Déclaration

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- Cette présentation peut comporter des données relatives à des produits non enregistrés ou à des indications non approuvées.

- Ne constitue pas une promotion de ces produits / indications pour une utilisation hors AMM.

- Reportez-vous aux exigences réglementaires locales pour des informations supplémentaires .

- Pour un usage externe des diapositives, des autorisations de droits d'auteur doivent être obtenues

Actualités et perspectives thérapeutiques dans le lymphome folliculaire

Pr Le Gouill Steven

CHU de Nantes

France

Maroc, Mai 2017

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

UNIVERSITÉ DE NANTES

Lysa
THE LYMPHOMA STUDY ASSOCIATION

Généralités

- Le second lymphome le plus fréquent dans les pays européens (Lymphome = 6 cause de cancer en France)
- Incidence en augmentation: de 2–3/100 000 il y a 50 ans à 5/100 000 recently
- Une pathologie mais plusieurs grades:
  - LF grade 1, 2 et 3A = lymphomes indolents
  - LF grade 3B = lymphome de haut grade (relecture par des experts conseillés)

ESMO 2016

Table 1. Grading of follicular lymphoma (FL)

Grade	Description
1	≤5 blasts/high-power field
2	6–15 blasts/high-power field
3A	>15 blasts/high-power field, centroblasts with intermingled centrocytes
3B	>15 blasts/high-power field, pure sheets of blasts

Le Bilan initial et la question du FDG-TEP

- Biologie classique de lymphome: hémogramme, biochimie standard (évaluation fonction rénale et hépatique, Ionnogramme..), lactate dehydrogenase (LDH), β2 microglobuline, ac urique, sérologie HIV, HVB et HVC
- Imagerie:
  - Scanner cou/thorax/abdo/pelvis
- FDG/TEP recommandé pour le bilan initial (ESMO 2016) car permet une meilleure évaluation du bilan d'extension:

  - « This is particularly important to confirm localised stage I/II before involved-field radiotherapy. »

  - doute sur une transformation (SUVmax, Bodet-Milin Haematologica) pour guider une biopsie

  - A discuter au cas par cas

Classification et facteurs pronostics

- Classification selon Ann Arbor
- Bulky si masse > 7cm
- Score FLIPI et FLIPI2: intérêt prédictif de la PFS MAIS pas la référence pour décider ou non de traiter un patient (critère GELF)

ESMO 2016

Table 4. 'Follicular Lymphoma-specific International Prognostic Index' (FLIPI) risk factors

Parameter	Definition of risk factors	
	FLIPI 1	FLIPI 2
Nodal sites	>4 lymph node regions (definition in [5])	Long diameter of largest lymph node >6 cm
Age	>60 years	>60 years
Serum marker	Elevated LDH	Elevated β2 microglobulin
Stage	Advanced (III–IV according to Ann Arbor classification)	Bone marrow involvement
Haemoglobin	<12 g/dl	<12 g/dl

0–1 risk factors, low risk; 2 risk factors, intermediate risk; 3–5 risk factors, high risk.
LDH, lactate dehydrogenase.

Table 5. High tumour burden criteria in FL [Groupe d'Etude des Lymphomes Folliculaires (GELF)

Parameter	High tumour burden criteria
Lymph nodes	Bulk (>7 cm) or 3 lymph nodes in distinct areas >3 cm
Spleen	Symptomatic splenic enlargement
(Potential) complication	Organ compression by tumour, pleural or peritoneal effusion
Serum markers	Elevated LDH or elevated β_2-microglobuline
Clinical presentation	B symptoms (see Table 2)

LDH, lactate dehydrogenase.

Démarche au diagnostic de LF relativement simple …..

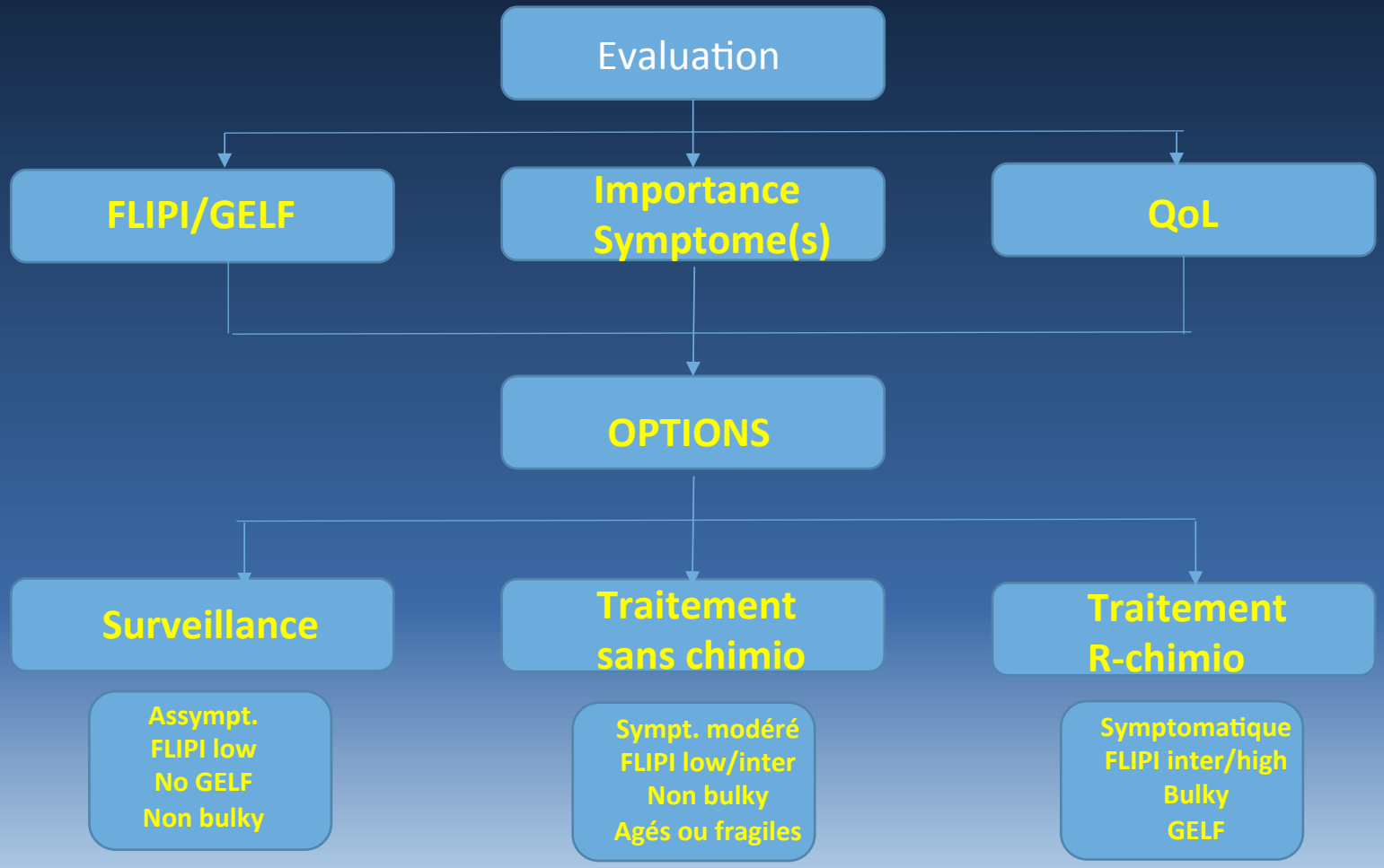
- Assurer le diagnostic sur la base d'une biopsie ganglionnaire
- Diagnostic selon la classification WHO (grade ++)
- Bilan clinique, biologique et iconographique (FGD-TEP à discuter):
  - Retentissement clinique et biologique du LF
  - Stade Ann Arbor
  - Score FLIPI (pronostic)
  - Critère GELF (pronostic et « decision-making »)
- **Les pièges:** méconnaitre un grade 3B, méconaitre une transformation agressive (FDG-TEP), se baser uniquement sur le stade pour décider un traitement

Mais un choix thérapeutique parfois plus compliqué ….

- Cas évident en faveur d'une traitement: forte masse, symptôme(s) en lien avec la pathologie influençant la qualité de vie …
- Cas évident en faveur d'une surveillance: exérèse complète de la tumeur sur la biopsie, patient sans symptômes

- Et pour tous les autres cas, on peut se poser la question:
  - « To treat or not to treat »

Restons simple et pratique en gardant en tête que la médiane de survie des LF est de plus de 10 ans: « Prima non nuocere! »



Assympt.
FLIPI low
No GELF
Non bulky

Sympt. modéré
FLIPI low/inter
Non bulky
Agés ou fragiles

Symptomatique
FLIPI inter/high
Bulky
GELF

Surveillance

Traitement sans chimio

Rituximab seul

Radiothérapie (localisée)

Radio-immunothérapie ?

Traitement R-chimio

Rituximab-
CHOP
CVP
Bendamustine
+
R maintenance

Symptomatique
FLIPI inter/high
Bulky
GELF

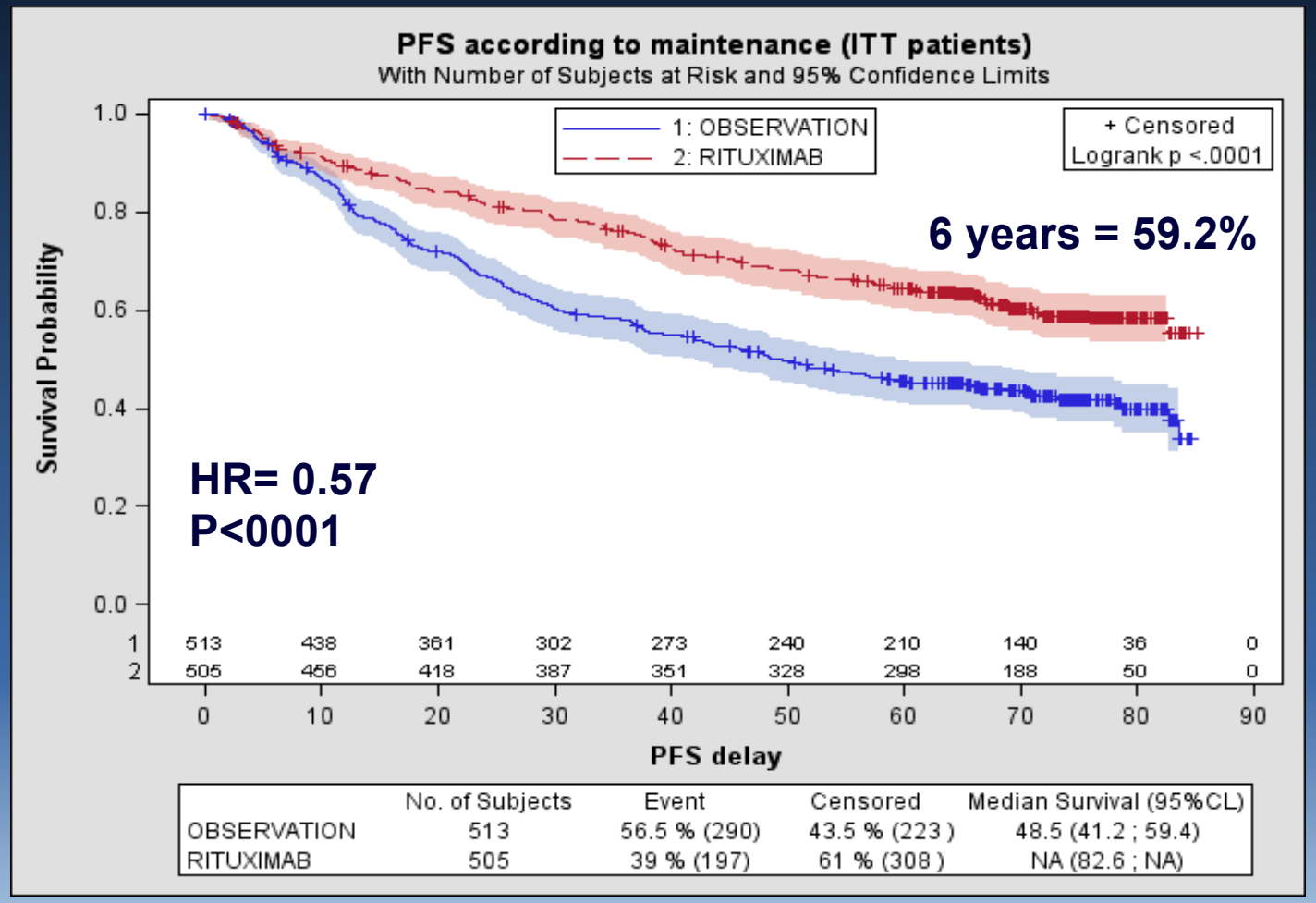
Traitement R-chimio

Rituximab-CHOP
CVP
Bendamustine
+
R maintenance

Study	No	mFU	ORR	TTF	OS
Marcus R-CVP	159	53m	81%	27m	83% 4y
Hiddeman R-CHOP	223	58m	96%	NR	90% 2y
Herold R-CMP	105	48m	92%	NR	87% 4y
Bachy R-CHVP-INF	175	99m	81%	66m	79% 8y
Rummel BR	139	34m	93%	NR	84% 4y

