Traitement de 1L des Lymphomes Folliculaires

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Outline

- What is the situation in 1L ?
- What are the questions in the therapy of 1L low tumor burden FL ?
- What are the questions in the therapy of 1L high tumor burden FL ?

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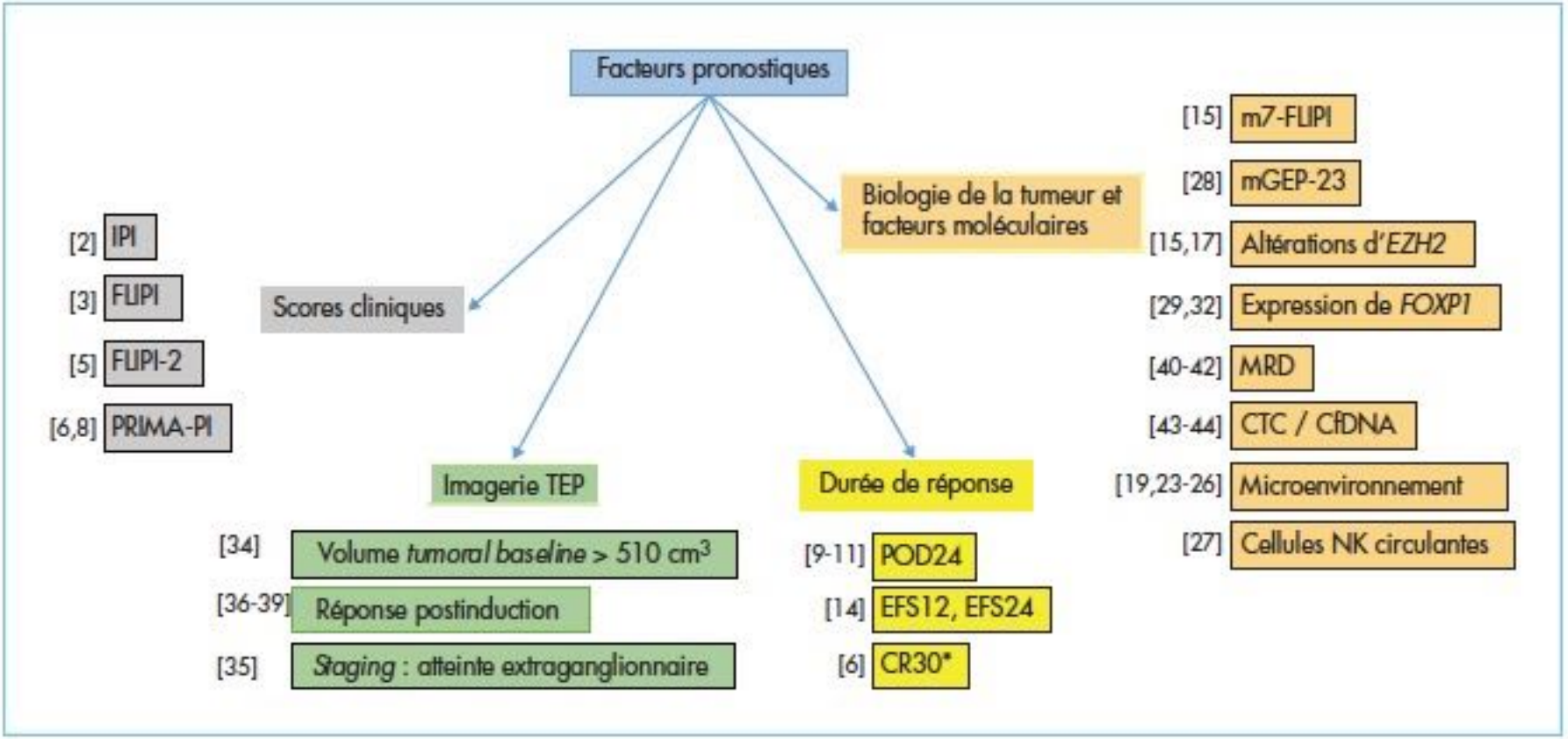
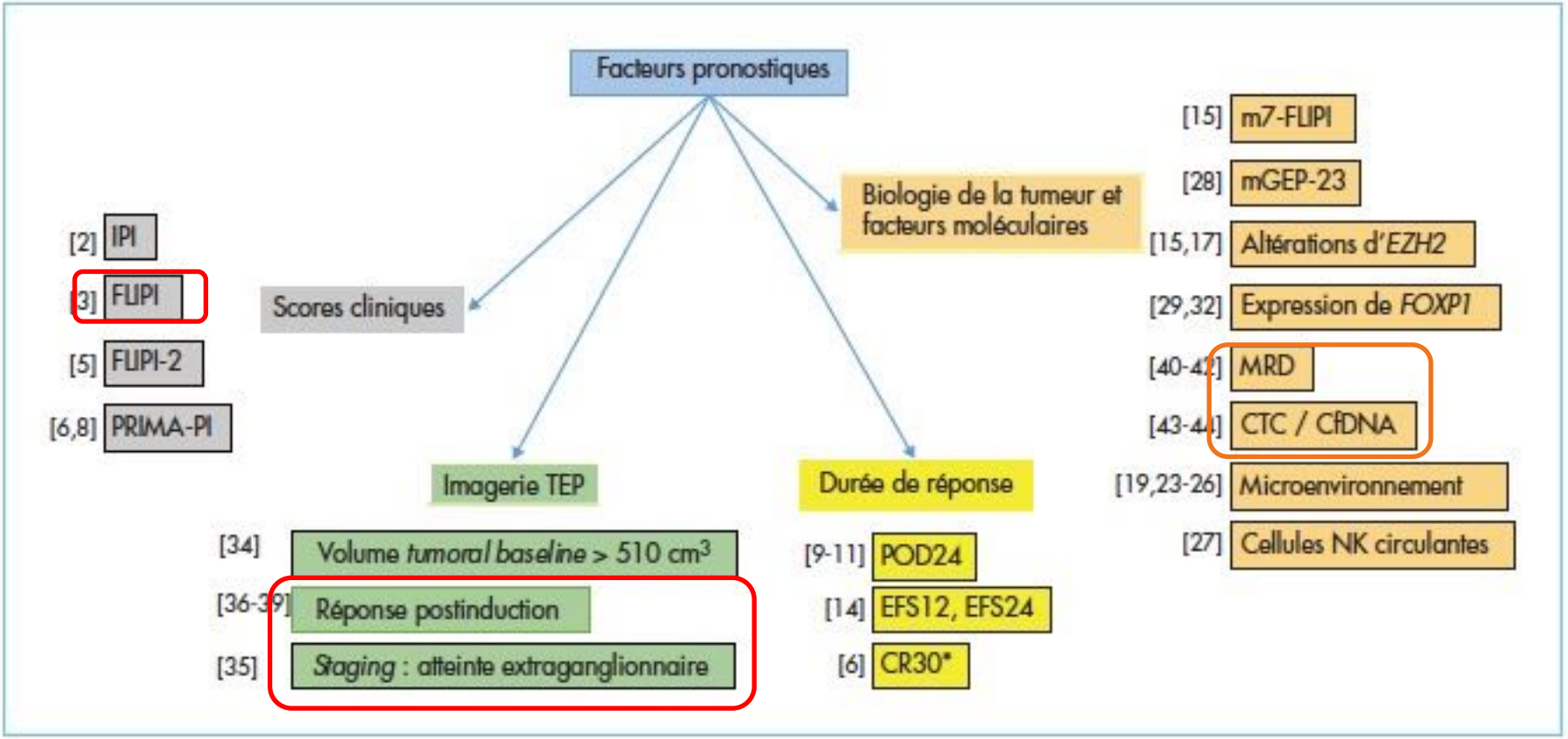
Liste des facteurs pronostiques



