-day cycles (if CR : then 10 mg) + Rituximab**

- **Co-primary endpoints** (superiority* trial)
  - **CR/CRu rate at 120 weeks**
  - **PFS**

RELEVANCE: R^2 did not demonstrate superiority over R-chemo for either of the co-primary endpoints (CR/CRu and PFS)

	R^2 (n=513)	R-chemo (n=517)	p-value
CR/CRu at 120 weeks, %			
By IRC	**48**	**53**	0.13
By INV	**55**	**58**	0.38
Interim PFS (~50% events)			
R^2 vs R-chemo: HR (95% CI) by IRC	1.10 (0.85, 1.43)		0.48
R^2 vs R-chemo: HR (95% CI) by INV	0.94 (0.73, 1.22)		0.63
3-year PFS (IRC / INV)	**77 / 77**	**78 / 78**	—
3-year OS, %	**94**	**94**	—

*Median follow-up : 37.9 months

Fowler NH, et al. ASCO , 2018 (Abstract 7500)

RELEVANCE: Neutropenia and Neutropenic Complications (Entire Treatment Period)

Patients, n (%)	R^2 (n = 507)	R-chemo (n = 503)
Grade 3/4 neutropenia*	160 (32)	252 (50)
Grade 4 neutropenia	41 (8)	154 (31)
Nadir ANC < 100/μL	5 (1)	32 (6)
Median time to onset of first grade 3/4 lab neutropenia	3.7 months	0.6 months
Grade 3/4 infections associated with grade 3/4 neutropenia	10 (2)	20 (4)
Febrile neutropenia*	11 (2)	34 (7)
Febrile neutropenia requiring hospitalization	8 (2)	26 (5)
Infections requiring hospitalization	46 (9)	60 (12)
Received growth factors	117 (23)	340 (68)

- Per protocol, patients in the R^2 arm had more frequent laboratory assessments than the R-chemo arm

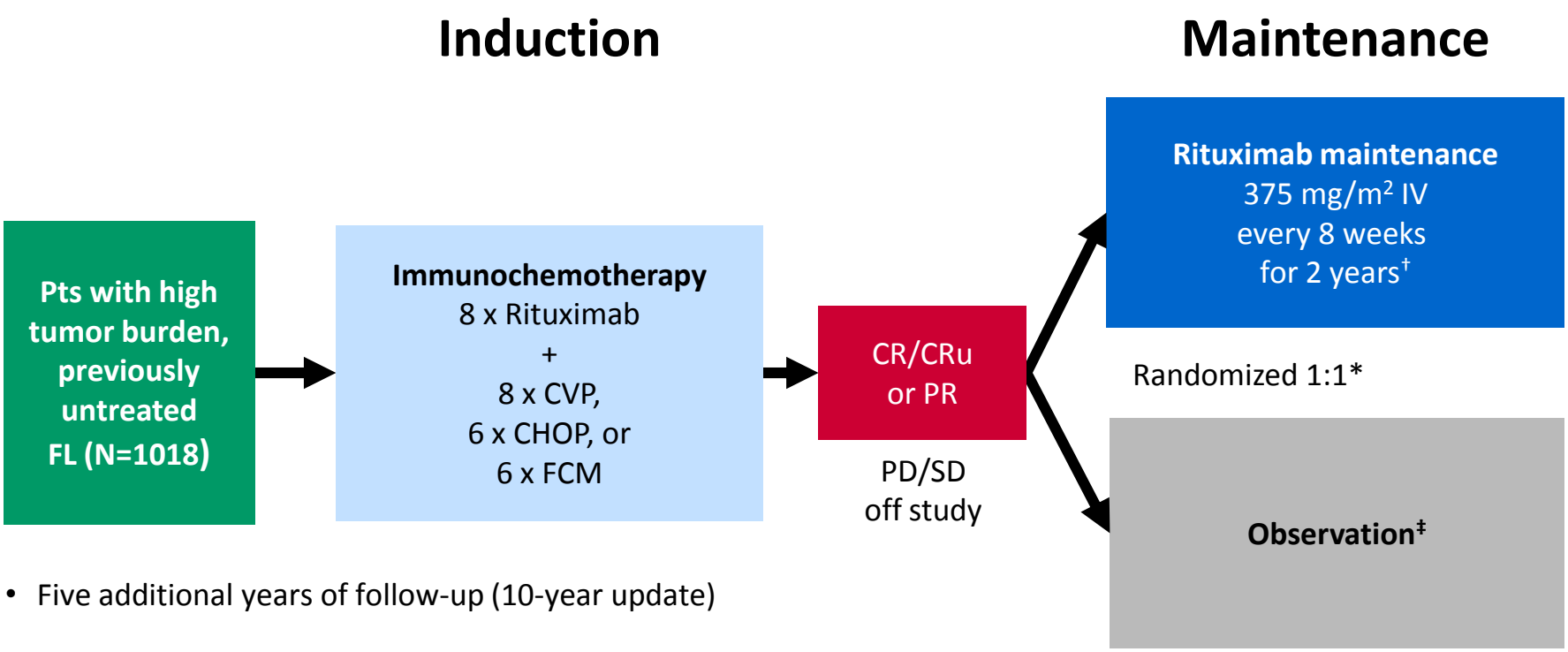
RELEVANCE : Conclusions

- R^2 was not superior to R-chemo based on CR/CRu at 120 weeks and interim PFS
  - **R^2 and R-chemo showed similar efficacy results**
  - Continued follow-up for more mature PFS and OS results is ongoing
- **Important differences in safety profiles were observed between arms :**
  - R-chemo: More frequent neutropenia (grade 3/4), febrile neutropenia, growth factor usage, nausea, vomiting, neuropathy, and alopecia
  - R^2: More frequent cutaneous reactions, tumor flare, and diarrhea
- **These results show that R^2, a novel immunomodulatory approach, is a potential first-line option for patients with FL requiring treatment**
- QOL, MRD, and PET data to be presented in future meetings

TREATMENT OF ADVANCED STAGE FOLLICULAR NHL

- Wait-and-see strategy
- Remission - induction treatment
- Maintenance treatment

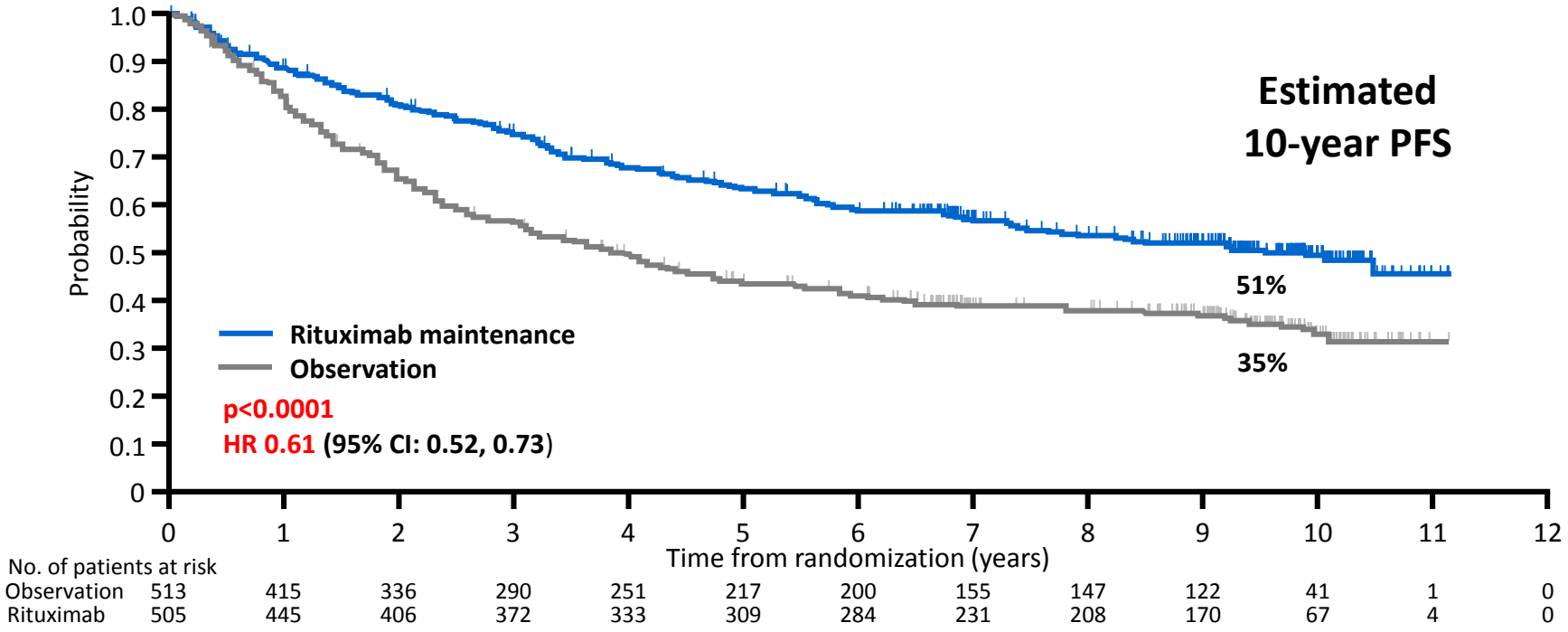
PRIMA study design : Rituximab maintenance versus observation after induction immuno-chemotherapy



- Five additional years of follow-up (10-year update)

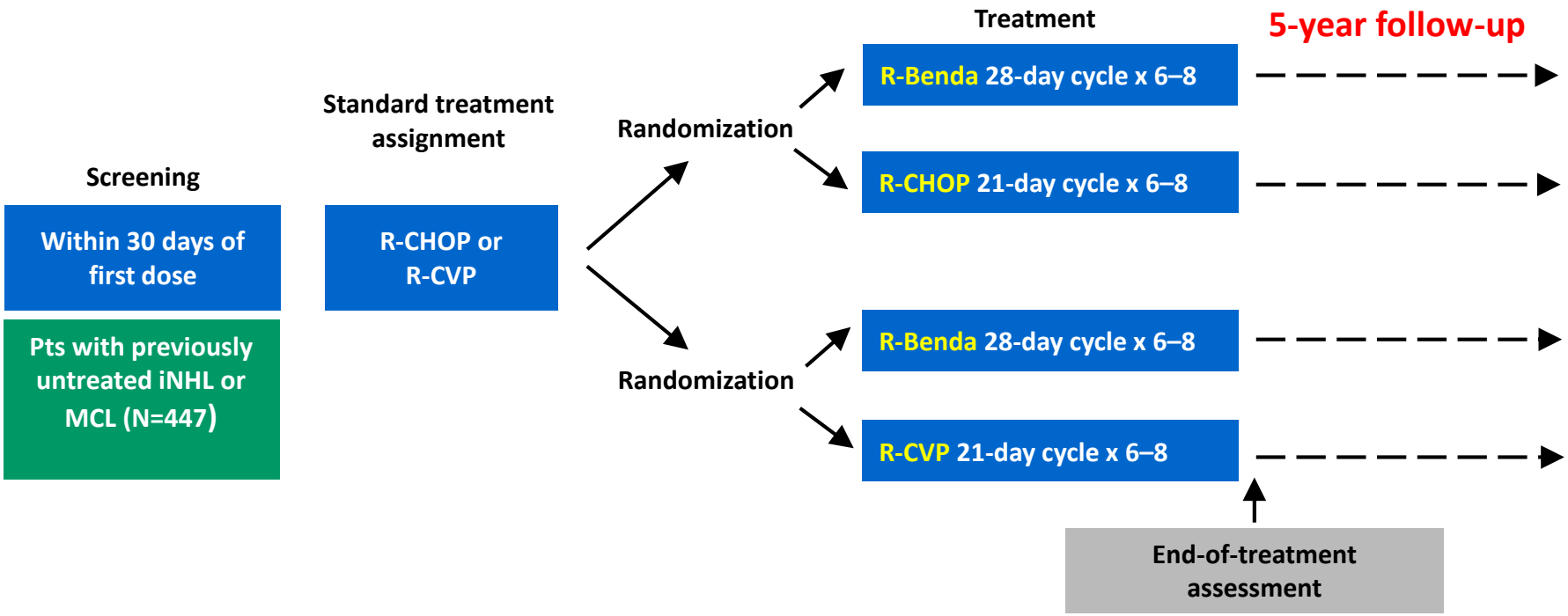
Salles G, et al. ASH presentation 2017 (Abstract 486)
Salles G, et al. Lancet 2011;377:42–51

PRIMA : PFS at 10 years from randomization confirmed benefit of Rituximab maintenance over observation (no difference in OS)



Salles G, et al. ASH presentation 2017 (Abstract 486)

BRIGHT study design : R-Bendamustine versus R-CVP/R-CHOP in previously untreated iNHL or MCL