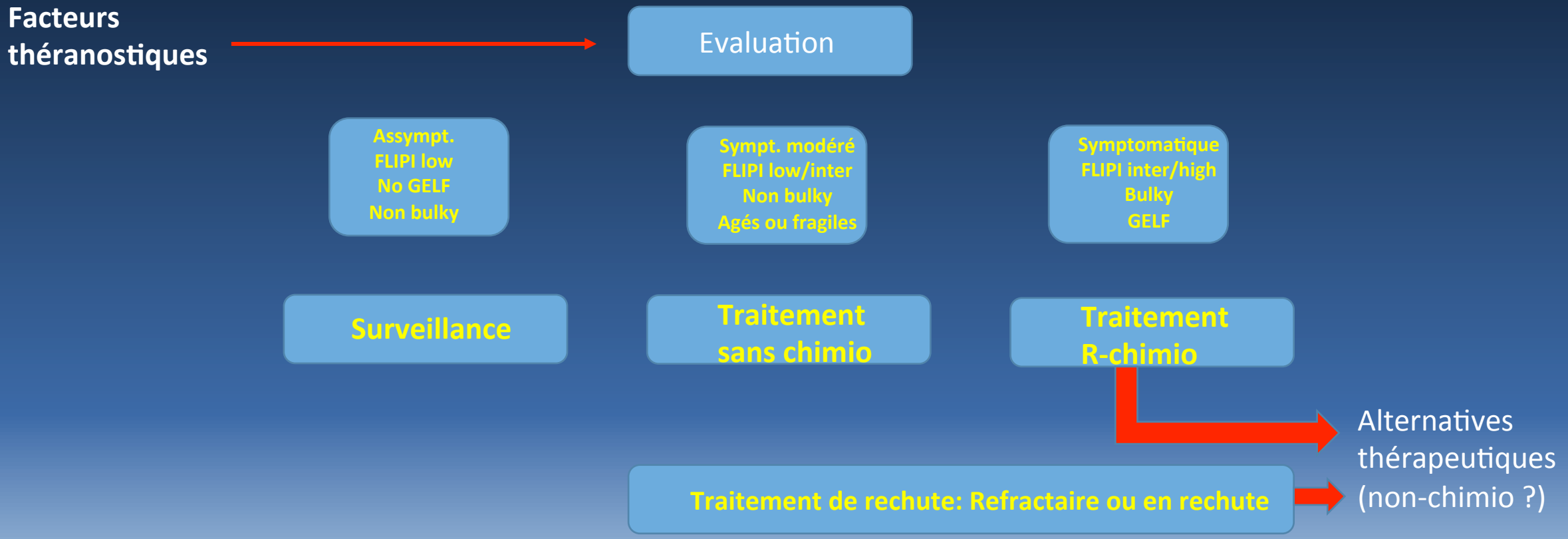
Adapted from ESMO 2016

High tumor burden FL
PRIMA 6 years follow-up
Progression free survival from randomization



Median follow-up since randomisation : 73 months

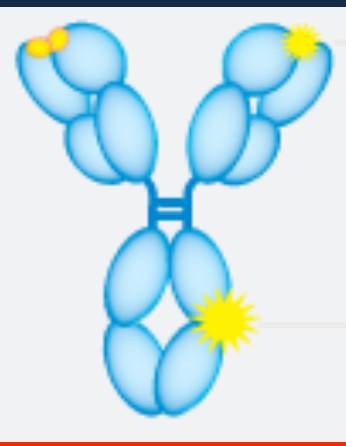
Les problématiques dans le LF en 2107



How to improve on current results in FL?

Optimization of Rituximab's efficacy

Optimizing the mAb itself



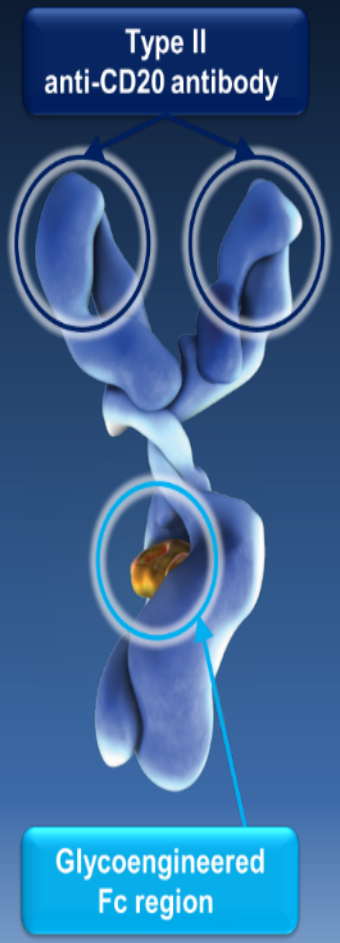
↑ Affinity
↑ PCD
Target a different epitope

↑ ADCC
↑ CDC
FcRn
Conjugates

Stimulating immune effector cells

GAZYVA is a novel type II anti-CD20 mAb

- GAZYVA (obinutuzumab) is a glycoengineered type II anti-CD20 mAb with **enhanced direct cell killing**, antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity compared with rituximab[1,2]
  - Type II character and glycoengineered Fc region confer unique properties



mAb, monoclonal antibody

1. Mössner E, et al. Blood 2010;115:4393–402;
2. Herter S, et al. Mol Cancer Ther 2013;12:2031–42

The functional activity of GAZYVA differs from MabThera

As a Type II antibody, GAZYVA binds differently than Type I mAbs, leading to distinct modes of cytotoxic activity against B-cell malignancies[1–7]

ADCC, antibody-dependent cellular cytotoxicity;
ADCP, antibody-dependent cellular phagocytosis;
CDC, complement-dependent cytotoxicity; mAb, monoclonal antibody

[1]Herter S, et al. Blood 2010;116:Abstract 3925; [2]Lim SH, et al. Haematologica 2010;95:135–43
[3]Beers SA, et al. Semin Hematol 2010;47;110–4; [4]Mossner E, et al. Blood 2010;115:4393–402
[5]Illidge TM. Expert Opin Biol Ther 2012;12:543–5
[6]Niederfellner G, et al. Blood 2011;118:358–67
[7]Golay J, et al. Blood 2013;122:3482–91

Améliorer la chimiothérapie en première ligne: étude GALLIUM

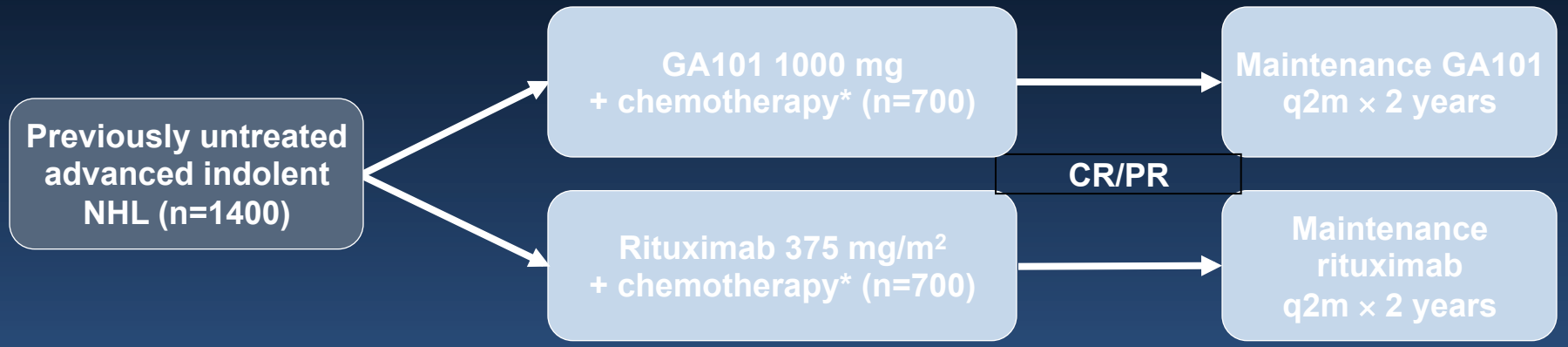
Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized Phase III GALLIUM study

Robert Marcus,[1] Andrew Davies,[2] Kiyoshi Ando,[3] Wolfram Klapper,[4] Stephen Opat,[5] Carolyn Owen,[6] Elizabeth Phillips,[7] Randeep Sangha,[8] Rudolf Schlag,[9] John F Seymour,[10] William Townsend,[7] Marek Trněný,[11] Michael Wenger,[12] Günter Fingerle-Rowson,[13] Kaspar Rufibach,[13] Tom Moore,[13] Michael Herold,[14] Wolfgang Hiddemann[15]

[1]Kings College Hospital, London, United Kingdom; [2]Cancer Research UK Centre, University of Southampton, Southampton, United Kingdom; [3]Tokai University School of Medicine, Isehara, Kanagawa, Japan; [4]University of Kiel, Kiel, Germany; [5]Monash Health and Monash University, Melbourne, Australia; [6]Foothills Medical Centre and Tom Baker Cancer Centre, Calgary, AB, Canada; [7]Cancer Research UK and UCL Cancer Trials Centre, London, United Kingdom; [8]Cross Cancer Institute, Edmonton, AB, Canada; [9]Gemeinschaftspraxis Dr. Rudolf Schlag/Dr. Björn Schöttker, Würzburg, Germany; [10]Peter MacCallum Cancer Centre, Melbourne, Australia; [11]Charles University, Prague, Czech Republic; [12]Genentech Inc, South San Francisco, CA, USA; [13]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [14]HELIOS-Klinikum, Erfurt, Germany; [15]Ludwig-Maximilians-University, Munich, Germany

GLSG NCRI National Cancer Research Institute OSHO

GALLIUM (BO21223) Phase III: Study design



***FL:** Each site to choose 1 of 3 chemotherapy regimens (CHOP, CVP, or bendamustine) which will; then be administered to all patients
Non-FL: CHOP, CVP, or bendamustine selected on a patient-by-patient basis

Phase III	**Open label study with induction and 2 years maintenance therapy** • **Primary Endpoint: PFS; HR 0,74; ⇑ median PFS from 72m to 97m** • **Secondary Endpoints: OS, EFS, ORR, CR, TNLT, safety and other** • **One futility analysis based on 33% PFS events; one IA based on 67% of PFS events** • **1200 patients from 250 sites, study duration approx. 6.1 years from FPI to final clinical data cutoff** • **200 additional patients with MZL, MALT, or SMZL** • **Fully recruited** • **First analysis in 2017**

- www.clinicaltrials.gov: NCT01332968

Baseline patient and disease characteristics (FL)

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)¶

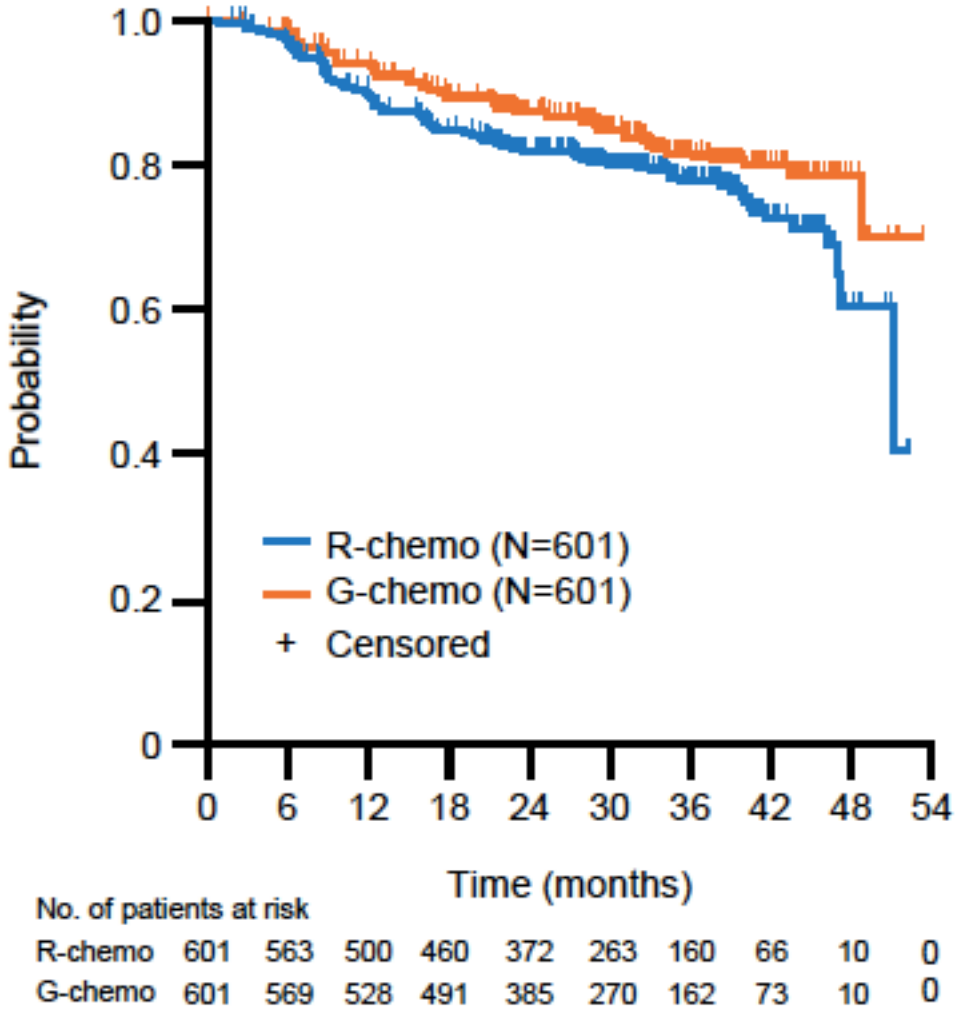
*n=597; †n=598; ‡n=600; §n=592; ¶n=598, value not determined in three pts