Liste des facteurs pronostiques: que faisons-nous en RCP ?

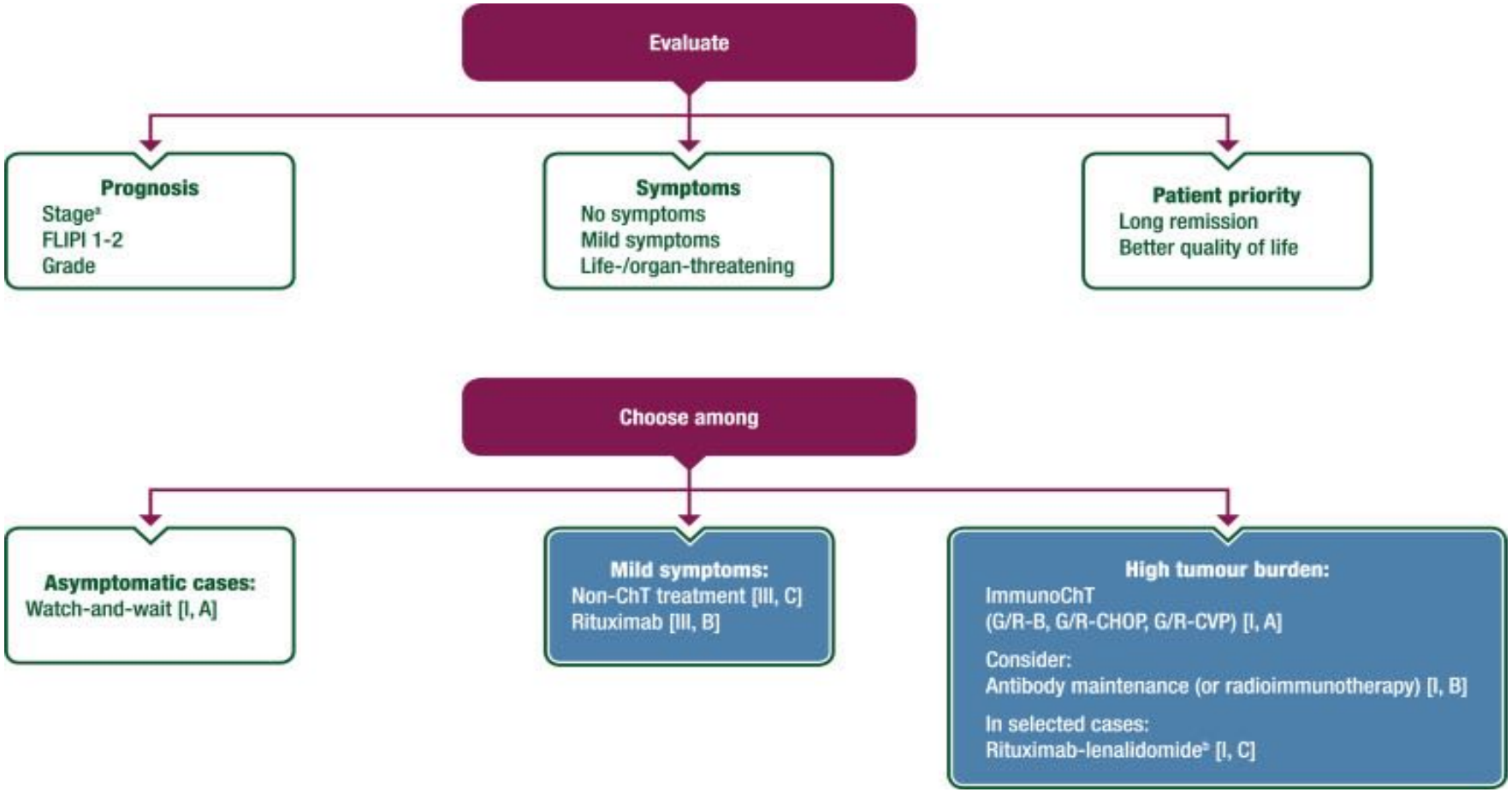


Induction d'une RCM, +/- Maintenance de cette réponse dans le temps

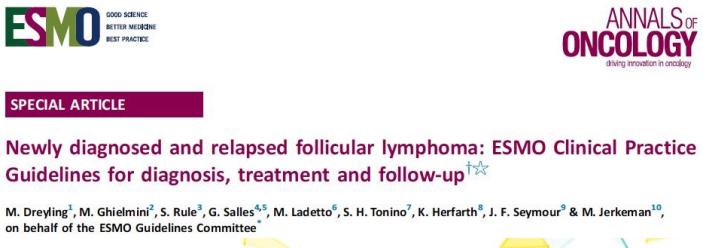
MRD, ctDNA…: outils en cours d'évaluation

Aucun traitement guidé par le profil mutationnel…

Nous avons des recommendations basées sur: choix du malade, scores FLIPI/GELF et dissémination de la maladie