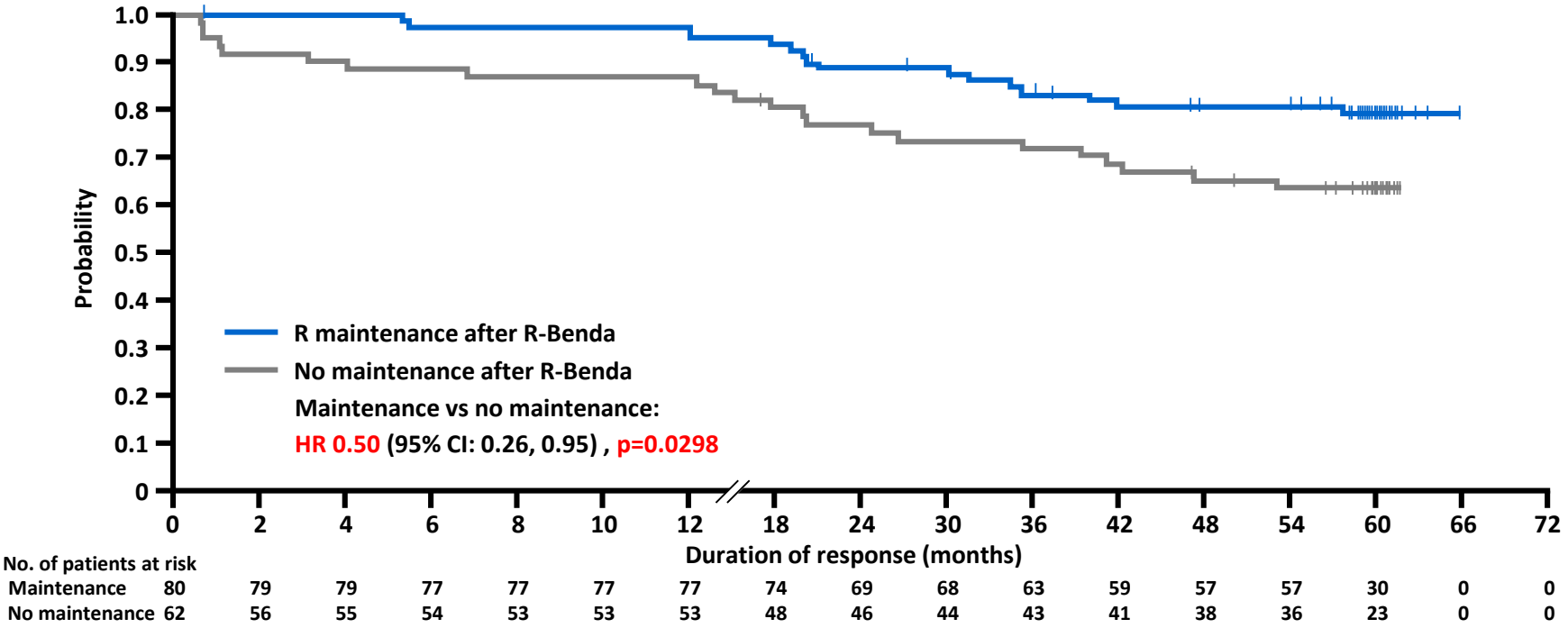


*Median follow-up: 65.0 months (R-Benda) ; 64.1 months (R-CVP/R-CHOP)

†

Flinn I, et al. ASCO presentation 2017 (Abstract 7500)
Flinn IW, et al. Blood 2014;123:2944–52

BRIGHT post-hoc analysis: Rituximab maintenance markedly prolonged duration of response in FL patients after first-line R-Bendamustine



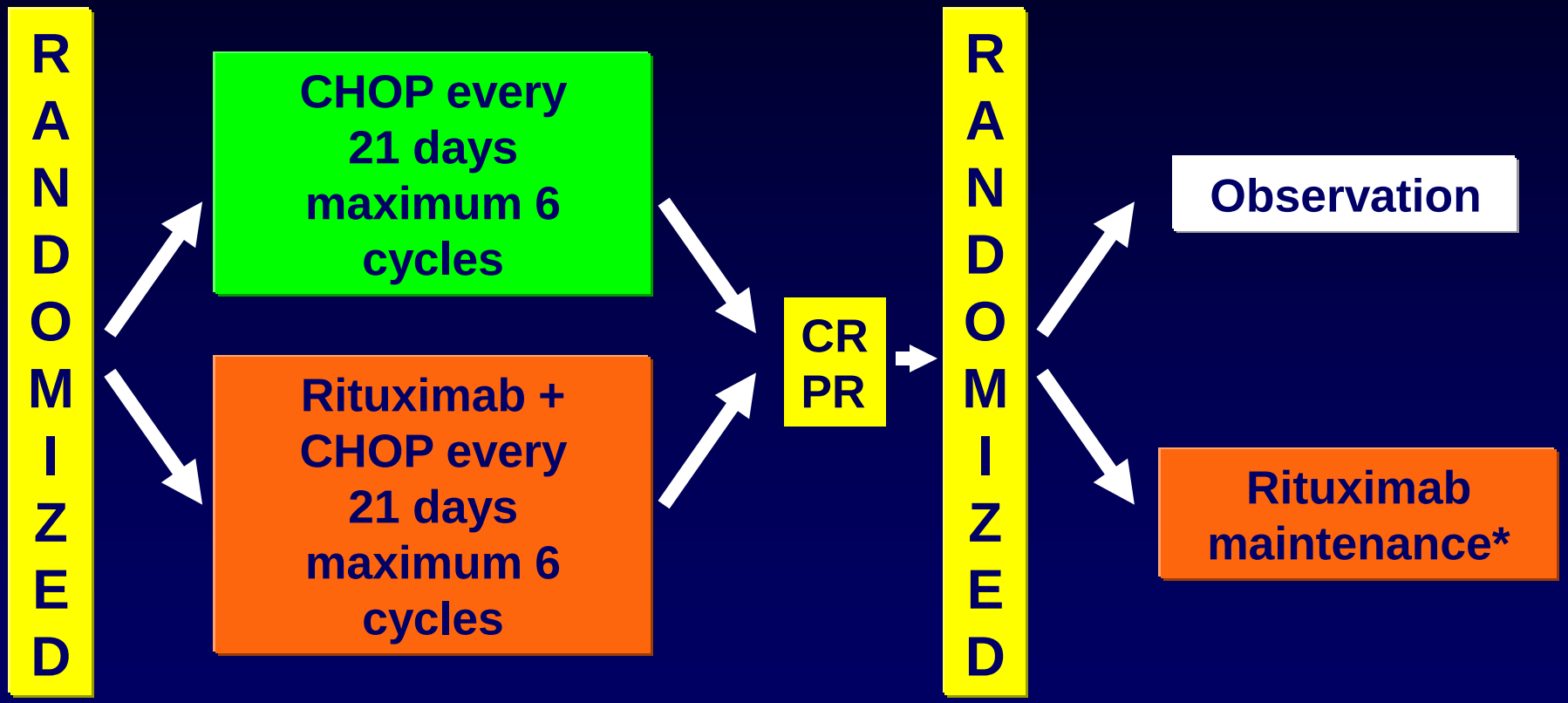
NB. No difference in Overall Survival

Kahl BS, et al. ASH presentation 2017 (Abstract 484)

TREATMENT OF RELAPSED FOLLICULAR NHL

- Re-induce a remission with R + non-cross resistant chemo ; antibody maintenance ?
- Consolidate with autologous / allogeneic stem cell transplantation in high risk patients ?
- Introduce new agents (clinical trials)

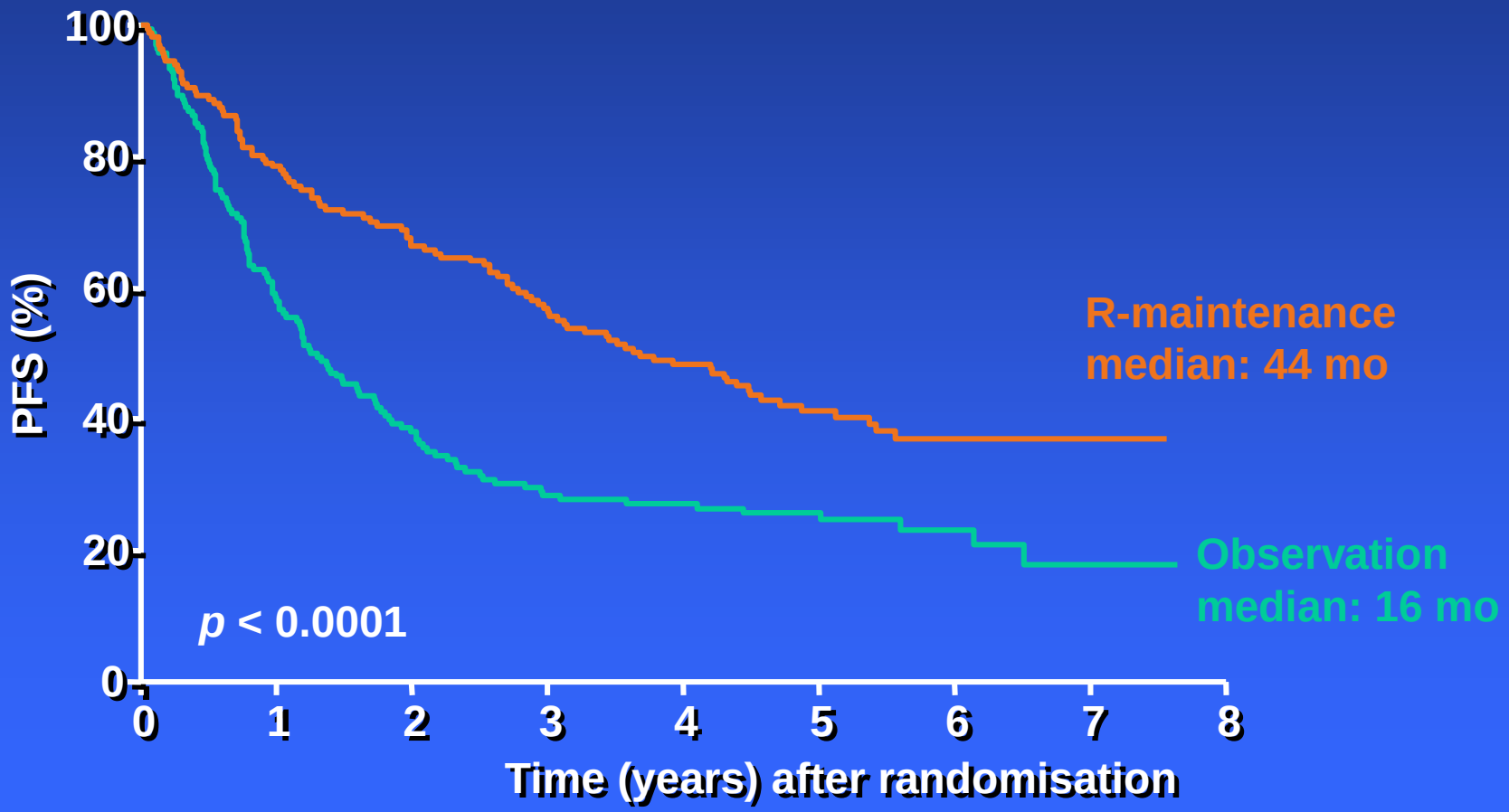
EORTC 20981 Intergroup Phase III Trial in Relapsed / Refractory Follicular Lymphoma : Study Design



*375mg/m^2 every 3 months for 2 years or until relapse

RITUXIMAB MAINTENANCE PROLONGS PFS IN RELAPSED FOLLICULAR NHL

(UPDATED EORTC 20981 STUDY)



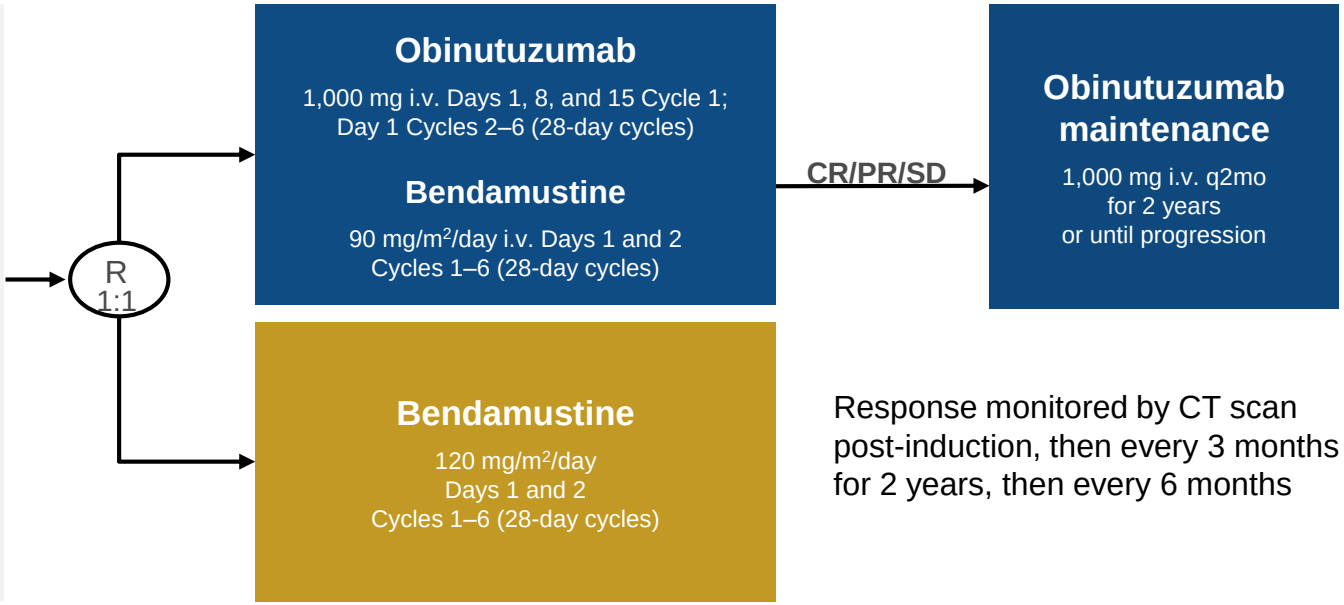
van Oers MHJ, *et al. J Clin Oncol* 2010; 28:2853-2858.