Response rates at end of induction (FL)*

	CT (by investigator)	
% (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)

*INV-assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson BD, et al. J Clin Oncol 2007)
INV, investigator

IRC-assessed PFS (FL)

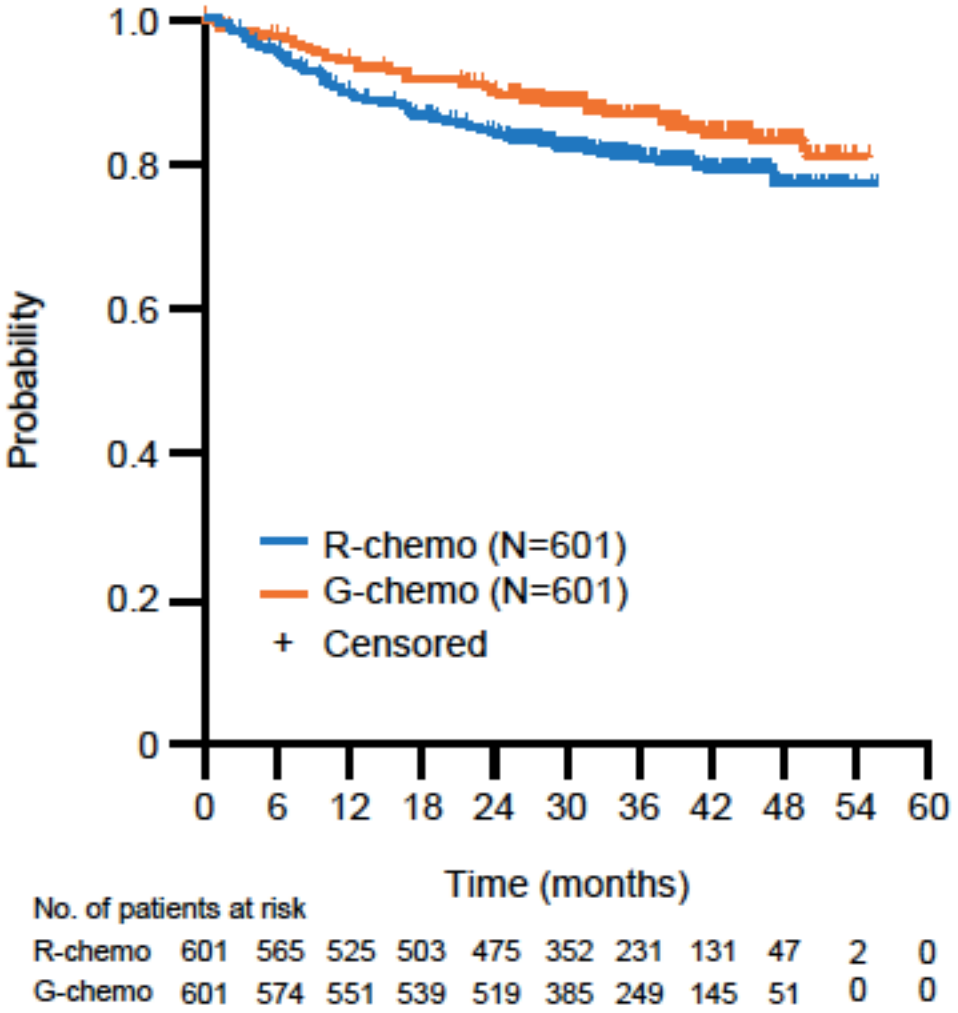


	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	125 (20.8)	93 (15.5)
3-yr PFS, % (95% CI)	77.9 (73.8, 81.4)	81.9 (77.9, 85.2)
HR (95% CI), p-value*	0.71 (0.54, 0.93), p=0.0138	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

TTNT (FL)

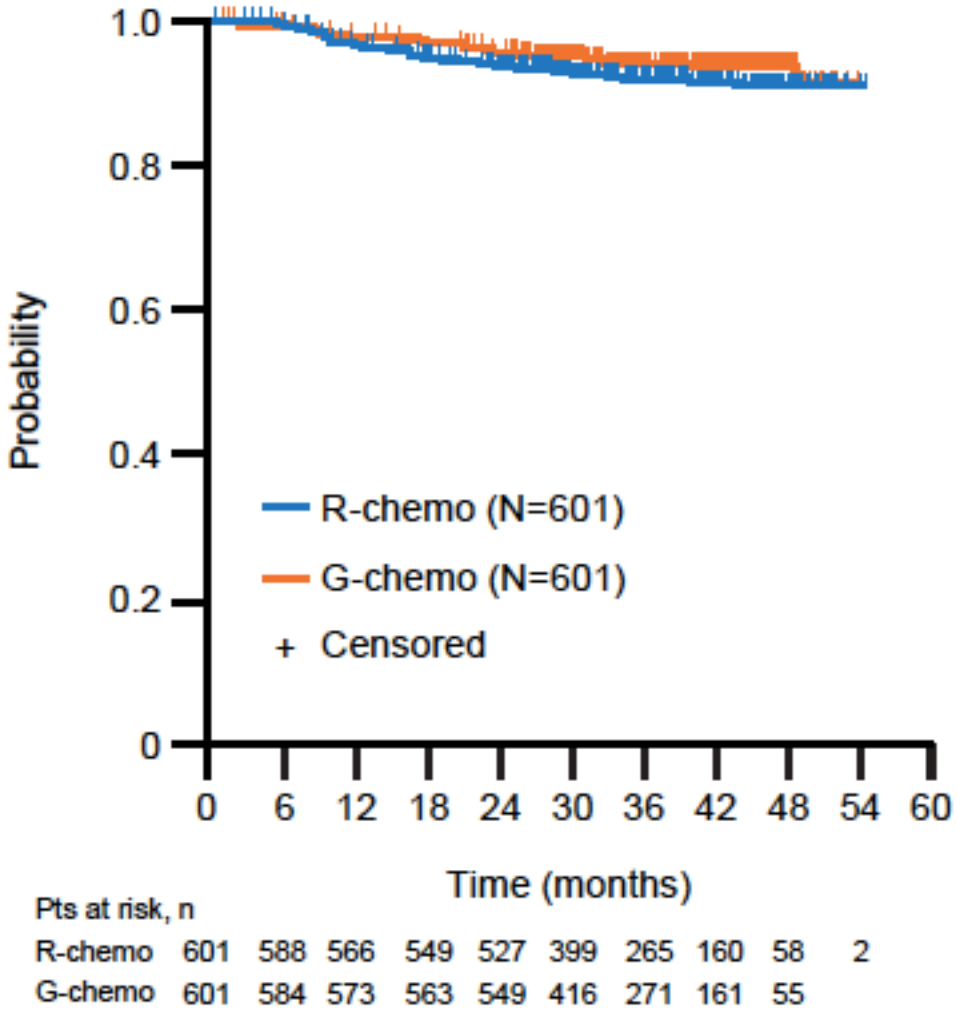


	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	111 (18.5)	80 (13.3)
3-yr TTNT, % (95% CI)	81.2 (77.6, 84.2)	87.1 (84.0, 89.6)
HR (95% CI), p-value*	0.68 (0.51, 0.91), p=0.0094	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

OS (FL)

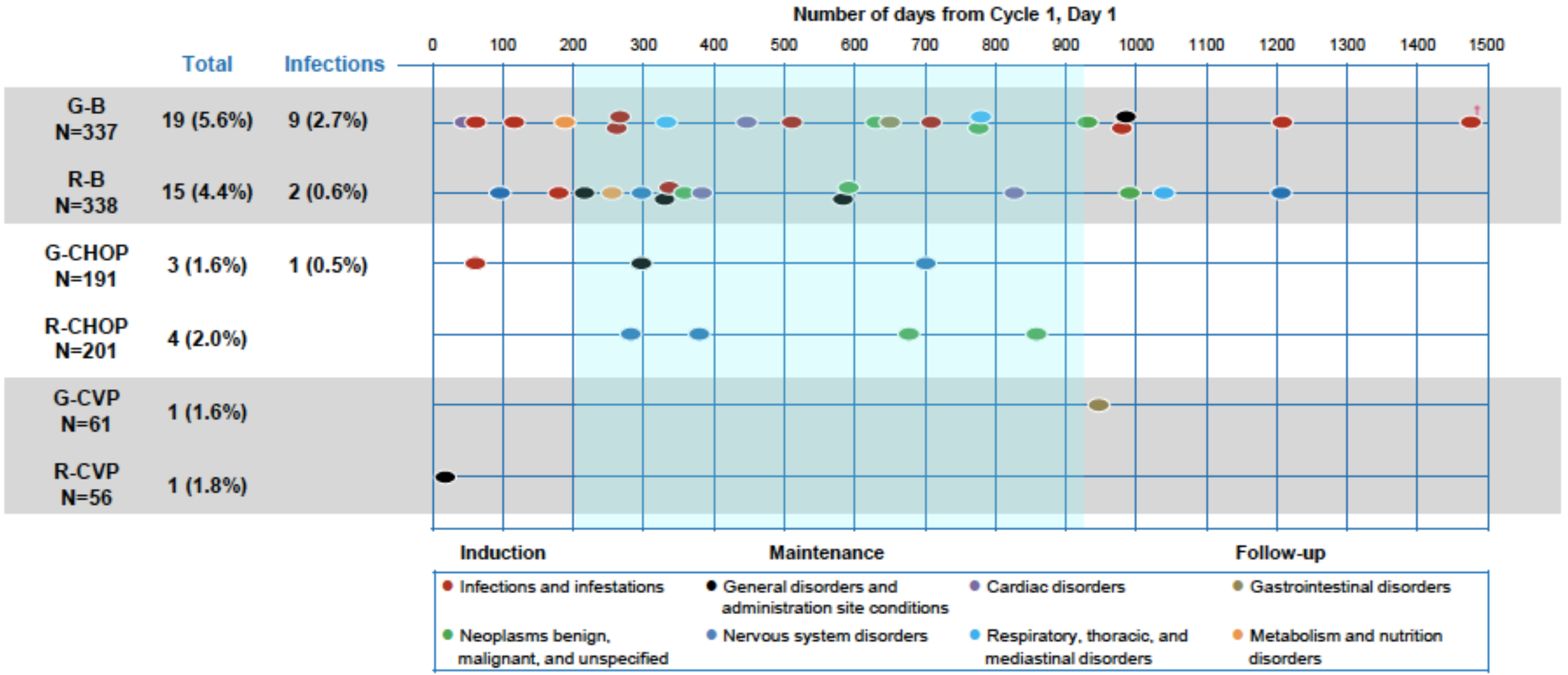


	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	46 (7.7)	35 (5.8)
3-yr OS, % (95% CI)	92.1 (89.5, 94.1)	94.0 (91.6, 95.7)
HR (95% CI), p-value*	0.75 (0.49, 1.17), p=0.21	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

Grade 5 (fatal) AEs by treatment (FL)*



*Includes only pts who died before clinical cut-off date; †this patient (G-B group) was initially assigned three causes of death (*Clostridium difficile* colitis, prostate cancer, and myelodysplastic syndrome); *Clostridium difficile* colitis was the most acute, so the patient has been assigned to the 'Infections and infestations' category and the number of fatal AEs in G-B pts in neoplasms SOC reduced from 5 to 3

Conclusions

- G-chemo + maintenance superior to R-chemo + maintenance in untreated advanced FL patients at interim efficacy analysis
  - Clinically meaningful improvement in PFS: 34% reduction in risk; HR=0.66
  - PFS result supported by other time-to-event endpoints
- Non-fatal AEs were higher in the G arm
  - IRRs, cytopenias, and infection
- Fatal AEs more common in patients on bendamustine in both arms
- G-based therapy significantly improves outcome compared with R-based therapy and should now be considered as a first-line treatment for FL

Le défi du LF « réfractaire »