Dreyling M, ESMO guidelines 2020



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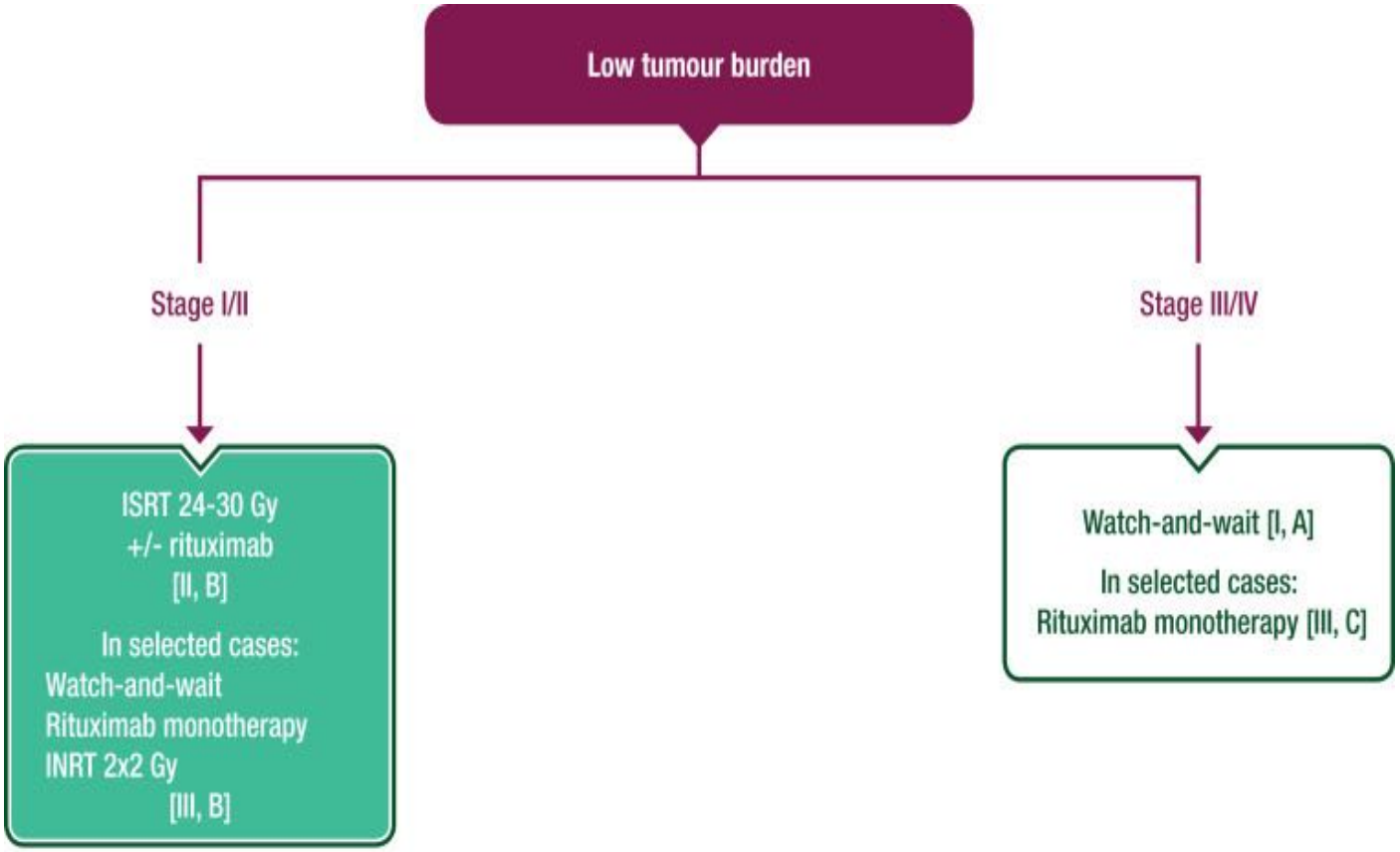

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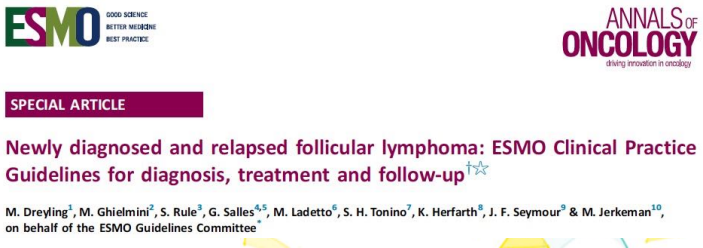
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†☆

M. Dreyling[1], M. Ghielmini[2], S. Rule[3], G. Salles[4,5], M. Ladetto[6], S. H. Tonino[7], K. Herfarth[8], J. F. Seymour[9] & M. Jerkeman[10], on behalf of the ESMO Guidelines Committee*