GADOLIN study: Bendamustine vs Bendamustine + Obinutuzumab in Rituximab-refractory iNHL

Rituximab-refractory CD20 + iNHL (including FL, MZL, and SLL), n = 413

Stratification factors

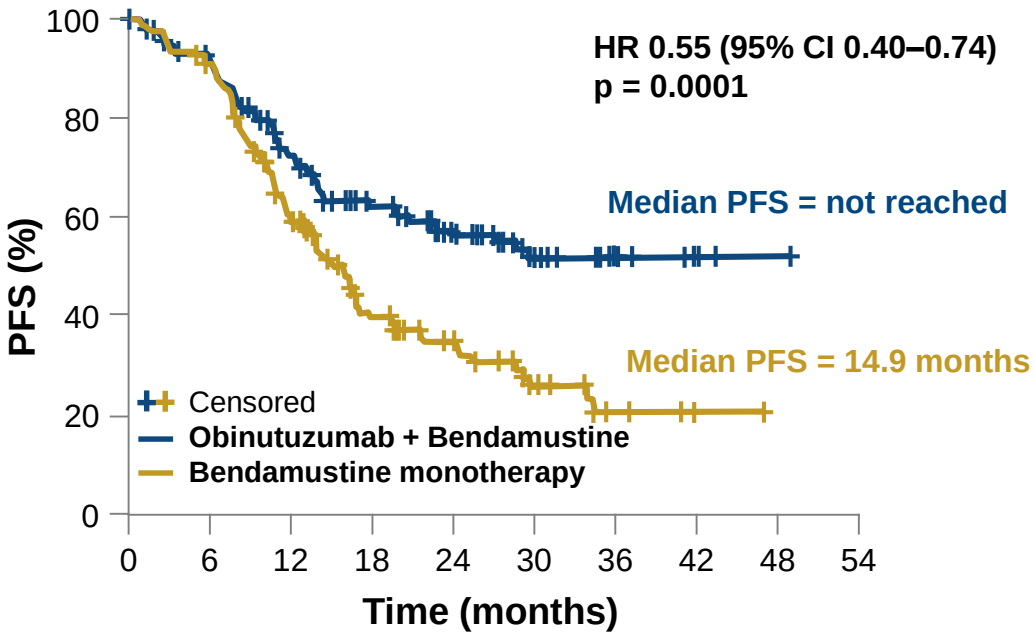
- NHL subtype (FL vs other)
- Prior therapies (≤ 2 vs > 2)
- Refractory type (R-mono vs R-chemo)
- Geographic region



Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months

Sehn LH, et al. Lancet Oncol. 2016;17:1081-93.

GADOLIN study: Obinutuzumab improves OS in recurrent iNHL when added to Bendamustine



- The addition of Obinutuzumab also improved PFS in patients who were refractory to both alkylators and rituximab
  - HR 0.56 (0.40–0.78)

Sehn LH, et al. Lancet Oncol. 2016;17:1081-93.

CHEMO-FREE TREATMENT OF RELAPSED FOLLICULAR NHL

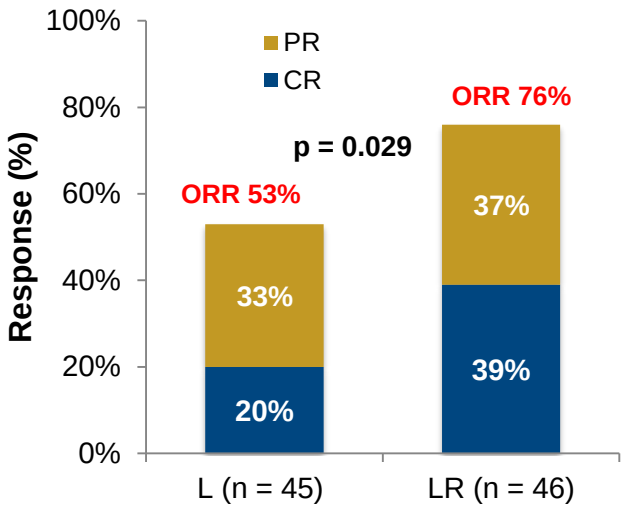
1. R2 versus Lenalidomide alone
   (randomized phase II **ALLIANCE** trial)

2. R2 versus Rituximab + Placebo
   (randomized phase III **AUGMENT** trial)

- **R2** : **R**ituximab + **R**evlimid / Lenalidomide

CALGB 50401 (ALLIANCE) : R^2 is more active than Lenalidomide alone in recurrent FL (with similar toxicity)

Phase 2 study in patients with grade 1–3a relapsed FL after ≥ 1 rituximab-based regimen



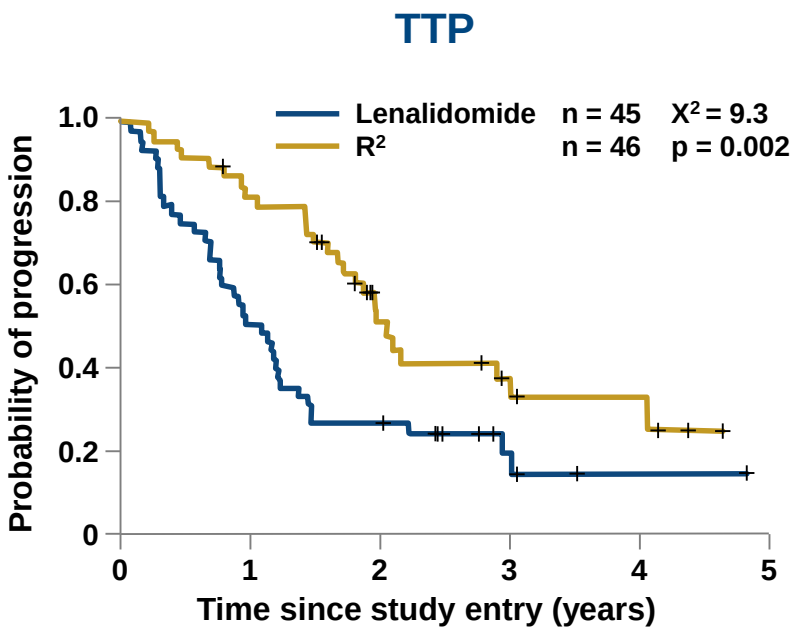
Grade 3–4 AEs in > 1 patient, %		Lenalidomide (n = 45)		R^2 (n = 44)	
		Gr. 3	Gr. 4	Gr. 3	Gr. 4
Haematologic	Neutropenia	16	0	16	4
	Thrombocytopenia	0	0	4	0
	Lymphopenia	1	0	3	0
Fatigue		9	0	11	2
Thrombosis		9	7	2	2
Rash		2	2	4	0
Infection (with neutropenia)		4	0	2	0
AST		4	0	0	0

- **Myelosuppression was the most common grade 3–4 AE in both arms**
- **No significant difference in thrombosis between arms (p = 0.157)**

Leonard JP, et al. J Clin Oncol. 2015;33:3635-40.

CALGB 50401 (ALLIANCE) : Lenalidomide and Rituximab (R^2) in patients with recurrent FL

Characteristic	Lenalidomide arm (n = 45)		R^2 arm (n = 46)	
	Patients, n	%	Patients, n	%
Age, years				
median	63		64	
range	34–85		36–89	
FLIPI	36		35	
Low		33.3		51.4
Intermediate		41.7		28.6
High		25.0		20.0
TTP since last lenalidomide dose, years	1.6		1.4	
Stage	4.5		45	
I–II		22.3		33.4
III–IV		77.8		66.7
LDH	44		44	
> NL		15.9		2.3



Leonard JP, et al. J Clin Oncol. 2015;33:3635-40.

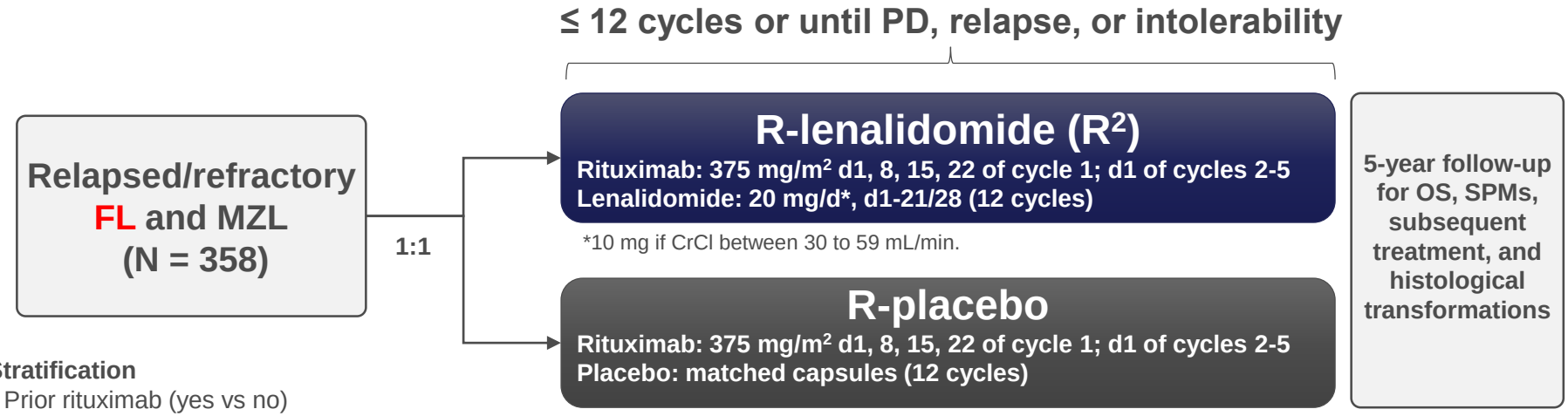
ASH 2018 , ABSTRACT 445

AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) vs Rituximab/Placebo in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

John P. Leonard,[1] Marek Trneny,[2] Koji Izutsu,[3] Nathan H. Fowler,[4] Xiaonan Hong,[5] Jun Zhu,[6] Huilai Zhang[7] Fritz Offner,[8] Adriana Scheliga,[9] Grzegorz Nowakowski,[10] Antonio Pinto,[11] Francesca Re,[12] Laura Maria Fogliatto,[13] Phillip Scheinberg,[14] Ian Flinn,[15] Claudia Moreira,[16] David Liu,[17] Stacey Kalambakas,[17] Chengqing Wu,[17] Pierre Fustier,[18] and John G Gribben,[19]
on behalf of the AUGMENT study investigators

[1]Meyer Cancer Center, Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY; [2]Charles University Hospital, Prague, Czech Republic ; [3]National Cancer Center Hospital, Tokyo, Japan; [4]The University of Texas MD Anderson Cancer Center, Houston, TX; [5]Fudan University Shanghai Cancer Center, Shanghai, China; [6]Beijing Cancer Hospital, Beijing, China; [7]Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [8]UZ Gent, Gent, Belgium; [9]INCA Instituto Nacional De Câncer, Rio de Janeiro, Brazil; [10]Mayo Clinic, Rochester, MN; [11]Istituto Nazionale Per Lo Studio E La Cura Dei Tumori Fondazione Giovanni Pascale, Napoli, Italy; [12]Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; [13]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [14] Division of Hematology, Hospital A Beneficência Portuguesa, São Paulo, Brazil; [15]SCRI Tennessee Oncology Nashville, Nashville, TN; [16]Instituto Português de Oncologia Do Porto Francisco Gentil Epe, Porto, Portugal; [17]Celgene Corporation, Summit, NJ; [18]Celgene Corporation, Boudry, Switzerland; [19]Centre for Haemato-Oncology, Barts Cancer Institute, London, United Kingdom

STUDY DESIGN AUGMENT TRIAL: RANDOMIZED DOUBLE BLIND PHASE III TRIAL



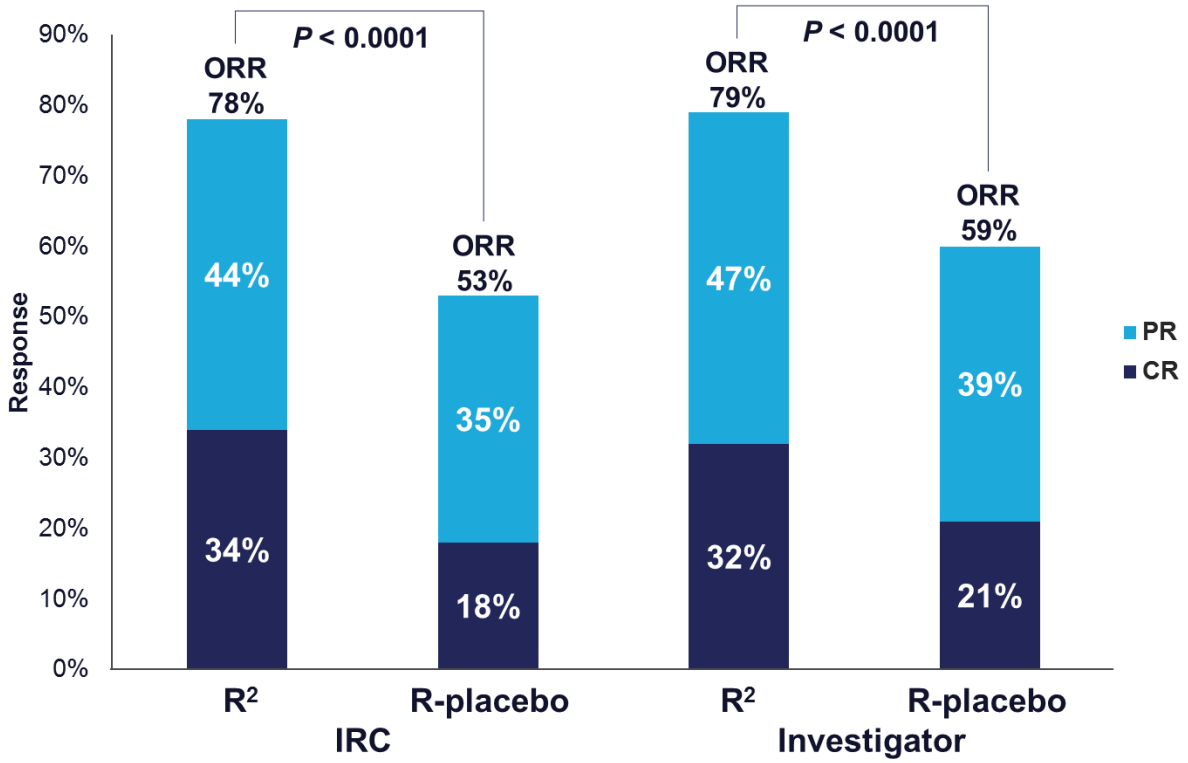
Stratification
- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