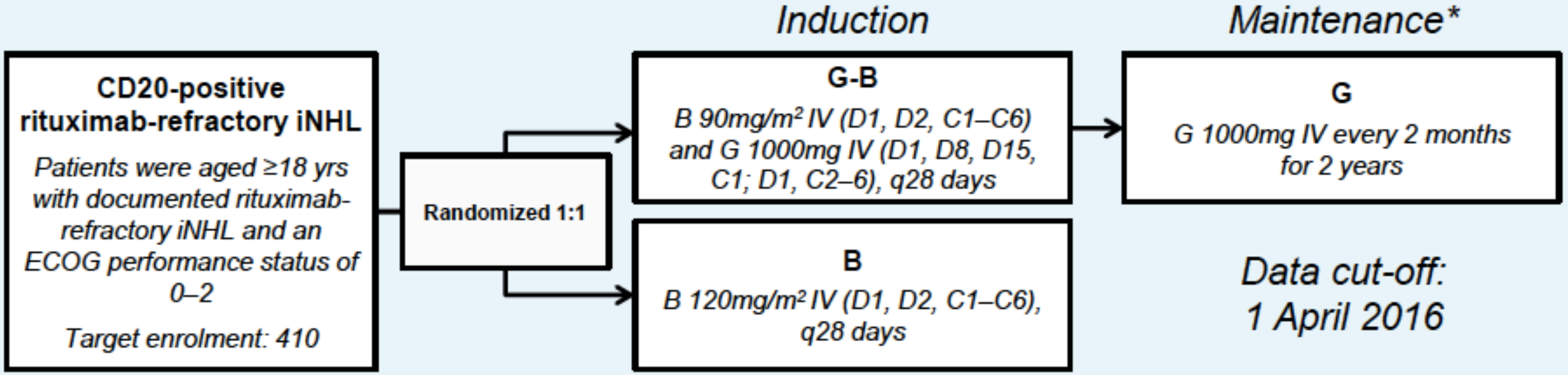
Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs overall survival compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma: updated results of the GADOLIN study

Bruce D Cheson,[1] Marek Trněný,[2] Kamal Bouabdallah,[3] Greg Dueck,[4] John Gribben,[5] Pieternella J Lugtenburg,[6] Oliver Press,[7] Gilles Salles,[8] Günter Fingerle-Rowson,[9] Federico Mattiello,[9] Elisabeth Wassner-Fritsch,[9] Laurie H Sehn[10]

[1]Georgetown University Hospital, Washington, DC, USA; [2]Charles University, Prague, Czech Republic; [3]University Hospital of Bordeaux, CHU Haut-Leveque, Bordeaux, France; [4]British Columbia Cancer Agency, Kelowna, BC, Canada; [5]Queen Mary University of London, London, United Kingdom; [6]Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [8]Hospices Civils de Lyon, Université Claude Bernard Lyon-1, Lyon, France; [9]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [10]British Columbia Cancer Agency and the University of British Columbia, Vancouver, BC, Canada

Study design

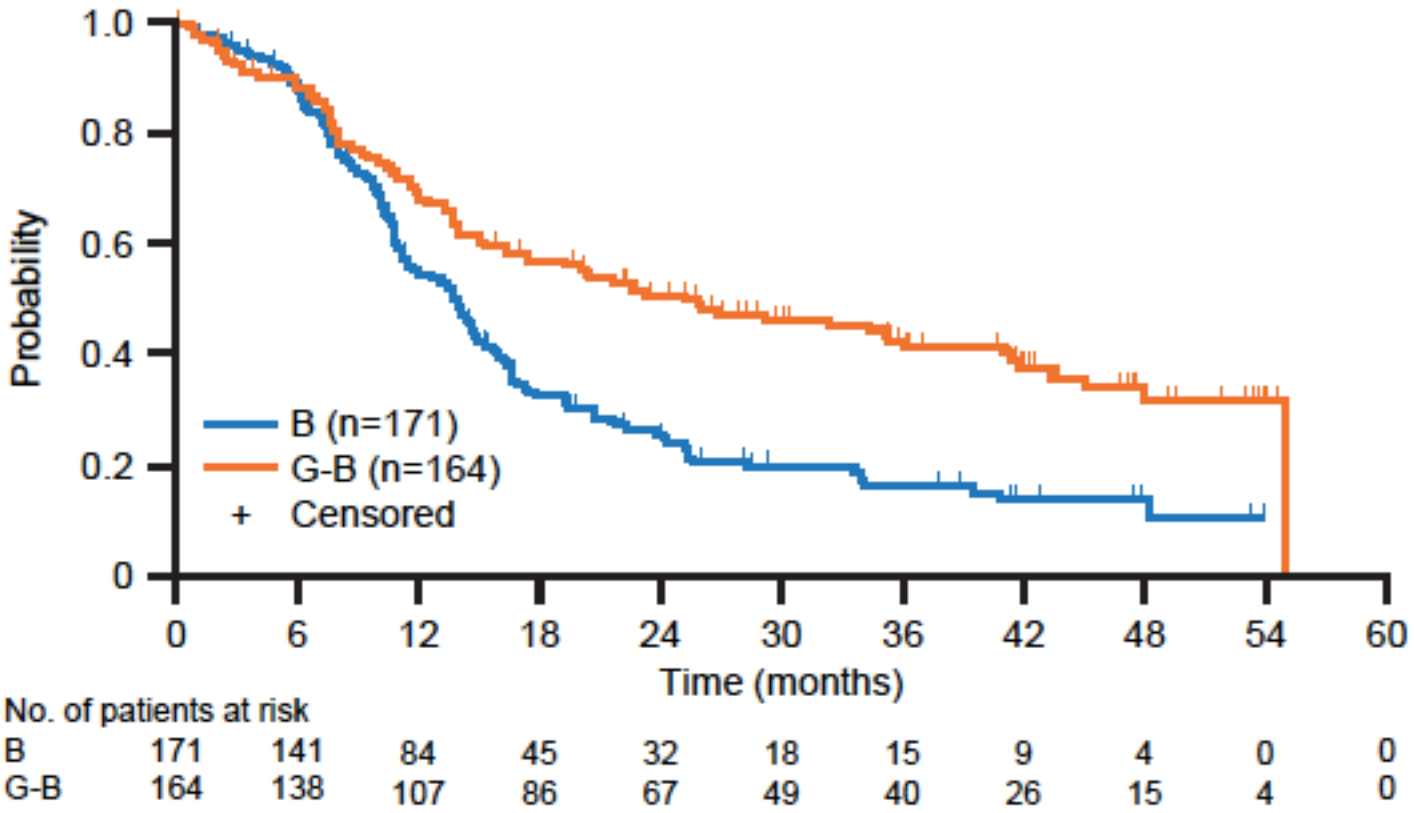
Open-label, multicenter, randomized, Phase III study in rituximab-refractory iNHL patients



- **Rituximab-refractory definition:** Failure to respond to, or progression during any prior rituximab-containing regimen (monotherapy or combined with chemotherapy), or progression within 6 months of the last rituximab dose, in the induction or maintenance settings
- **Endpoints considered in current analysis:** PFS (INV), OS, TTNT, safety

INV-assessed PFS in the FL population

Kaplan-Meier plot of INV-assessed PFS by treatment arm (FL)



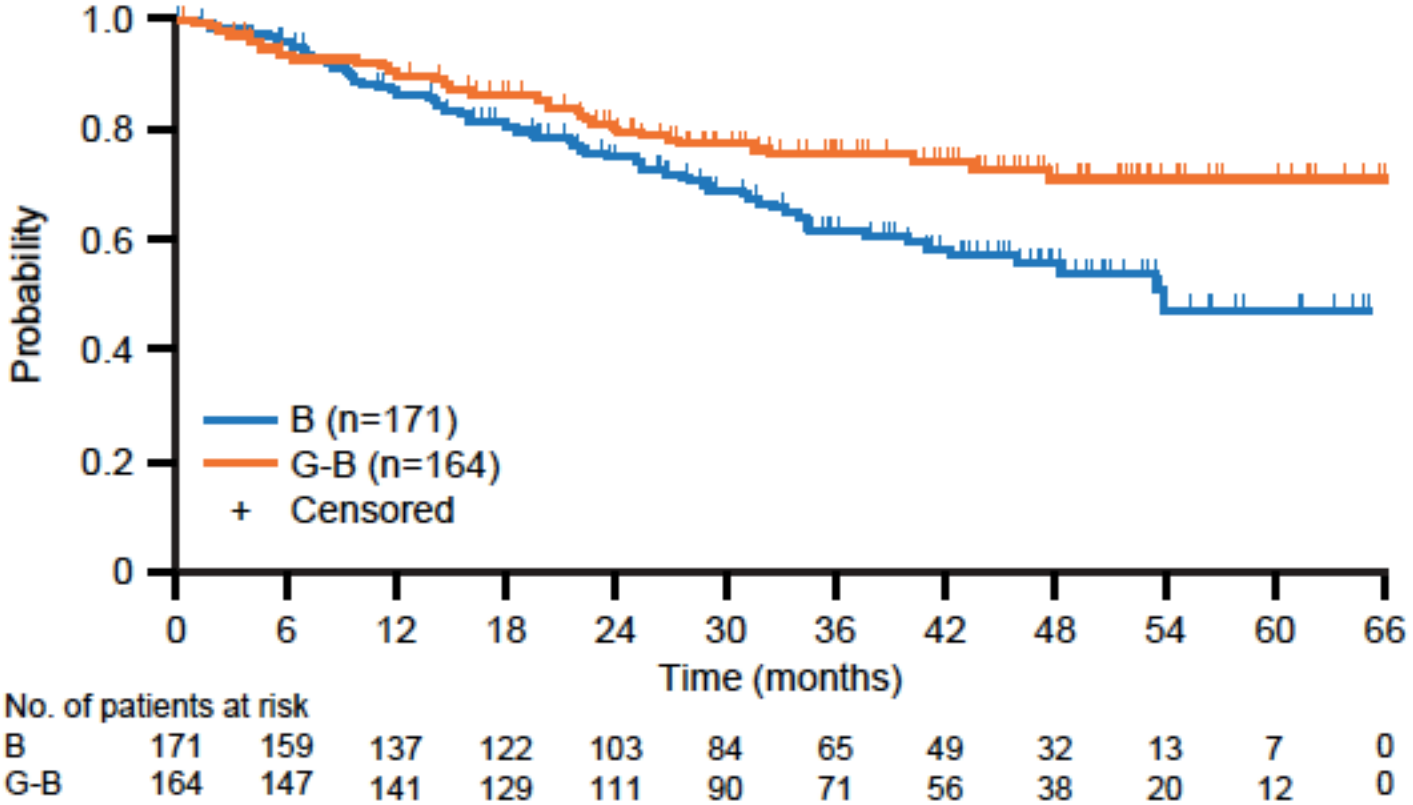
	G-B, n=164	*B, n=171*
Pts with event, n (%)	93 (56.7)	125 (73.1)
Median PFS (95% CI), mo	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CI), p-value*	0.52 (0.39, 0.69), p<0.0001	

Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

OS in the FL population

Kaplan-Meier plot of OS by treatment arm (FL)



NR, not reached

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

	G-B, n=164	*B, n=171*
Pts with event, n (%)	39 (23.8)	64 (37.4)
Median OS (95% CI), mo	NR (NR, NR)	53.9 (40.9, NR)
HR (95% CI), p-value*	0.58 (0.39, 0.86), p=0.0061	

Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

- GALLIUM montre que G-chimio > R-chimio
  MAIS montre aussi:
  - absence de bénéfice en OS
  - Toxicité inattendue de la bendamustine ++

  La Questions actuelle:
  fin de la chimiothérapie en première ligne?

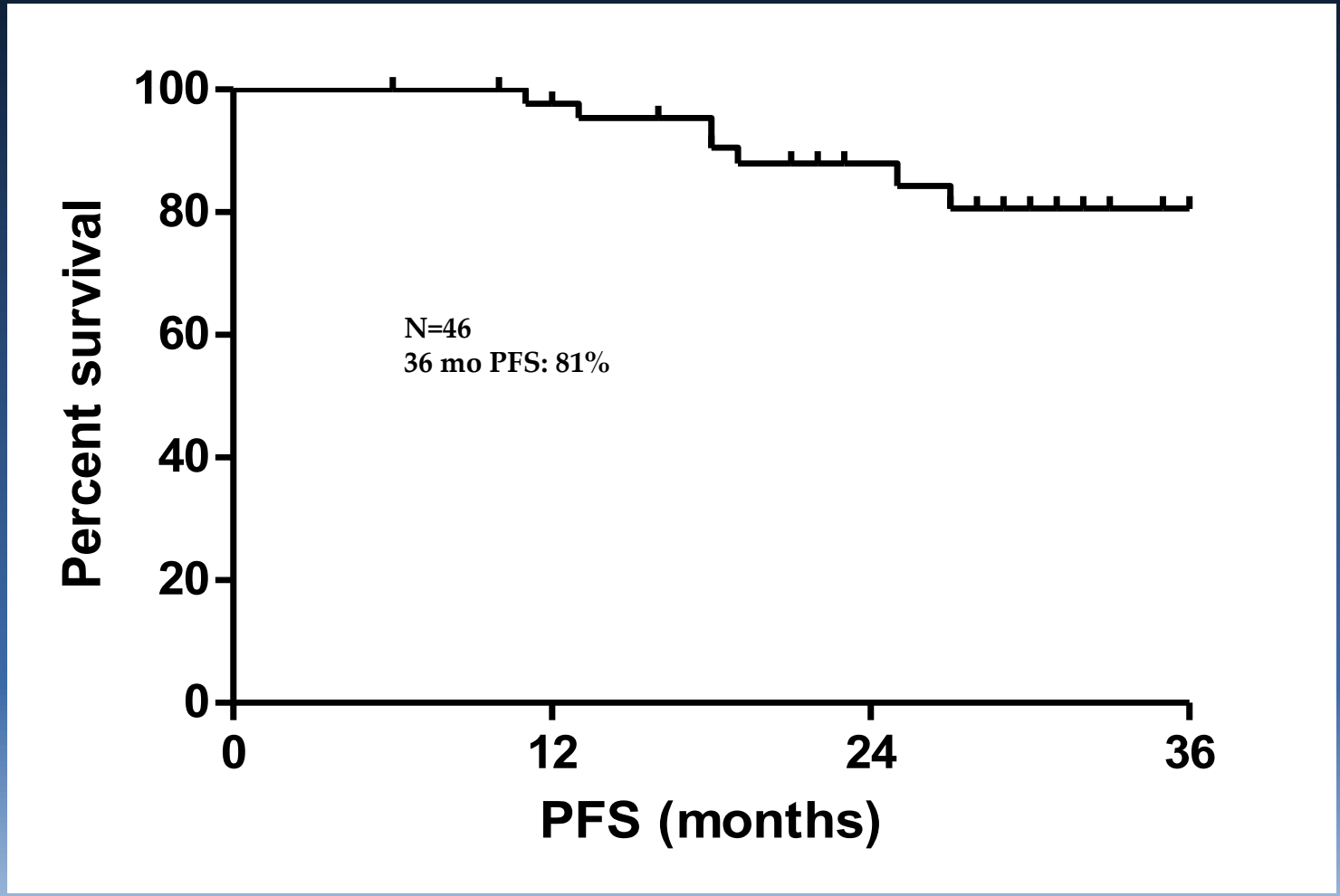
R^2 as Frontline Combination for Follicular Lymphoma: Clinical Response