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

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

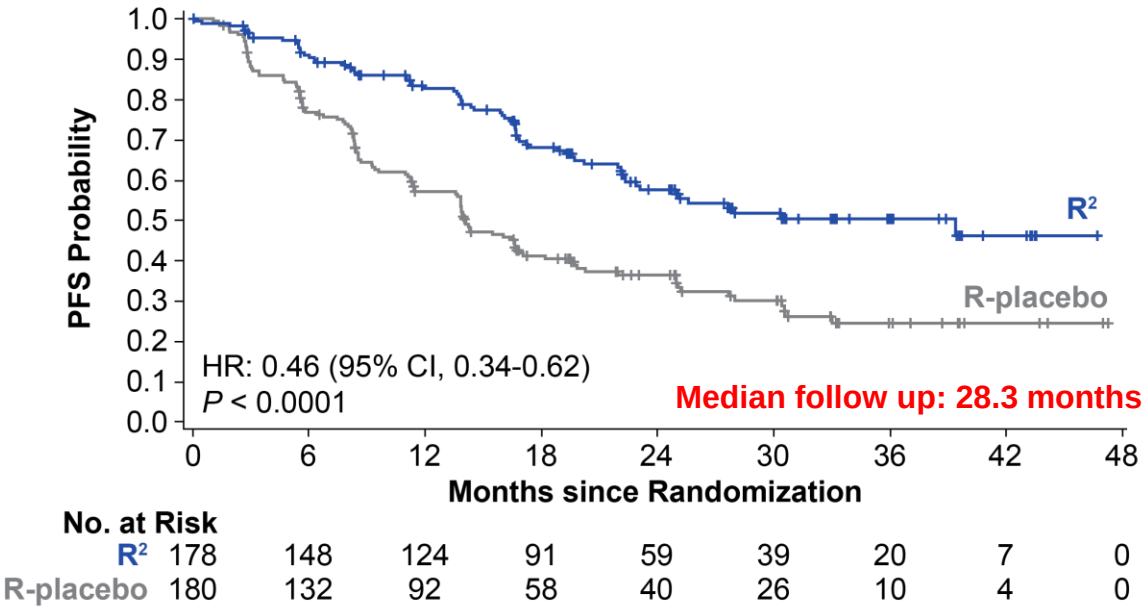
- **Primary endpoint: PFS by IRC (2007 IWG criteria w/o PET)**

RESPONSE (ITT) – AUGMENT TRIAL



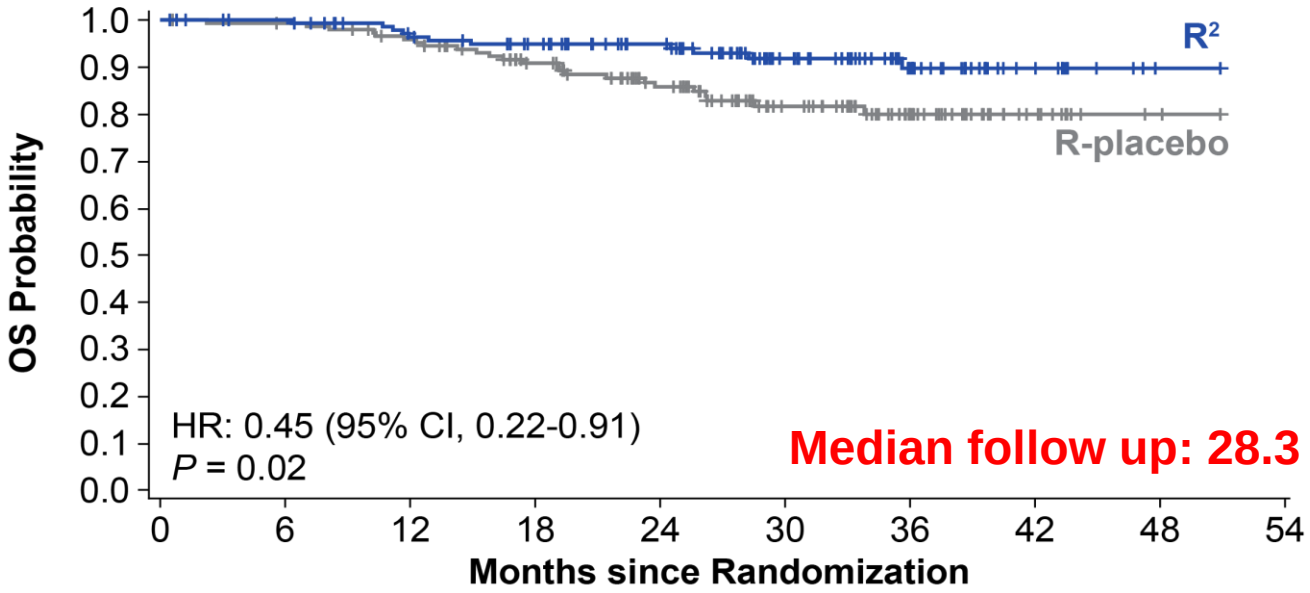
- **Median DOR was 36.6 mo** (95% CI, 22.9-NR) **for R^2 vs 21.7 mo** (95% CI, 12.8-27.6) **for R-placebo**, **HR 0.53** (95% CI, 0.36-0.79), ***p* = 0.0015**

PRIMARY ENDPOINT AUGMENT : PROGRESSION-FREE SURVIVAL (ITT, IRC)



Median PFS	R² (n = 178)	R-placebo (n = 180)	HR (95% CI)	*P* Value
By IRC, mo (95% CI)	39.4 (22.9-NE)	14.1 (11.4-16.7)	**0.46** (0.34-0.62)	**< 0.0001**
By investigator, mo (95% CI)	25.3 (21.2-NE)	14.3 (12.4-17.7)	0.51 (0.38-0.69)	< 0.0001

OVERALL SURVIVAL IN PATIENTS WITH FOLLICULAR LYMPHOMA (PRESPECIFIED SUBGROUP ANALYSIS) – AUGMENT TRIAL



Median follow up: 28.3 months

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

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

Data cutoff June 22, 2018.

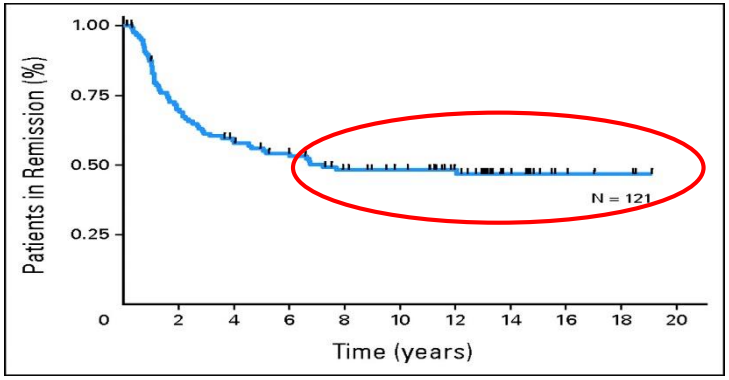
CONCLUSIONS – AUGMENT TRIAL

- **AUGMENT met its primary endpoint as R^2 demonstrated statistically significant and clinically relevant superiority over R-placebo for the primary endpoint of PFS**
  - PFS advantage in prespecified subgroups, except MZL, was consistent with overall population
  - **Overall survival advantage for R^2 in the follicular lymphoma subgroup**

R^2 represents an important new treatment option in patients with previously treated indolent NHL

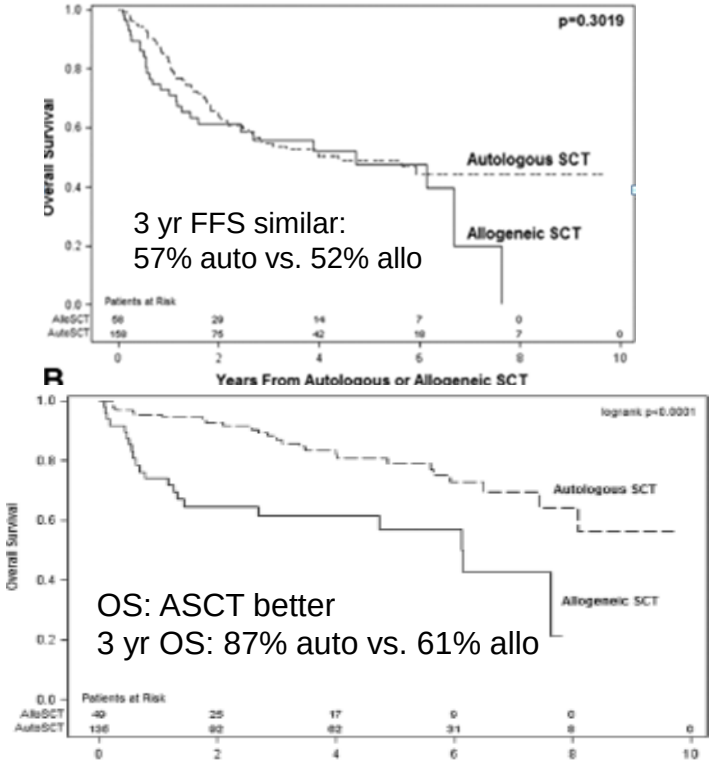
Stem cell transplantation in high-risk FL

Autologous SCT in second remission for FL[1]



- N= 121, median FU 13 yrs
- Pre-rituximab era
- 60 patients have relapsed
- 15 deaths from MDS/AML
- Apparent PFS plateau at 48%

NCCN FL database: auto-SCT vs. allo-SCT[2]



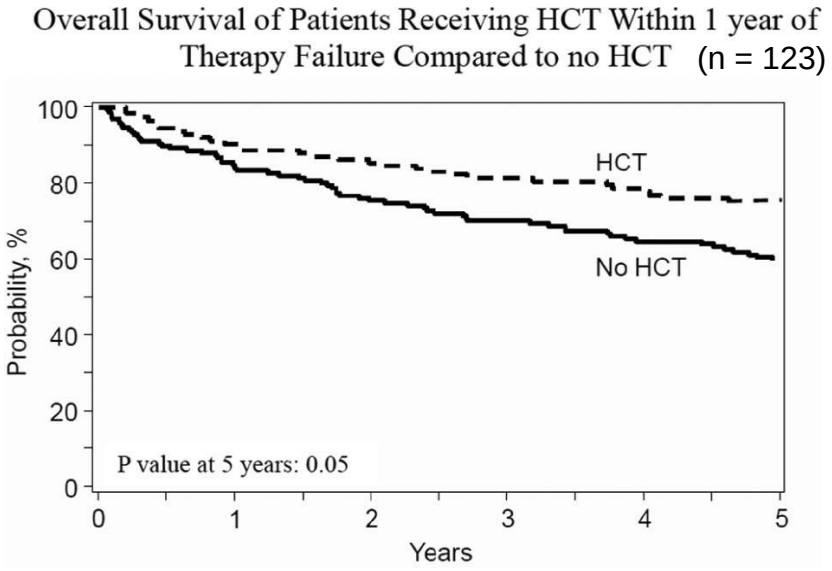
1. Rohatiner AZ, et al. J Clin Oncol. 2007 ;25:2554-9.
2. Evens AM, et al. Cancer. 2013;119:3662-71.

Autologous SCT in early progressor FL

- Retrospective analysis NLCS/CIBMTR
- 349 early progressors on rituximab-based ICT (2 years)
- Matched, half received auto-SCT, half did not
- 5-year OS 60 and 67% (p = 0.16)

Improved OS when receiving auto-SCT within 1 year of treatment failure

5 yr OS with auto-HCT **73%**
5 yr OS without auto-HCT **60%**
p-value 0.05



CIBMTR, Center for International Blood and Marrow Transplant Research;
NLCS, National LymphoCare Study.

Casulo C, et al. Biol Blood Marrow Transplant. 2018;24:1163-71.

The role of allogeneic transplantation in R/R FL

Autologous transplantation

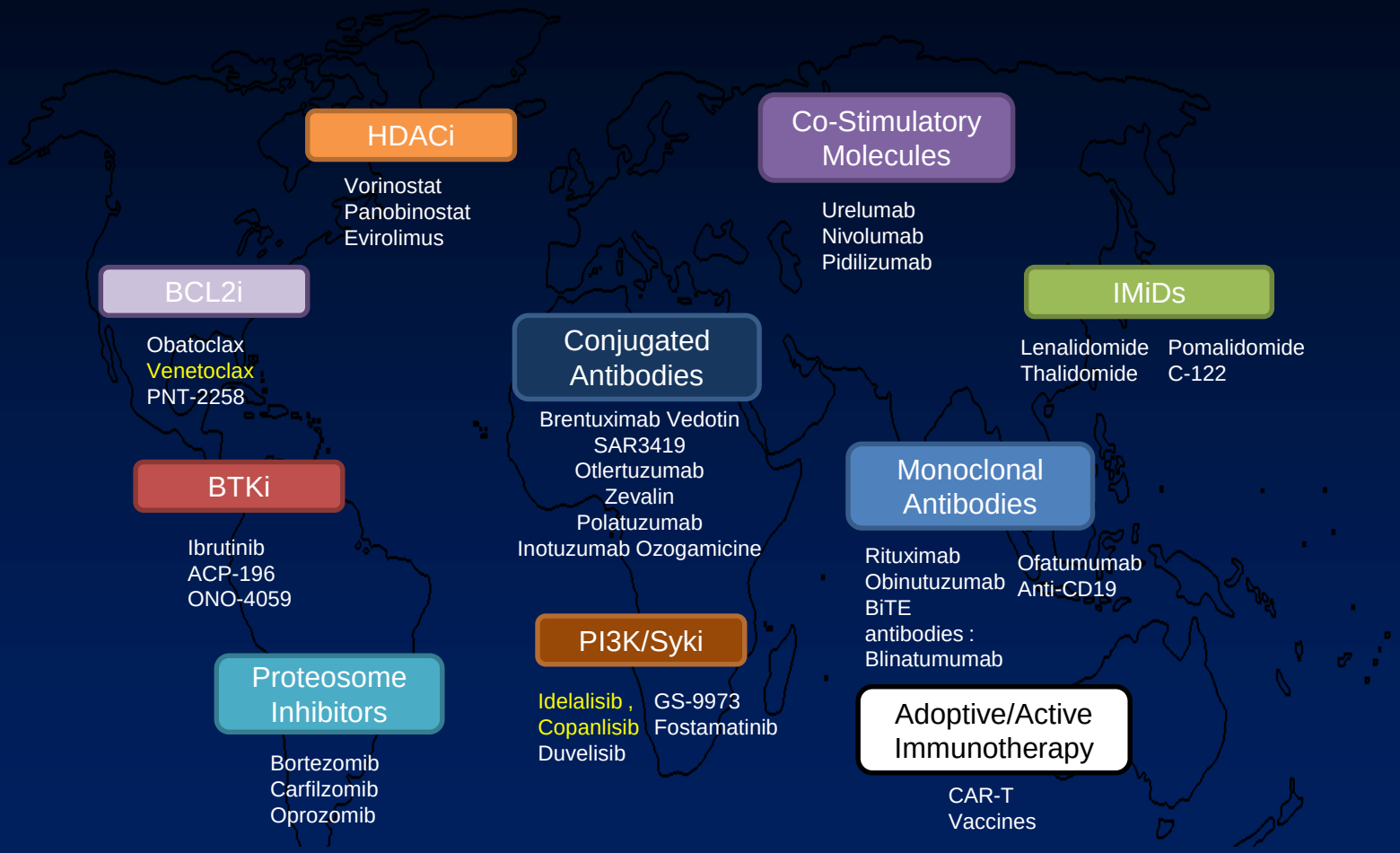
- Early use of auto-HCT consolidation should be considered a standard therapy option for high-risk patients who experience early failure of chemo-immunotherapy (< 2 years)
- For patients with FL who experience failure of frontline therapies late (> 2 years), deferring auto-HCT until later in the disease course is reasonable

Allogeneic transplantation

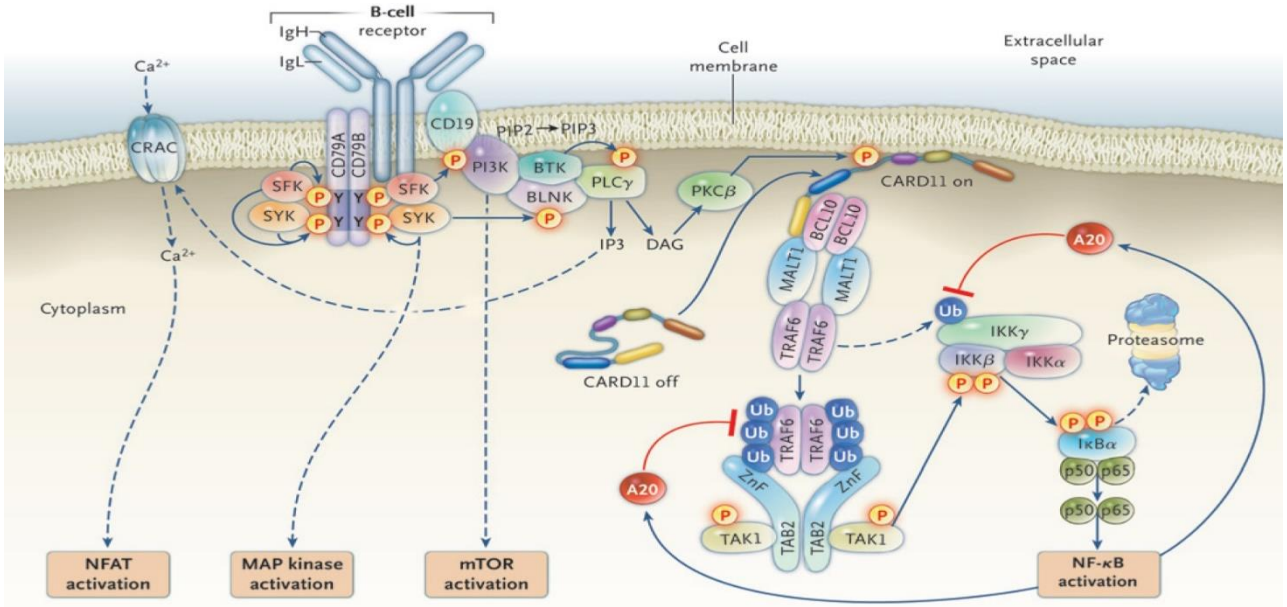
- Best reserved for medically fit patients with heavily pretreated disease, persistent marrow involvement, refractory, but low-bulk, disease
- For patients who experience a failure to mobilize stem cells for auto-HCT
- A reasonable option for patients who experience failure with a prior autograft

Hamadani M, Horowitz MM. J Oncol Pract. 2017;13:798-806.

The World of “Biologics” in NHL

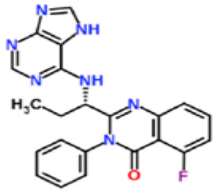


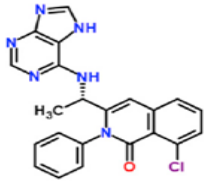
B-cell receptor signaling activates different oncogenic pathways

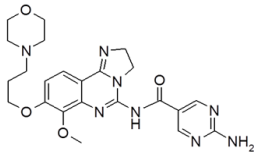


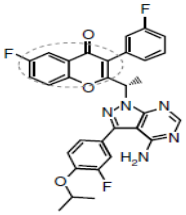
Lenz G, Staudt LM. N Engl J Med. 2010;362:1417-29.

PI3K inhibitors inhibit different PI3K isoforms









Isoform	Idelalisib (IC_{50}-nM)[1]	Duvelisib (IC_{50}-nM)[2]	Copanlisib (IC_{50}-nM)[3]	TGR-1202 (IC_{50}-nM)[4]
P110a	20,000	1410	0.4–1	10,000
P110b	1,900	26.2	10–18	800
P110g	3,000	19.6	93	400
P110d	8	0.36	3–10	24

1. Lannutti, Blood, 2011
2. Winkler DG, Faia KL, et al.Chem Biol. 2013 20:1364-74.
3. Haike K et al. Presented at: American Society of Hematology Meeting on Lymphoma Biology; August 10–13, 2014; Colorado Springs, Colorado. Abstract 48.
4. Vakkalanka et al Poster from RP5264 Rhizon

Idelalisib : Selective PI3K inhibitor in double refractory iNHL

Rituximab + alkylator-refractory iNHL

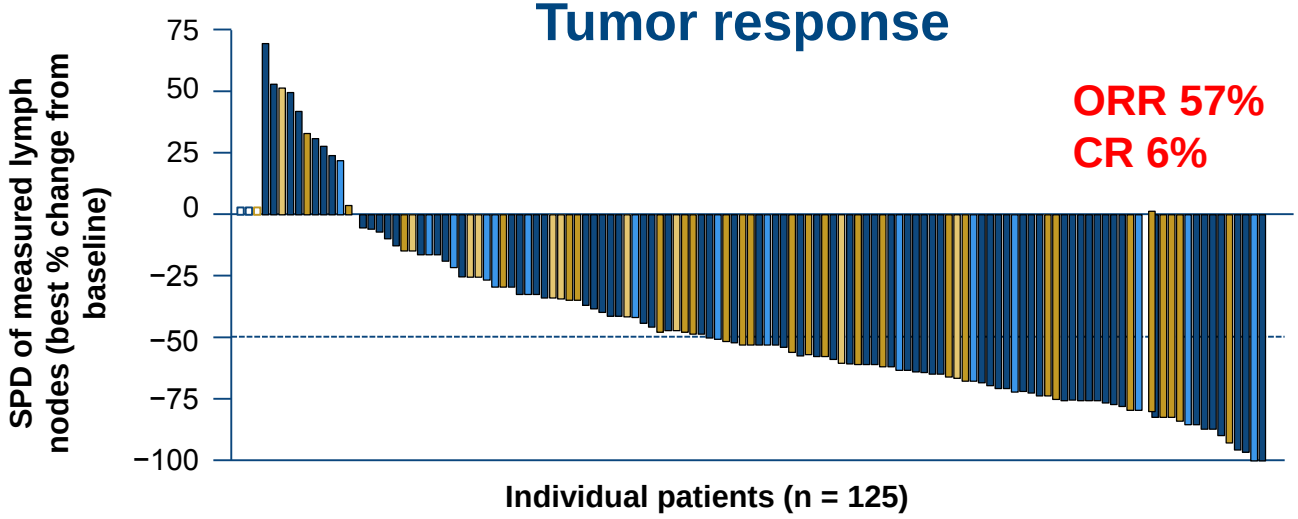
Single-arm phase 2 study (n = 125)

Idelalisib 150 mg b.i.d. continuously

Therapy maintained until progression

Long-term follow-up

Tumor response



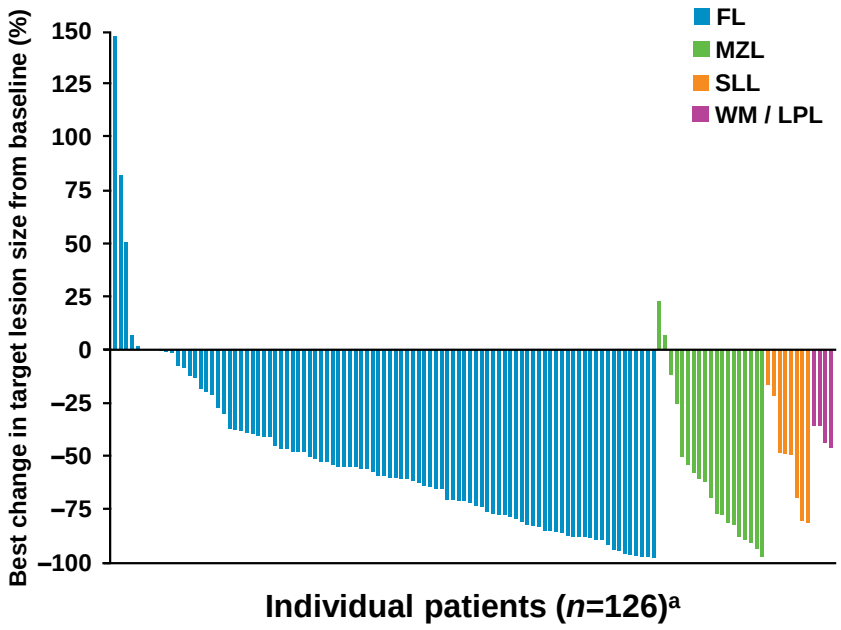
ORR 57%
CR 6%

- FL (n = 72)
- SLL (n = 28)
- MZL (n = 15)
- LPL/WM (n = 10)

Gopal AJ, et al. N Engl J Med. 2014;370:1008-18.