BY GELF CRITERIA N=45							
GELF (+) N=22 (49%)				GELF (-) N=23 (51%)			
SD	PR	CR/CRu	ORR	SD	PR	CR/CRu	ORR
0	1 (5%)	21(95%)	100%	1(5%)	4(17%)	18 (78%)	95%

BY BULK OF DISEASE N=45							
BULKY N=13 (29%)				NON-BULKY N=32 (71%)			
SD	PR	CR/CRu	ORR	SD	PR	CR/CRu	ORR
0	1(8%)	12(92%)	100%	1(3%)	4 (13%)	27 (84%)	97%

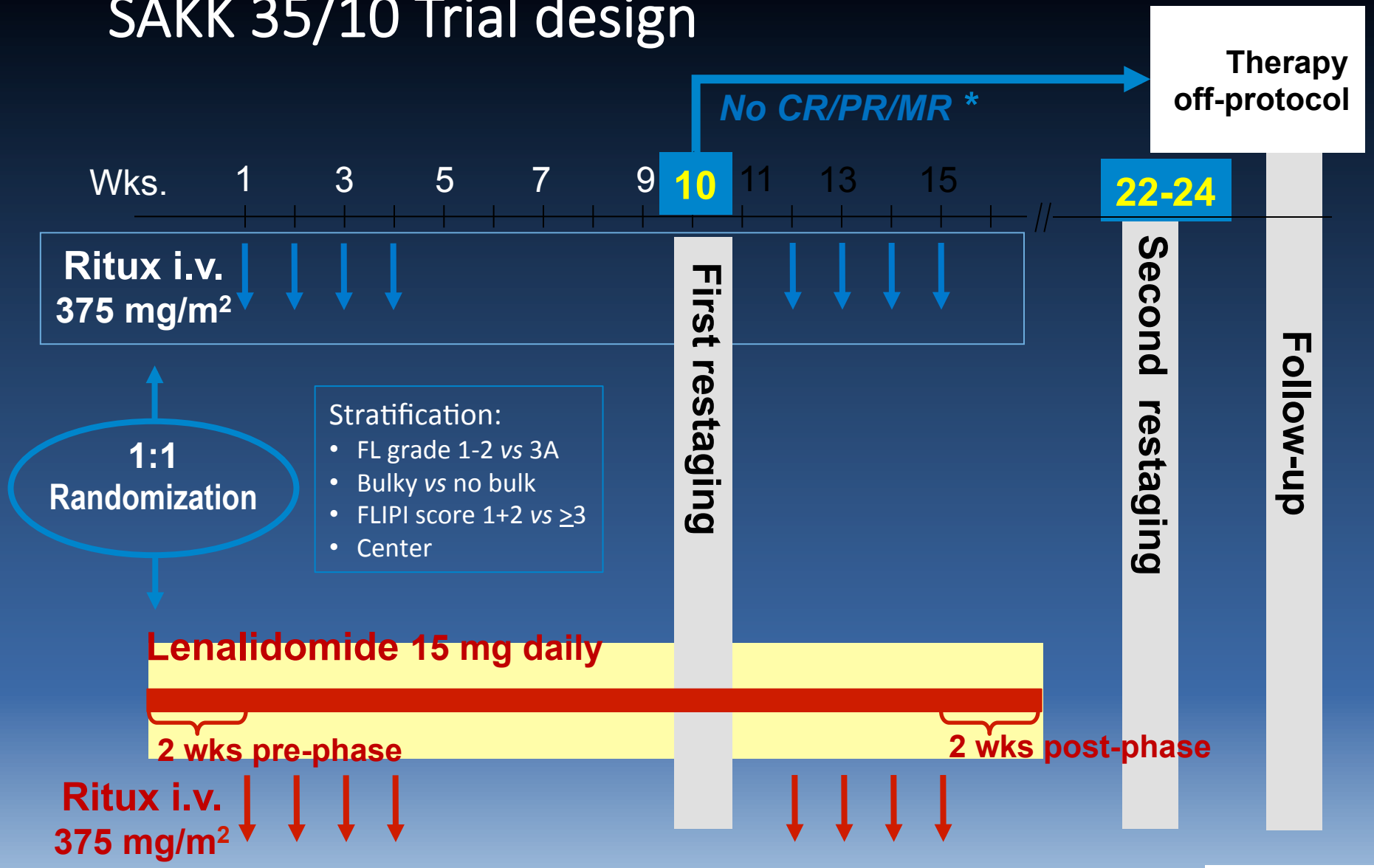
Fowler, N. et al. ICML 2011. Abst#137.

R^2 as Frontline therapy in FL: PFS



Fowler, N. et al. ASH 2012.

SAKK 35/10 Trial design



*MR >25% decrease in SPD

SAKK WE BRING PROGRESS TO CANCER CARE NLG

Response at week 23 – ITT

Investigator Assessment ORR: 82% *vs* 61%[1]

	Rituximab (N=77)		Rituximab + Lenalidomide (N=77)	
Response	**n (%)**	**[95% CI]**	**n (%)**	**[95% CI]**
CR/CRu	19 (**25**%)	[16-36%]	28 (**36**%)	[26-48%]*
PR	28 (36%)	[26-48%]	35 (45%)	[34-57%]

IRR Assessment ORR: 78% *vs* 57%

CR/CRu	28 (**36**%)	[26-48%]	47 (**61**%)	[49-72%]*
PR	16 (21%)	[12-32%]	13 (17%)	[9-27%]
SD	7 (9%)	[4-18%]	2 (3%)	[0.3-9%]
PD	3 (4%)	[0.8-11%]	1 (1%)	[0-7%]
NE **	23 (30%)	[20-41%]	14 (18%)	[10-29%]

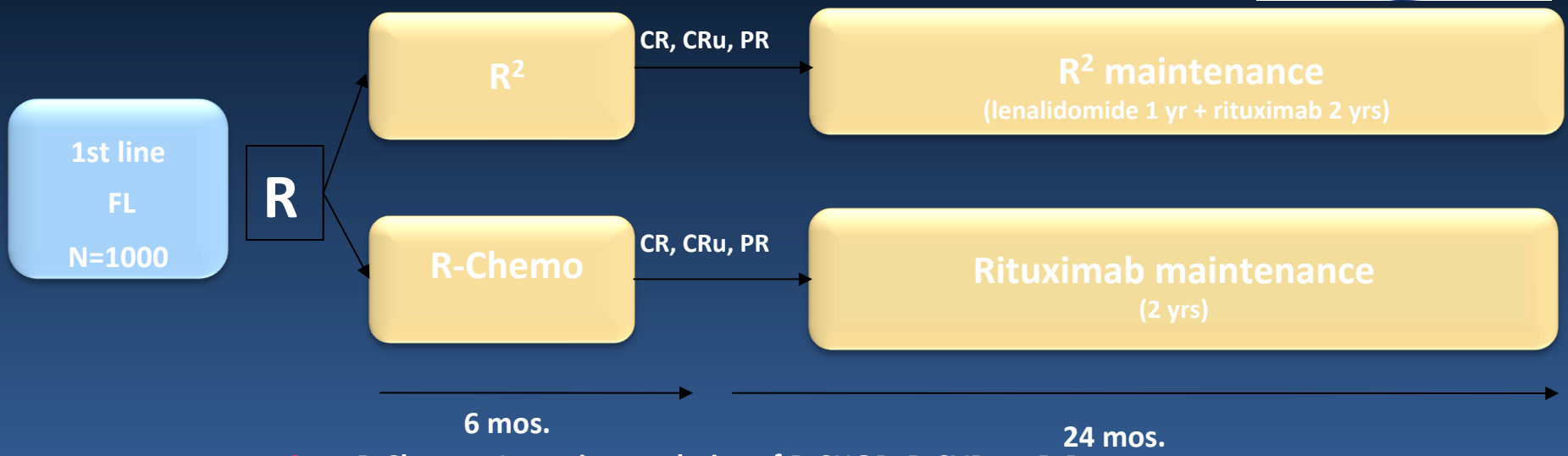
*** Statistically significant**

**** Patients not evaluable at week 23 including those with early PD or not achieving a minimal response at week 10**

[1] Kimby et al. *Blood (ASH Annual Meeting Abstracts). 2014;124:799*

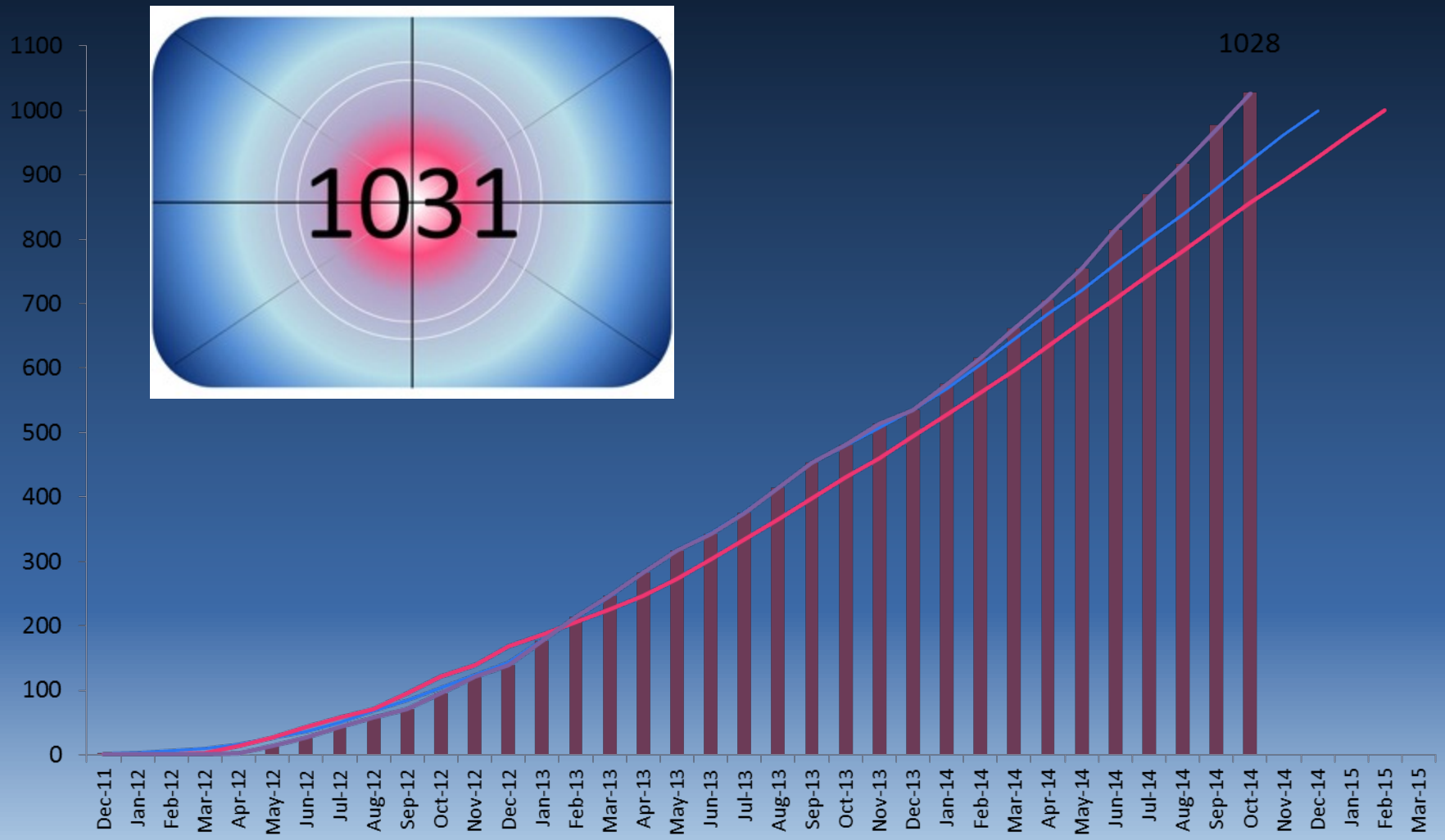
SAKK WE BRING PROGRESS TO CANCER CARE NLG