Copanlisib in r/r indolent B-cell lymphoma
2-year follow-up of CHRONOS-1

	FL (*n*=104)	MZL (*n*=23)	SLL (*n*=8)	WM / LPL (*n*=6)	Total (*N*=142)
Best response, *n* (%)					
Complete response	**21 (20.2)**	3 (13.0)	0	0	24 (16.9)
Partial response	40 (38.5)	15 (65.2)	6 (75.0)	1 (16.7)	62 (43.7)
Stable disease	34 (32.7)	2 (8.7)	1 (12.5)	3 (50.0)	40 (28.2)
Unconfirmed stable disease	1 (1.0)	0	0	0	1 (0.7)
Progressive disease	2 (1.9)	0	1 (12.5)	0	3 (2.1)
NE / NA	0	3 (13.0)	0	2 (33.3)	12 (8.5)
ORR, *n* (%)	**61 (58.7)**	**18 (78.3)**	**6 (75.0)**	**1 (16.7)**	**86 (60.6)**
DCR, *n* (%)	91 (87.5)	20 (87.0)	7 (87.5)	4 (66.7)	122 (85.9)

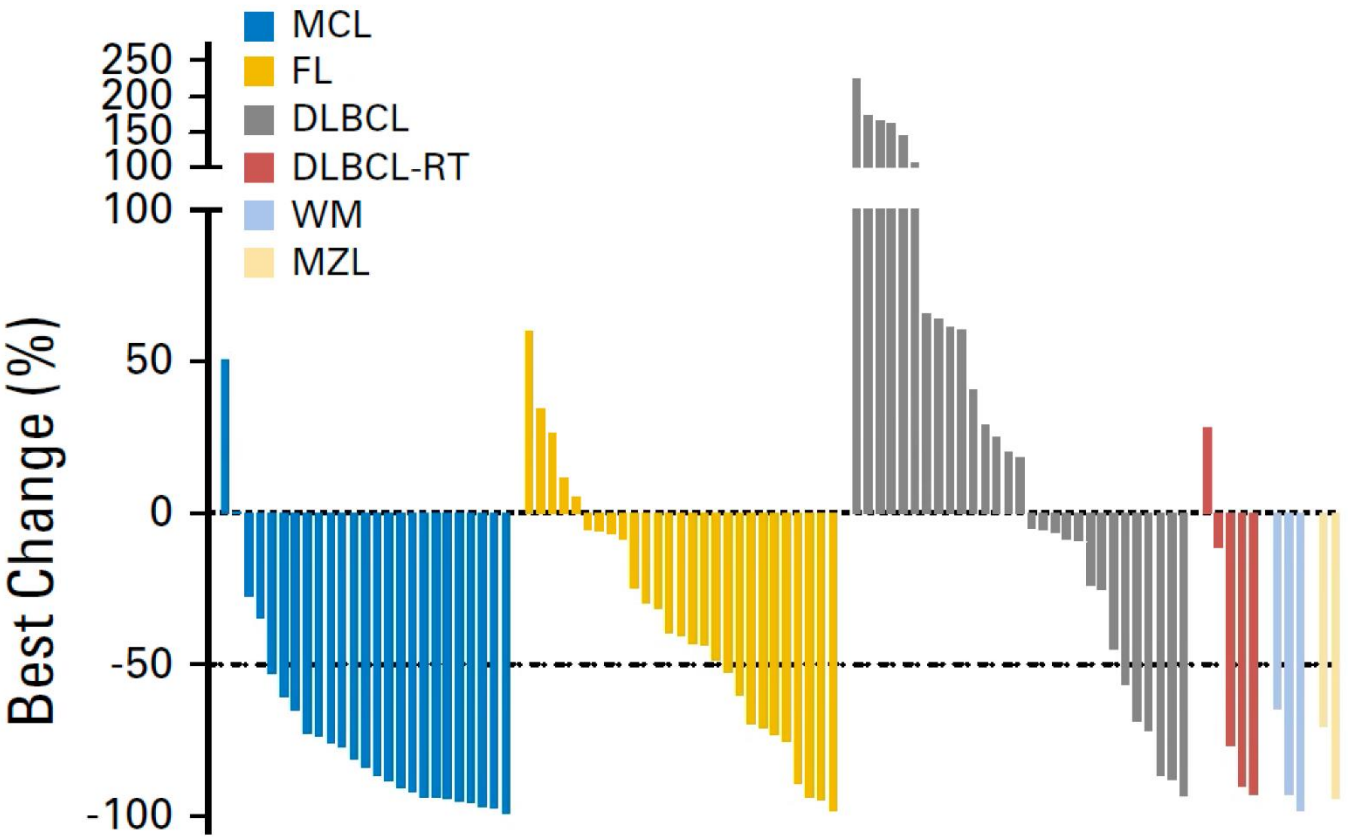


Dreyling M et al. , ASH 2018 , poster # 1595

Idelalisib : ORR 57% ; CR 6%

Venetoclax in NHL: phase I/II study

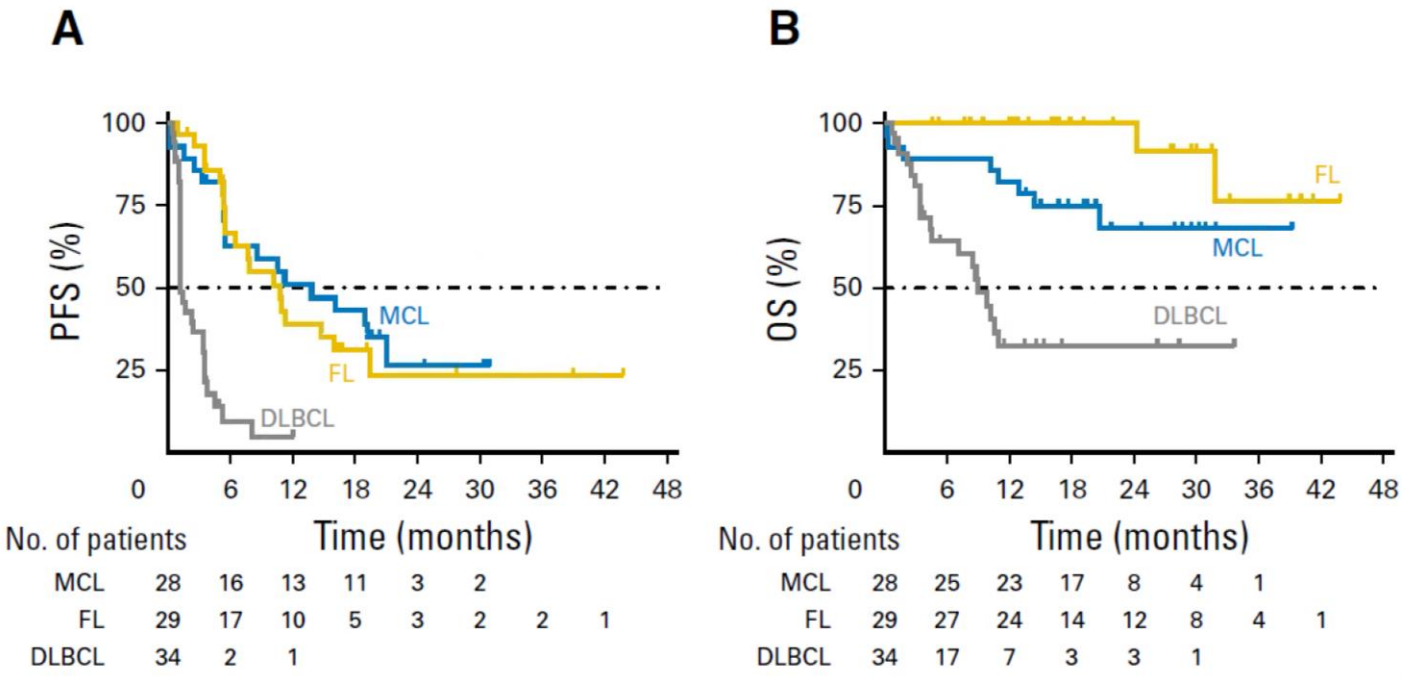
Fowler, ASH 2016



- **ORR FL (n=29) 38%** (44% at 1200 mg); **CR 14%**
- **No clinical TLS**

Venetoclax in NHL: Phase I/II study

Fowler, ASH 2016



- **Median PFS FL 11 months**
- **High bcl2 expression not a perfect biomarker for venetoclax activity**
- **combination with Rituximab?**

Care in combination of more than two agents in FL?

Caveats about chemo-free combinations (no preclinical models to predict…)

Study	Patient population	Key points
Rituximab + Lenalidomide + Ibrutinib (Alliance A051103)[1]	Previously untreated FL	• High incidence of rash (all grades: 82%) • Efficacy of the triplet similar to Rituximab-Lenalidomide in the same patient population
Idelalisib + Lenalidomide + Rituximab (phase I Alliance A051201 and A051202)[2]	R/R lymphoma	• Excessively toxic combination • Grade 3–4 neutropenia in 63% • Grade 3–4 rash in 50%
Idelalisib + Lenalidomide + Rituximab (NCT01088048)[3]	R/R indolent lymphoma	• Significant hepatotoxicity • ALT elevation (all grades) was noted in 85% • Two patients died due to toxicity

1. Ujjani CS, et al. Blood. 2016;128:2510-6.
2. Smith SM, Lancet Haematol. 2017;4:e176-82.
3. Cheah CY, et al. Blood. 2015;125:3357-9.

Future strategies for the management of patients with Follicular Lymphoma

1. Monoclonal antibodies
   - Antibody-drug conjugates
   - Bispecific antibodies
2. New kinase inhibitors
3. Improving Rituximab efficacy with other agents (chemo-free regimens)
   - IMiDs® (lenalidomide), anti-PD-(L)1 / Immune Checkpoint Inhibitors …
1. New targeted agents
   - Venetoclax
   - Tamezetostat
   - Many others
2. CAR T-cells
3. Intelligent combinations

Current Knowledge About Novel Agents

Limitations

- No head-to-head trials of novel agents
- No literature defining optimal sequence

Good News

- Sustained response possible from any of these medications
- If one does not work, try another; many patients will receive multiple agents

PROGNOSTIC FACTORS IN FOLLICULAR LYMPHOMA :

1. PRIOR TO STARTING 1st LINE TREATMENT

2. DURING TREATMENT

RISK PROGNOSTIFICATION IN FOLLICULAR LYMPHOMA : PRIOR TO STARTING TREATMENT

FLIPI

FLIPI-2

PRIMA-PI

Total Metabolic Tumor Volume

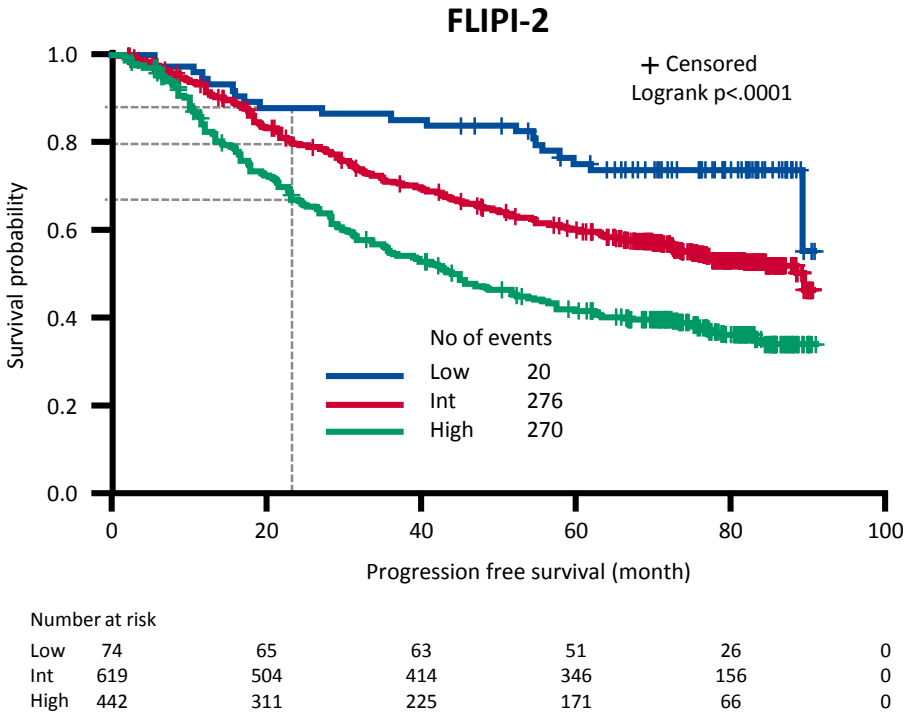
Circulating Tumor DNA (liquid biopsies)

m7-FLIPI

23 gene score by GEP

FLIPI-2, an externally validated prognostic tool, predicts PFS

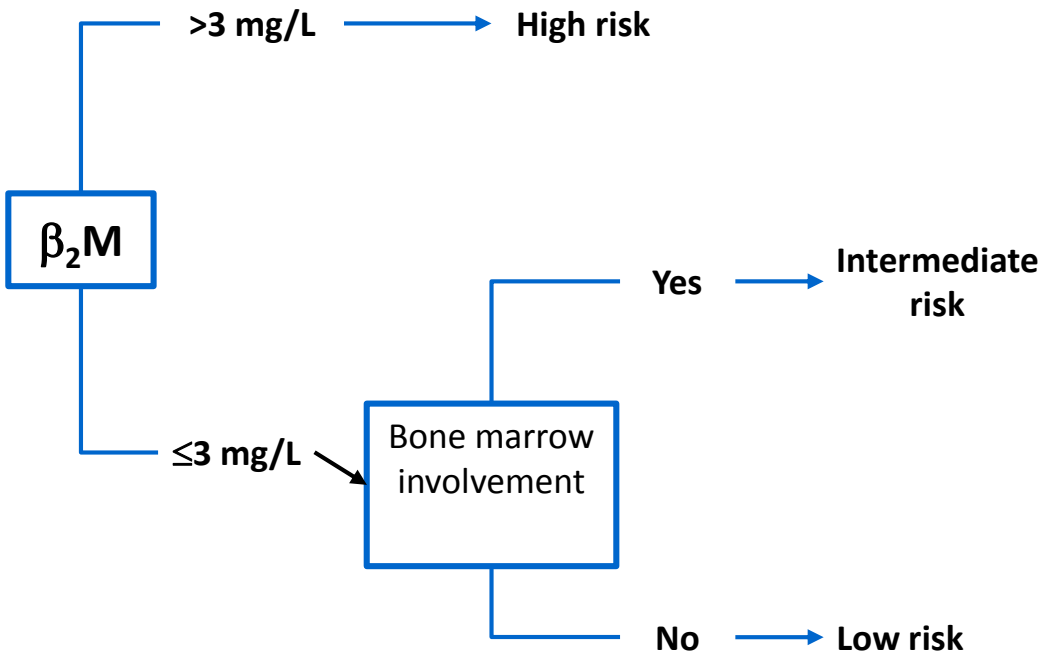
- Derived from prospective data (mostly - 68% - in R-treated patients !) **may be more relevant than FLIPI**
- Simplified score calculation
- Includes baseline characteristics from FLIPI (age, haemoglobin level) plus:
  - **Bone marrow infiltration**
  - **Longest diameter of largest lymph node >6cm**
  - **β_2 microglobulin level >ULN**



1. Federico M, et al. J Clin Oncol 2009;27:4555–62
2. Casulo C. Best Pract Res Clin Haematol 2018;31:15–22
3. Bachy E, et al. Blood 2018 [Epub ahead of print]

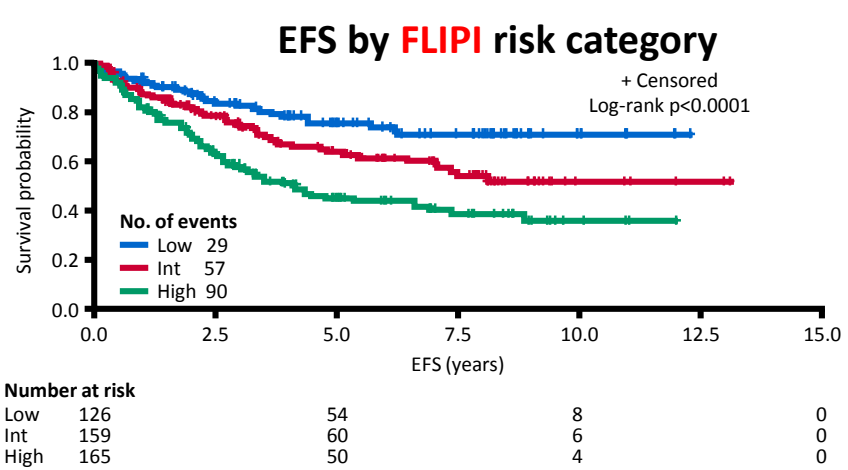
PRIMA-PI is a new prognostic index for FL patients treated with first line immuno-chemotherapy

- **2 parameters,** both easily measured clinically
  - **Bone marrow involvement**
  - **β_2 microglobulin**
- Easy to score
- **Primary objective:** to provide basis for building more sophisticated and integrated biomolecular scores



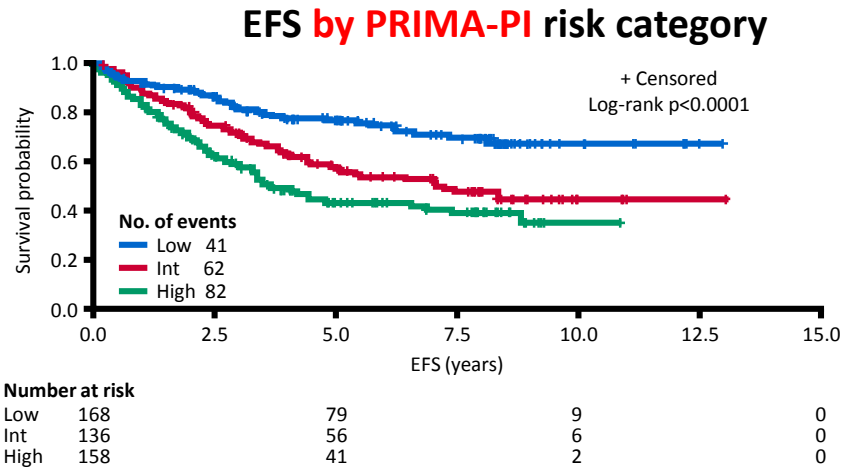
Bachy E, et al. Blood 2018 [Epub ahead of print]

PRIMA-PI identifies high-risk patients at least as successfully as FLIPI and is at least as discriminatory for EFS



Number at risk

Low	126	54	8	0
Int	159	60	6	0
High	165	50	4	0



Number at risk

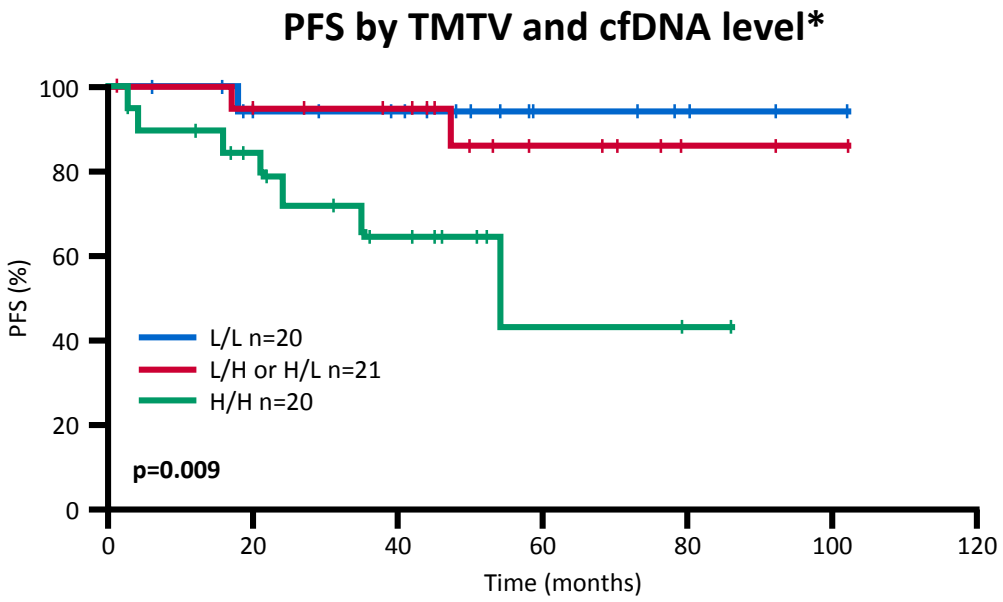
Low	168	79	9	0
Int	136	56	6	0
High	158	41	2	0

	FLIPI		PRIMA-PI	
	n (%)	5-year EFS, % (95% CI)	n (%)	5-year EFS, % (95% CI)
Low	**126** (28)	**76** (66, 83)	**168** (36)	**77** (69, 83)
Intermediate	**159** (35)	**64** (55, 72)	**136** (29)	**57** (48, 66)
High	**165** (37)	**45** (37, 53)	**158** (34)	**44** (35, 52)

Bachy E, et al. Blood 2018 [Epub ahead of print]

Prognostic parameters in FL at diagnosis : Total Metabolic Tumor Volume (TMTV), circulating tumor cells and cell-free DNA

- Significant correlation between TMTV and both CTCs and cfDNA
- 4-year PFS is lower in FL patients with:
  - TMTV >510 cm^3
  - CTCs >0.0018 PB cells
  - cfDNA >2550 equivalent-genome/mL
- Compared with TMTV alone:
  - cfDNA is predictive of outcome
    - PFS is shorter in patients with high levels of both TMTV and cfDNA
  - CTCs do not provide additional prognostic information



Delfau-Larue MH, et al. Blood Advances 2018;2:807–16

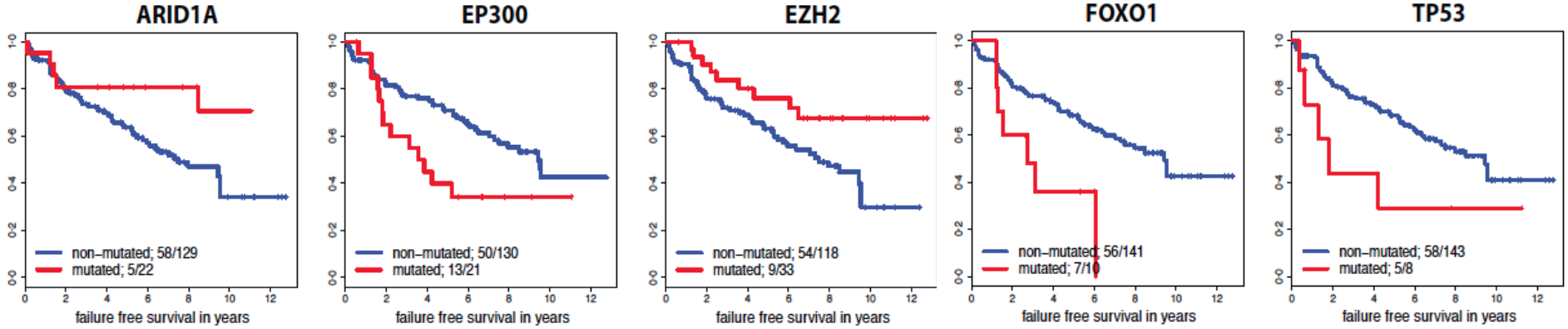
INTEGRATION OF GENE MUTATIONS IN RISK PROGNOSTIFICATION IN FOLLICULAR LYMPHOMA

The m7-FLIPI

Pastore et al. , Lancet Oncology , September 2015

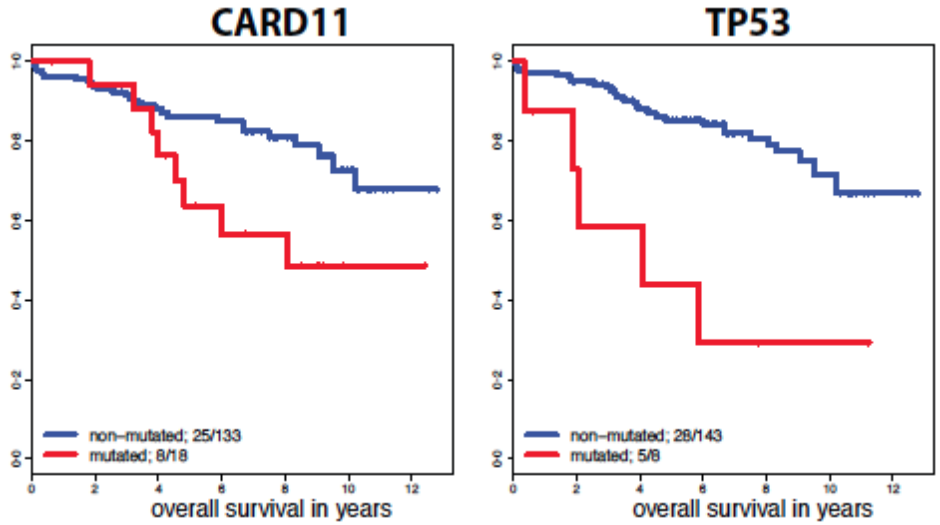
M7FLIPI : FAILURE-FREE SURVIVAL (FFS)

PASTORES ET AL. 2015



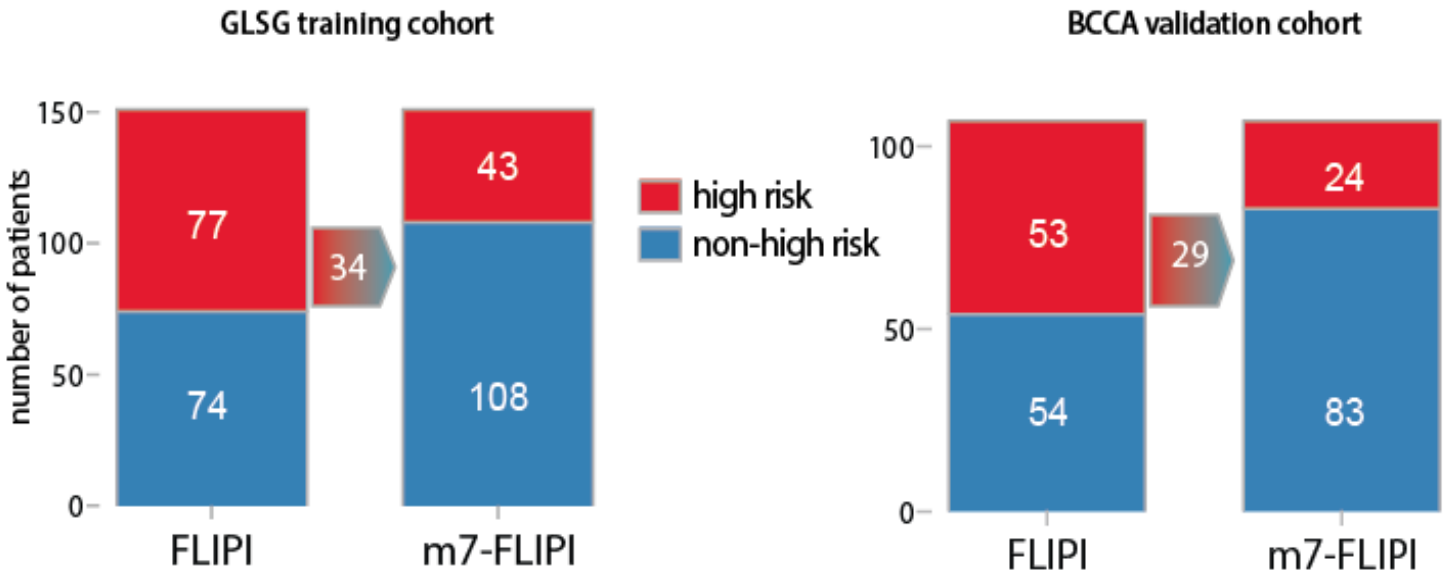
	Univariate			With adjustment for FLIPI and ECOG		
Gene	HR	p-value	p-value Holm	HR	p-value	p-value Holm
FOXO1	2·74	0·013	0·47	2·67	0·018	0·62
EP300	1·99	0·028	0·95	2·00	0·028	0·91
EZH2	0·46	0·030	0·99	0·42	0·018	0·62
ARID1A	0·42	0·064	> 0·99	0·40	0·049	> 0·99
TP53	2·18	0·096	> 0·99	2·85	0·029	0·91

M7FLIPI : OVERALL SURVIVAL (OS)



	Univariate			With adjustment for FLIPI and ECOG		
Gene	HR	p-value	p-value Holm	HR	p-value	p-value Holm
TP53	4·67	0·0015	0·054	6·32	0·00026	0·009
CARD11	2·43	0·029	0·993	3·71	0·0024	0·082

RECLASSIFYING RISK GROUPS



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dkfz.
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RISK PROGNOSTIFICATION IN FOLLICULAR LYMPHOMA : DURING TREATMENT

POD 24

EFS12 / EFS24

CR30

PET-CT status at the end of induction

MRD status at the end of induction

Early Relapse of Follicular Lymphoma After R-CHOP Uniquely Defines Patients at High Risk for Death: an Analysis From the National LymphoCare Study