The "RELEVANCE" Trial

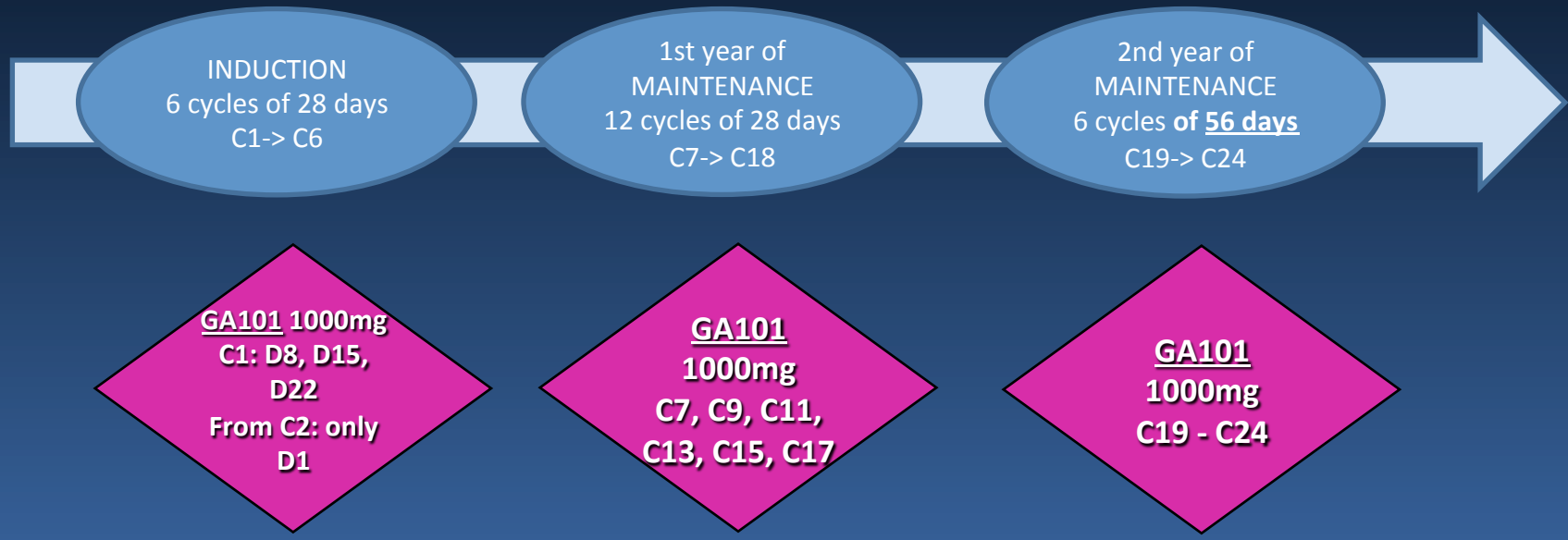


- R-Chemo: Investigator choice of R-CHOP, R-CVP, or R-B
- Eligibility: Patients who need treatment (GELF criteria)
- Stratification: FLIPI (0-1 v 2 v 3-5), Age (>60 v ≤ 60), diameter of largest node (> 6 v ≤ 6 cm)
- Endpoints: PFS, CR/CRu? At 30 months
- R^2 Regimen:
  - Rituximab weekly x 4, then day 1 of each cycle 2 to cycle 6, 8 weeks later responding patients continue every 8 weeks for 12 cycles
  - Lenalidomide 20 mg x 6 cycles
    - CR-10 mg lenalidomide 10 mg for 12 cycles
    - PR- 20 mg lenalidomide 3-6 months then, 10 mg ≤18 cycle

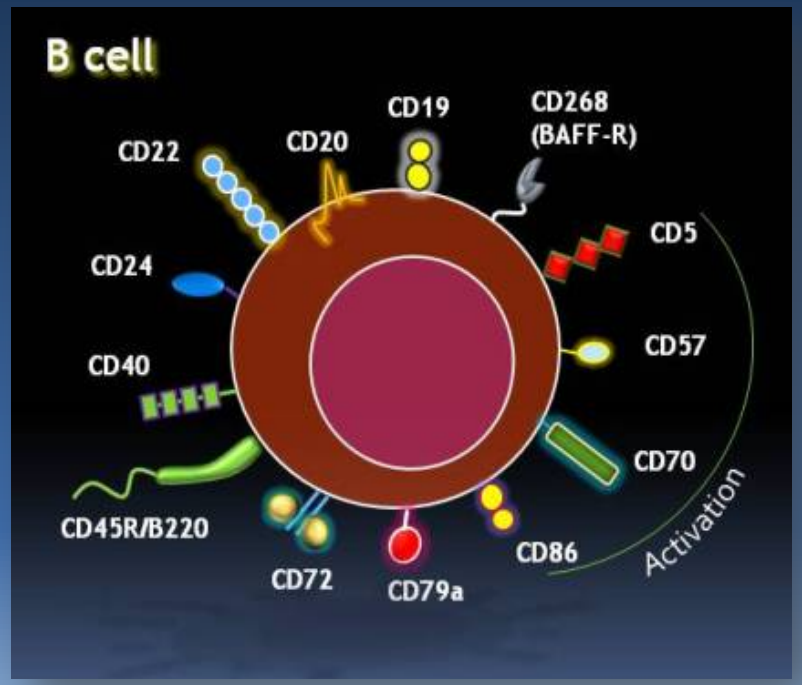
Final Recruitment Status



Study schema – Phase II- GALEN



New treatment targeted modalities 1 – Antibodies and immunomodulation



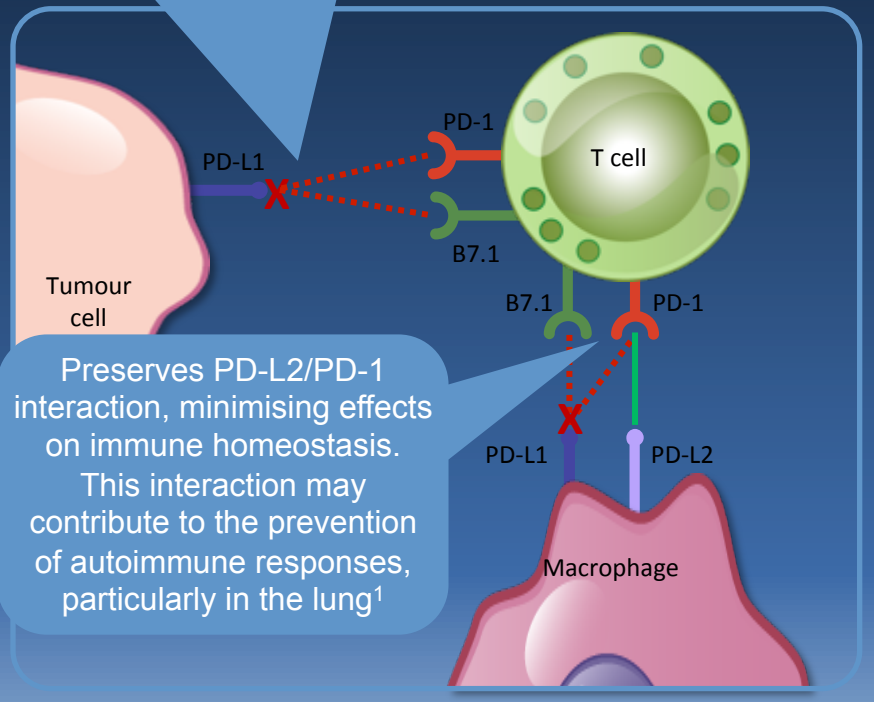
- New anti CD20 (obinutuzumab, ublituximab)
- Enhance antiCD20 MoAb with lenalidomide
- Immunomodulating antibodies:, anti-CD136, CD40, PD1, PDL1
- ADC or radioconjugates: MMAE (CD79,CD22), MMAF (CD19A), Lutetium (CD37)
- BITE (anti CD19-CD3)

- Combinations

Targeting PD1 or PD-L1?

Anti-PDL1

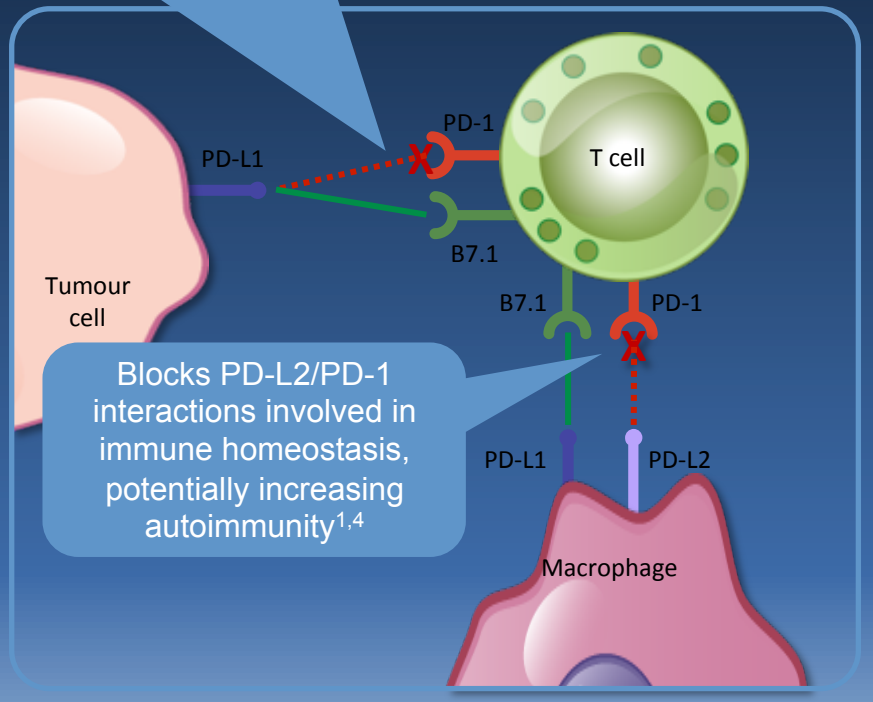
Targeting of PD-L1 can block co-inhibitory signalling between the tumour cell and both PD-1 and B7.1, preventing down-regulation of T-cell activity[1,2,3]



Preserves PD-L2/PD-1 interaction, minimising effects on immune homeostasis. This interaction may contribute to the prevention of autoimmune responses, particularly in the lung[1]

Anti-PD1

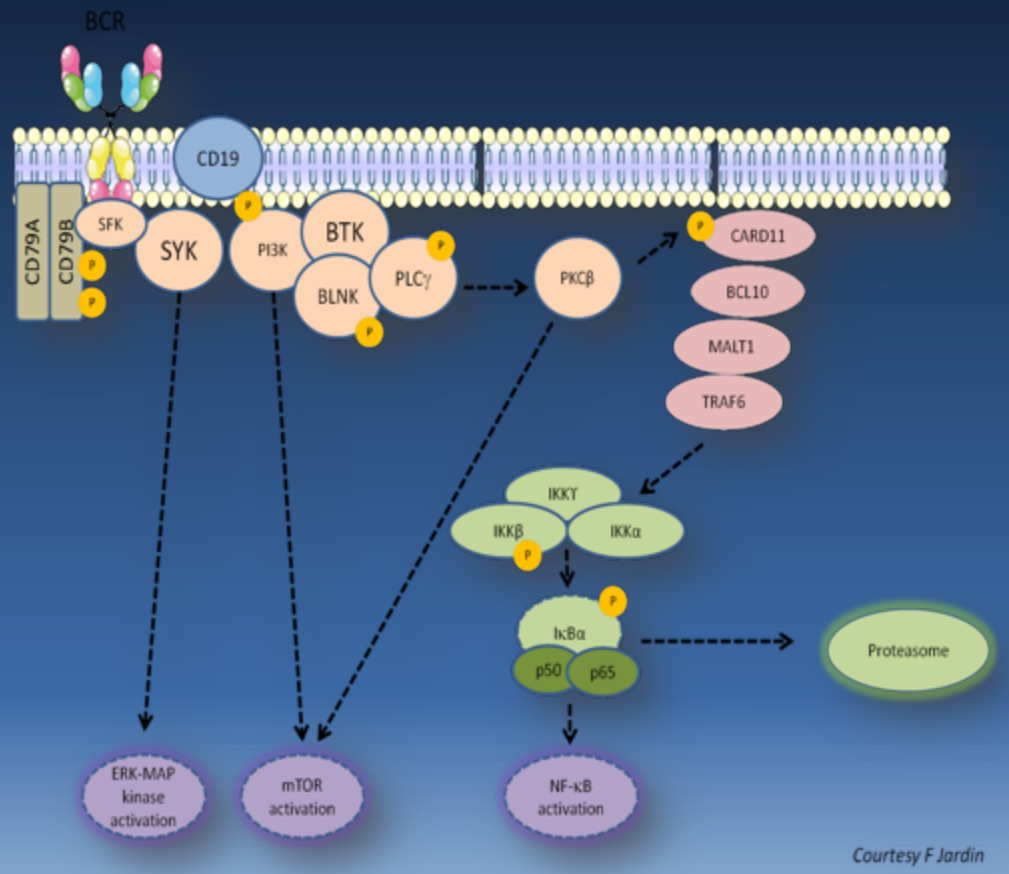
Targeting of PD-1 blocks co-inhibitory signalling between the tumour cell and PD-1, sparing the interaction between the tumour cell and B7.1[1,2,3]



Blocks PD-L2/PD-1 interactions involved in immune homeostasis, potentially increasing autoimmunity[1,4]

1. Chen, et al. 2012; 2. Paterson, et al. 2011
3. Yang, et al. 2011; 4. Brahmer, et al. 2012

Cibler les voies de transduction intracellulaire



BCR signature:
- – SYK inh
- – PI3K inh
- – PKC-β inh
- – BTK: ibrutinib
- – mTOR inh

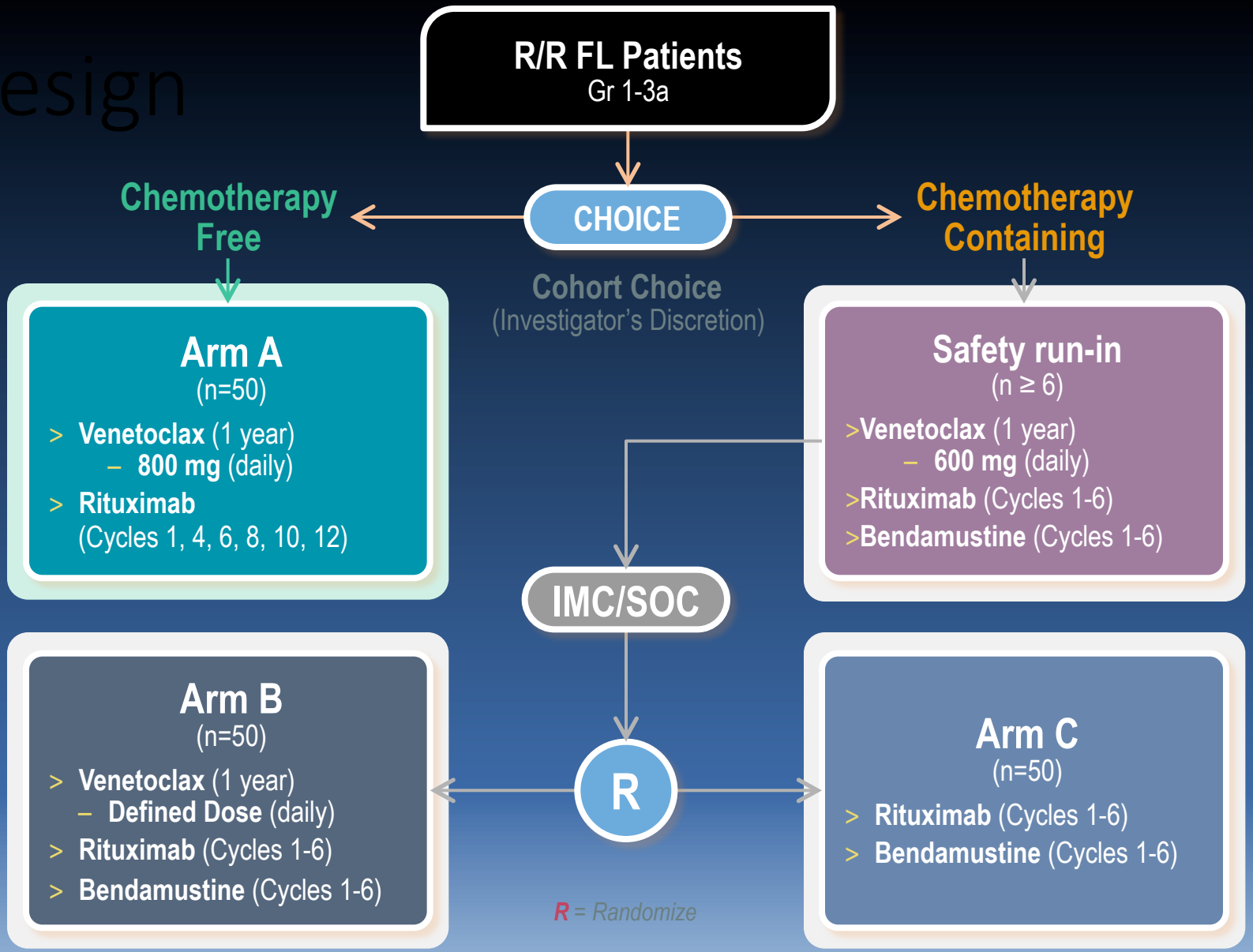
Apoptosis:
- BH3 mimetic

Epigenetic
- HDAC inhibitors
- EZH2 inhibitors

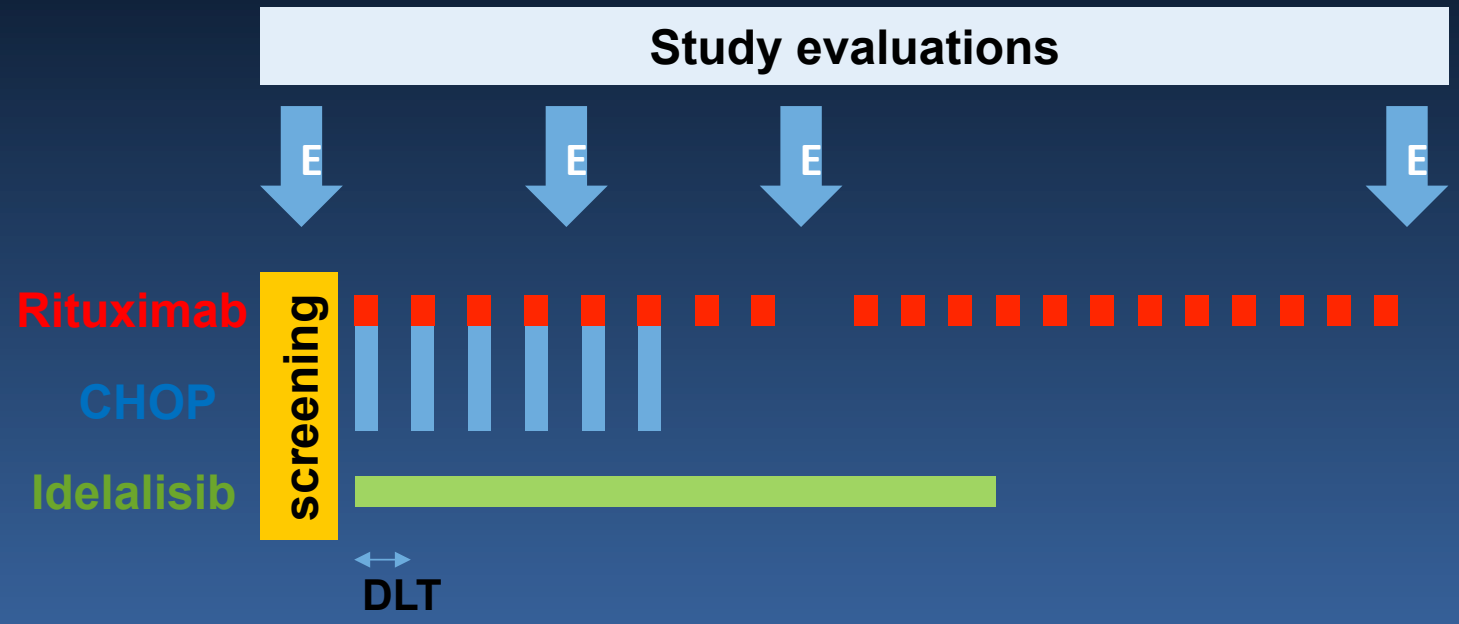
Nuclear export
- Selinexor

CONTRALTO:
ABT et chimio

Study Design



RIDE&CHOP Study design: IDELA+ chimio



R-CHOP :
Rituximab 375 mg/m² D1
Cyclophosphamide 750 mg/m² D1
Doxorubicin 50 mg/m² D1
Vincristine 1.4 mg/m² (max 2 mg) D1
Prednisone 100 mg D1-5

Idelalisib : according to a 3+3 dose-escalation schedule (no intent to exceed 150 mg BID)

- Level 0 : idelalisib 100 mg qd PO
- Level 1 : idelalisib 100 mg bid PO
- Level 2 : idelalisib 150mg bid PO
- Level R (reduced) : same dosing as above D1 to D14

Apoptosis:

- **BH3 mimetic**

BCR signature:

- SYK inh
- PI3K inh
- PKC-β inh
- BTK: ibrutinib
- mTOR inh

Epigenetic

- HDAC inhibitors
- EZH2 inhibitors

Combinaison ????

Nuclear export

- Selinexor

• Immunomodulating antibodies:, anti-CD136, CD40, PD1, PDL1
•ADC or radioconjugates: MMAE (CD79,CD22), MMAF (CD19A), Lutetium (CD37)
•BITE (anti CD19-CD3)

PD1 or PD-L1

Chimiothérapie

OUTILS pour bâtir un traitement personnalisé dans le LF

- Caractérisation moléculaire, génomique, épigénomique: identification de cibles thérapeutiques potentielles pour éventuellement combiner les nouvelles molécules avec ou sans chimiothérapie

- Evaluation de la MRD: FDG-TEP, MRD biologique

Preliminary Biomarker Results

Biomarker	DLBCL (n=2)		Follicular Lymphoma (n=6)						Marginal Zone Lymphoma (n=3)		
Best Response	PR	PD	CR	CR	CR	CR	PR	PD	CR	PR	PR
Best % Change in Tumor Size	-98.7	-47.1	-94.7	-96.9	-97.2	-97.4	-89.2	+23.6	-97	-86.5	-52.9
Bcl-2 IHC	Pos	Neg	Pos	Pos	Pos	Neg	Pos	Pos	Pos	Pos	Pos
Bcl-XL IHC	Neg	Pos	Pos	Neg	Pos	Neg	Neg	Neg	Pos	Neg	ND
Mcl-1 IHC	Neg	Pos	ND	Neg	Neg	Pos	Neg	Neg	Neg	Neg	ND
c-MYC IHC	Pos	Pos	ND	Neg	Pos	Neg	Neg	Neg	Neg	Neg	ND
t(14;18) FISH	ND	Pos	ND	ND	Neg	Pos	Pos	Pos	-	-	-
BCL-2 Amp FISH	ND	Neg	ND	ND	Pos	Neg	Neg	Neg	-	-	-
c-MYC trans FISH	ND	Neg	ND	ND	Neg	Neg	Neg	Neg	-	-	-
Cell of Origin	ABC	GCB	-	-	-	-	-	-	-	-	-
Days on Venetoclax	109	34	934+	990+	444+	472+	597+	60	297+	661	206

Bcl-2 family IHC: (Pos) ≥ 50% tumor cell staining ≥ 2+ intensity; Myc IHC: (Pos) ≥ 40% positive nuclear staining of any intensity; (ND) not determined; (GCB) Germinal Center B-cell-like; (ABC) Activated B-cell-like

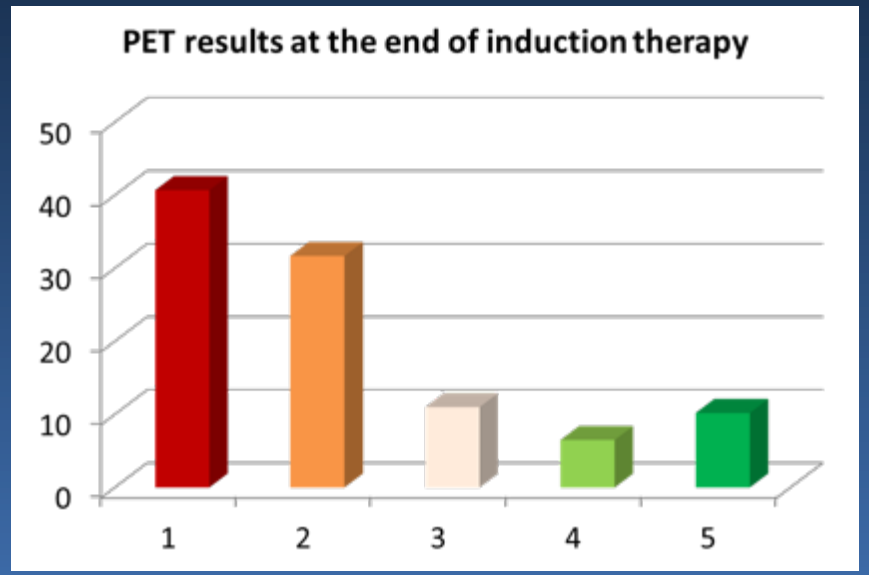
Adapted from the de Vos presentation at ICML on 20 June 2015

FDG-TEP-driven strategy in FL ?