Carla Casulo, Michelle Byrtek, Keith L. Dawson, Xiaolei Zhou, Charles Farber, Christopher R. Flowers, John D. Hainsworth, Brian K. Link, Andrew D. Zelenetz,

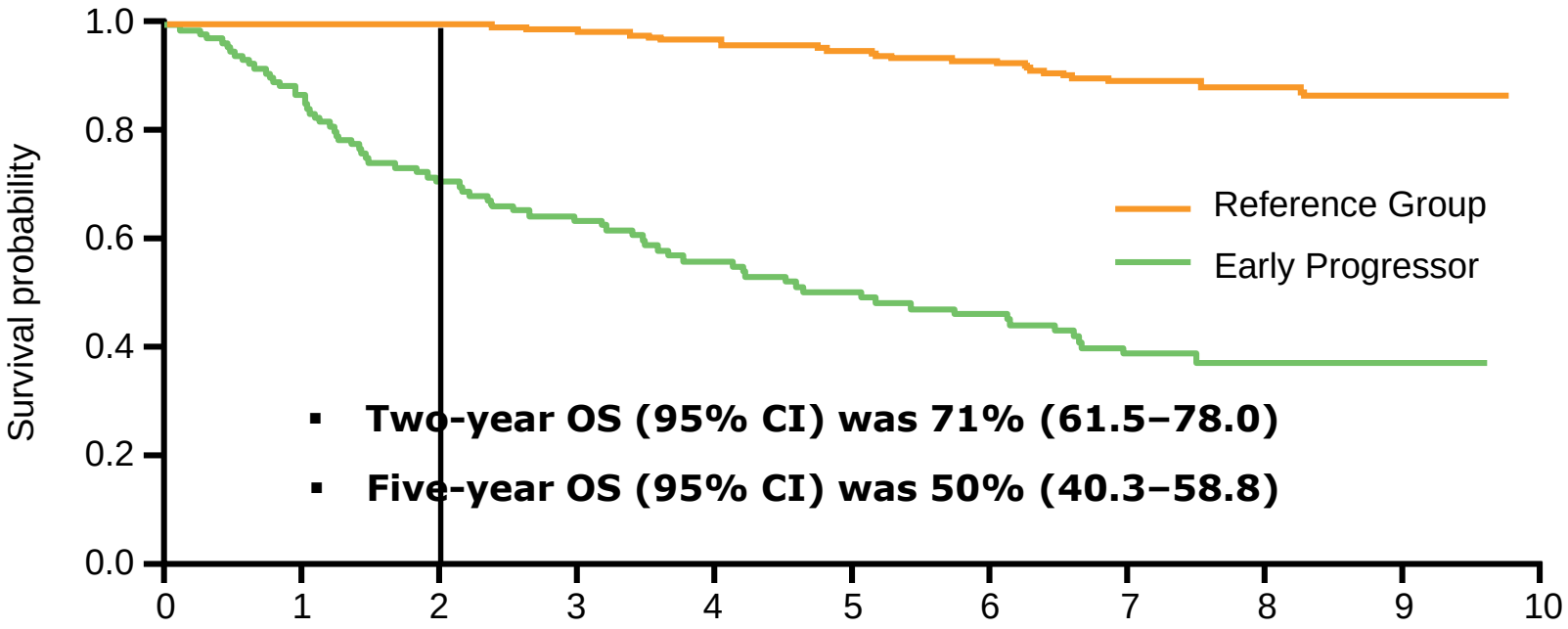
Jonathan W. Friedberg

MEDICINE of THE HIGHEST ORDER

UNIVERSITY of ROCHESTER MEDICAL CENTER

Overall Survival of Patients With Follicular Lymphoma Who Relapsed (POD)Within 2 Years of R-CHOP

- 122 (21%) patients were classified as early progressors



Patients at risk:

Early =	122	101	78	69	58	49	45	33	14	6	0
Reference=	420	420	420	407	387	363	344	252	144	33	0

Evaluation of Complete Response Rate at 30 Months as a Surrogate Endpoint for Progression-Free Survival in First-Line Follicular Lymphoma Studies: Analyses of Individual Patient Data of 3837 Patients From the FLASH Database

Daniel J. Sargent, Qian Shi, Sabine De Bedout, Christopher Flowers, Nathan Hale Fowler, Tommy Fu, Anton Hagenbeek, Michael Herold, Eva Hoster, Jane Huang, Eva Kimby, Marco Ladetto, Franck Morschhauser, Tina Nielsen, Kenichi Takeshita, Nancy Valente, Umberto Vitolo, Emanuele Zucca, Gilles A. Salles, on behalf of the FLASH (Follicular Lymphoma Analysis of Surrogacy Hypothesis) group

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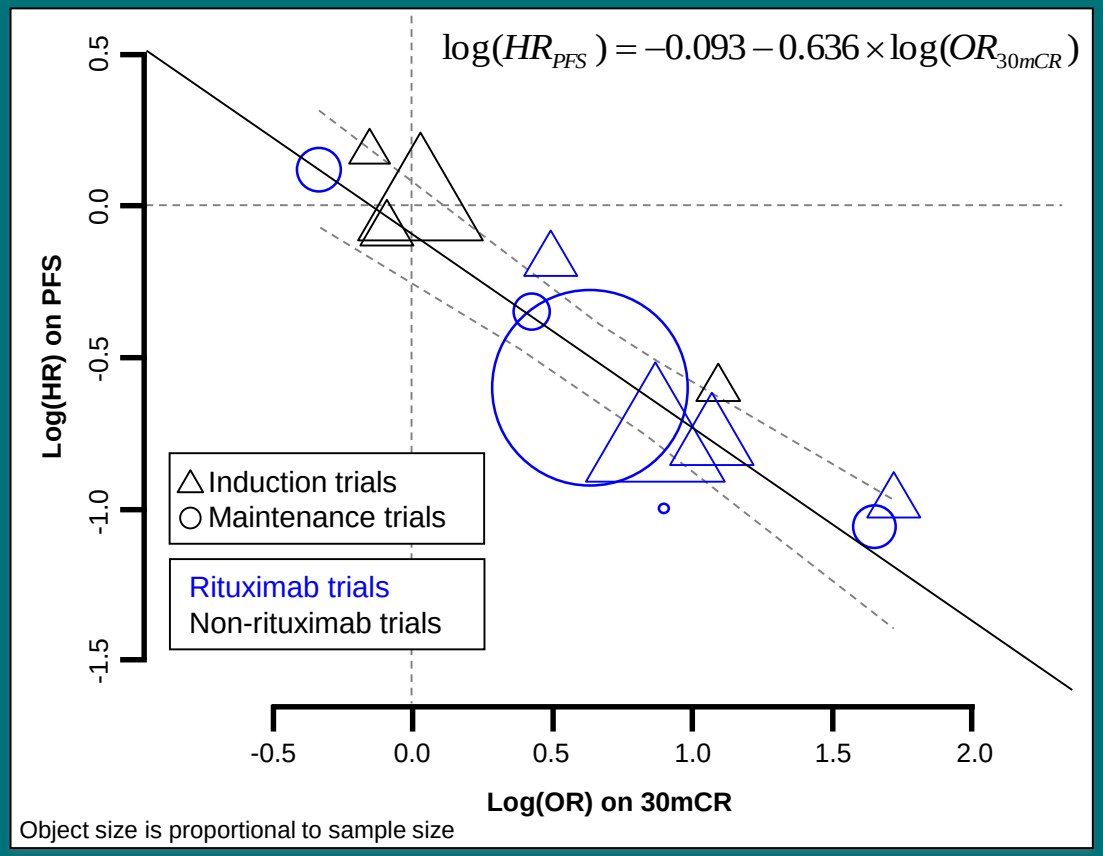
PRESENTED AT: ASCO Annual '15 Meeting

Results : Primary Surrogacy Evaluation



R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.88 (0.77, 0.96)	0.86 (0.72, 1.00)

30 months complete response rate met the pre-specified surrogacy qualification criteria for PFS

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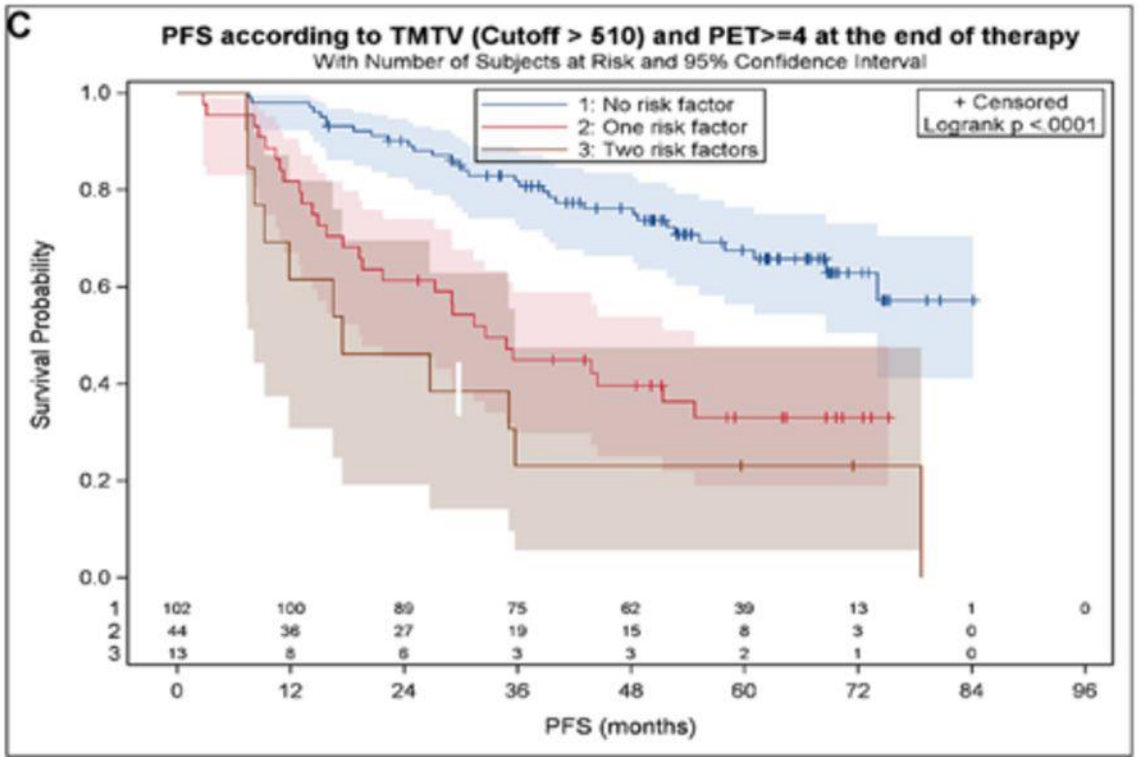
Prognostic model for high tumor burden follicular lymphoma incorporating baseline Total Metabolic Tumor volume and end induction PET: a pooled analysis from LYSA and FIL



Low TMTV and negative eotPET
5-year PFS of 67%

High TMTV or positive eotPET
5-year PFS of 33%

High TMTV and positive eotPET
5year-PFS of 23%

Anne Ségolène Cottereau et al. Blood 2018;131:2449-2453

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Summary - Prognostic Factors in Follicular Lymphoma

- Optimal implementation of prognostic tools in FL has yet to be achieved
  - Standard indices , such as FLIPI , are still used but may overestimate an individual patient's level of risk
  - m7-FLIPI remains a research tool, but is being validated prospectively in several trials
  - Gene-Expression Profiling shows promise and may allow for individualised therapy
  - Early disease progression (POD24) is a robust predictor of reduced OS and provides an opportunity to evaluate novel agents

- Until prognostic tools are available in the clinic to determine which patients are at high risk, this population remains unidentifiable

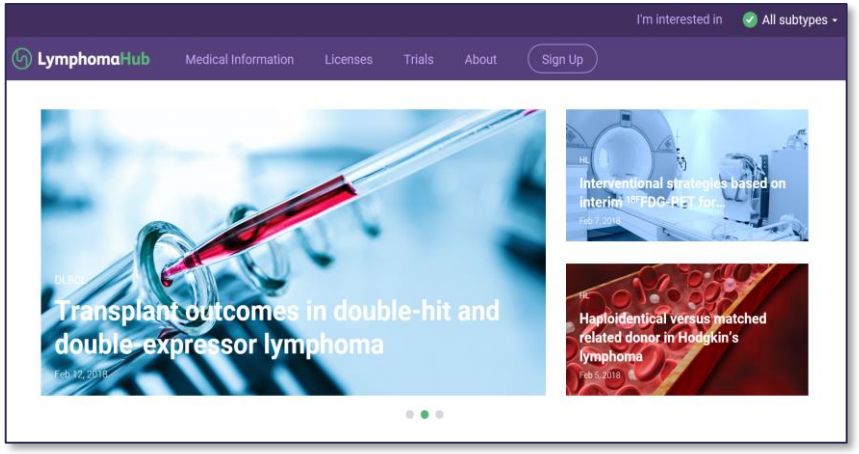
FOLLICULAR LYMPHOMA : CONCLUSIONS AND CHALLENGES FOR THE FUTURE

- Many promising new agents available
- Improve results by….
  - Better understanding of lymphomagenesis
  - Better understanding of succes and failure of treatment
  - Develop tailored treatment based on prognostic factors
  - Rational development of novel combinations / chemo-free regimens
  - Perform correlative studies of response with molecular and cellular characteristics of the lymphoma

 If possible, treat patients in clinical trials !

LymphomaHub

Steered by world leaders in hem-oncology, the Lymphoma Hub is an online resource of key information on lymphoma and CLL. The Lymphoma Hub supports community hematologists and oncologists in making informed treatment decisions and ensuring patients have access to the latest therapies available.



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