Postinduction PET status (n = 246)

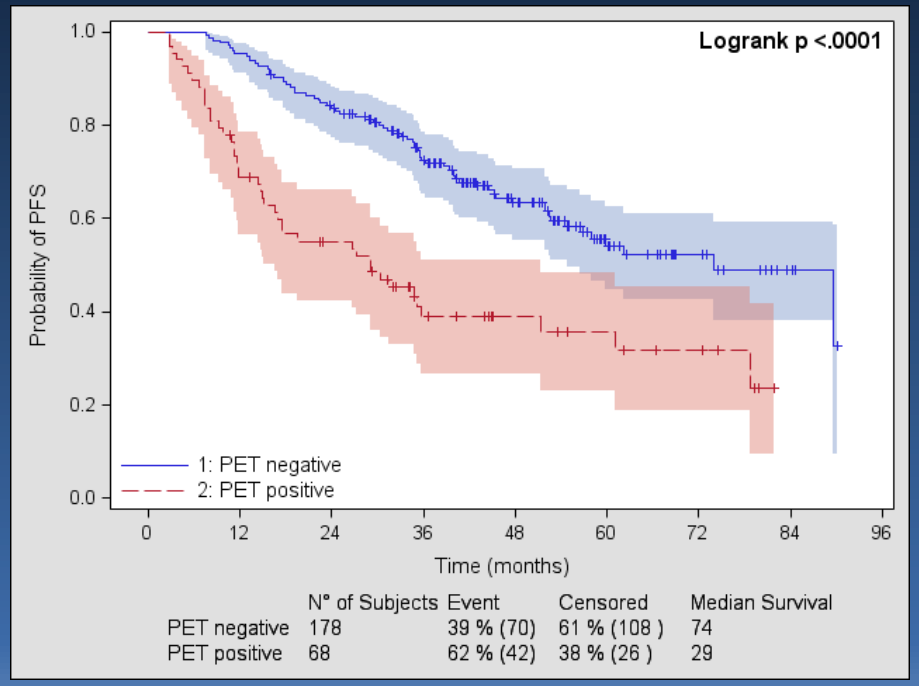
68 (28%) PET+ with cut-off ≥3 (uptake > mediastinum)

41 (17%) PET+ with cut-off ≥4 (uptake moderately > liver)

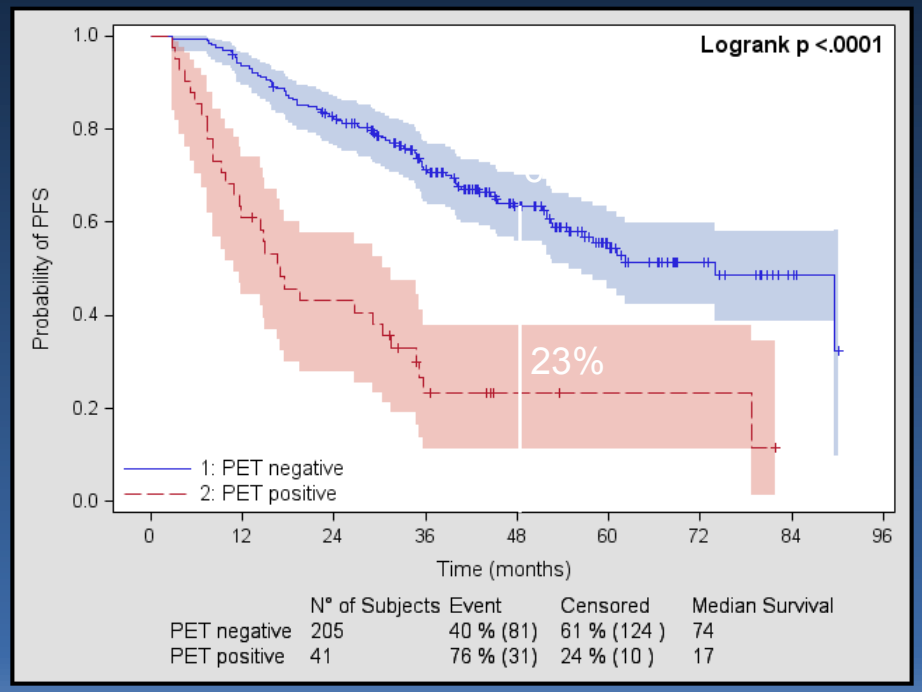


Both PET cut-offs predictive of PFS

Score ≥3

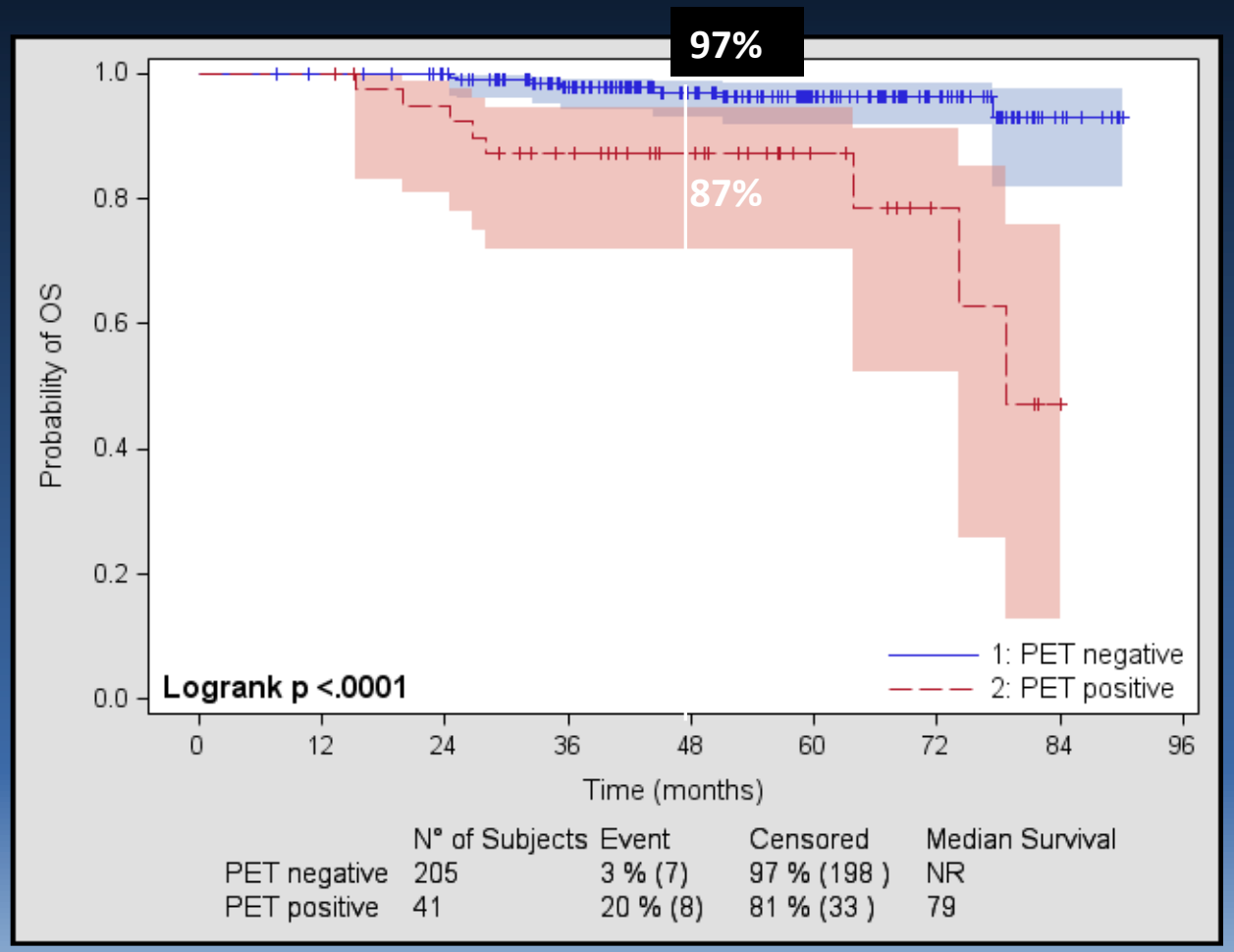


Score ≥4



HR 3.9 (95% CI 2.5-5.9, p<.0001)
Median PFS:
16.9 (10.8-31.4) vs. 74.0 mo (54.7-NR)

Postinduction PET status (cut-off ≥4) and Overall Survival



HR 6.7, 95% CI 2.4-18.5, p=0.0002

Median OS: 79 months vs. NR

CONCLUSION (1): enthousiasme et prudence

- Nombre impressionnant de nouvelles molécules ciblées
- Développement sans précédent des outils de caractérisation tumorales et d'evaluation de la MRD

MAIS

- Garder en tête que LF = lymphome indolent
- Patients ont une longue durée de vie: efficacité et tolérance +++
- Les nouvelles molécules ne sont pas sans toxicité
- Les combinaisons des nouvelles molécules encore moins
- A l'inverse les toxicités (court, moyen et long) de la chimiothérapie sont bien connues
- DONC GARDER UN SENS CLINIQUE +++

CONCLUSION (2): les fondamentaux = les AMM

Assympt.
FLIPI low
No GELF
Non bulky

Sympt. modéré
FLIPI low/inter
Non bulky
Agés ou fragiles

Symptomatique
FLIPI inter/high
Bulky
GELF

Surveillance

Traitement sans chimio

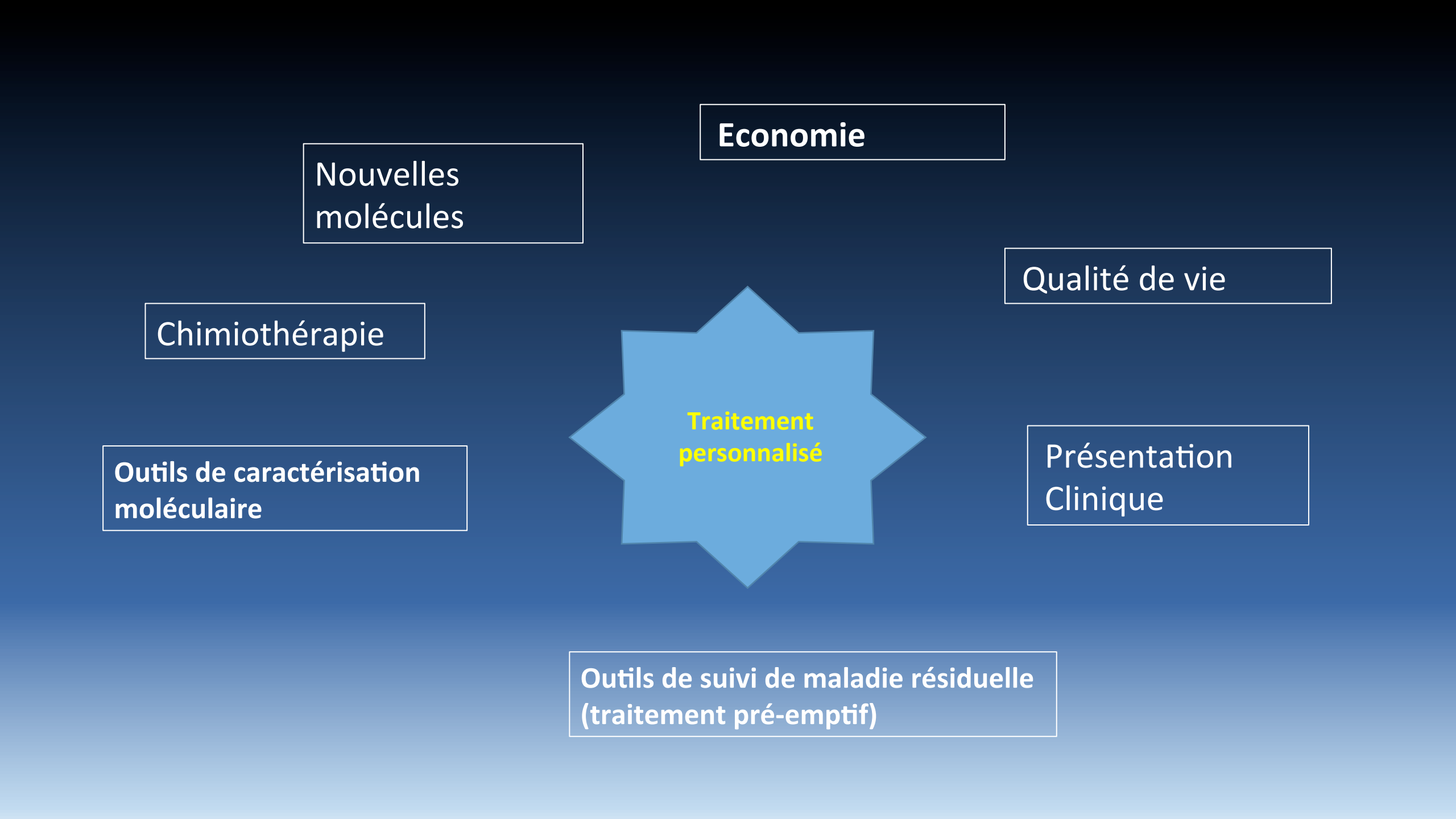
Rituximab seul

Radiothérapie (localisée)

Radio-immunothérapie ?

Traitement R-chimio

Rituximab-CHOP
CVP
Bendamustine
+
R maintenance


Economie
Nouvelles molécules
Qualité de vie
Chimiothérapie
Traitement personnalisé
Outils de caractérisation moléculaire
Présentation Clinique
Outils de suivi de maladie résiduelle (traitement pré-emptif)

MERCI

Pr Le Gouill Steven
CHU de Nantes
France
Maroc, Mai 2017

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