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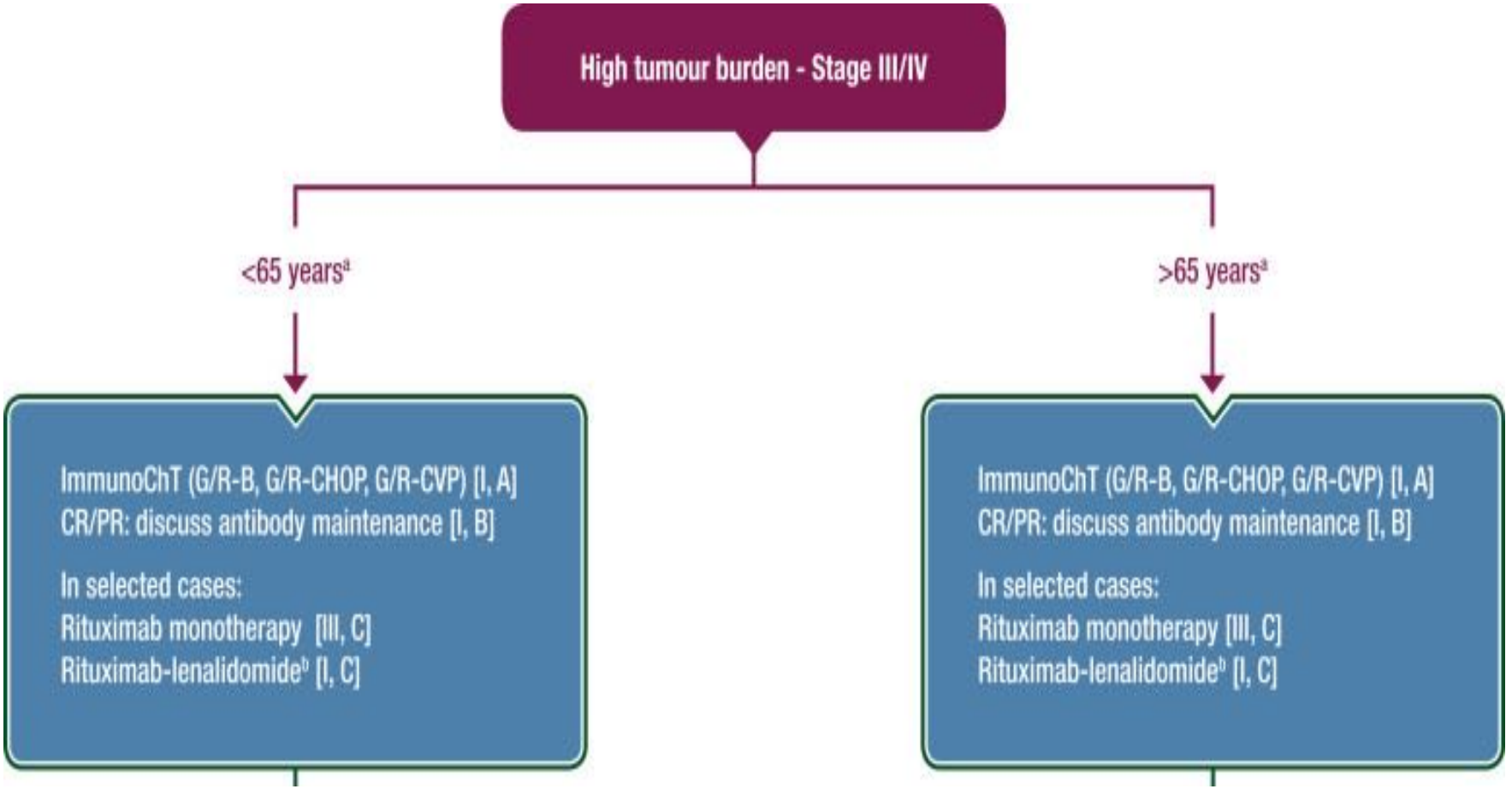


Dreyling M, ESMO guidelines 2020

Que devons-nous améliorer ?

Follicular lymphoma

„Aggressive FL“ (20%) ← need to be identified → **„Indolent FL“ (80%)**

Immunochemotherapy alone
not sufficient
Greatest need for novel approaches

Patients benefit from
immunochemotherapy
Some patients are overtreated?

High risk model = prediction of OS

Most models in FL predict PFS (not a surrogate of OS)

new therapies have to

- identify biomarkers
- define targets
- enable tailored therapy
  (+/- chemotherapy)

new therapies have to

- reduce toxicity (early – late)
- maintain/increase efficacy
- be economically acceptabel

Individualization of therapy
Avoid over/under-treatment
Optimize outcomes for patients and population

Adapted from Dreyling M, ESMO 2017

What is the situation – 1L

- What do we use in practice ?
- What do patients and clinicians need ?
- Do patients still die from FL ?

Quel est le but du traitement ?

- **Un cancer :**
  - -- > ne pas en mourir !
  - - - > guérir ?
- **Pour le clinicien :**
  - OS, PFS, EFS, DOR, réponse globale, réponse complète
  - Toxicités & AE/SAE
  - Critères de susbtitution, analyses de sous-groups
- **Pour les patients :**
  - Supprimer les symptômes liés au traitement
  - Limiter / éviter les effets secondaires liés aux traitements à court & long terme
  - Anxiété du risque de rechute
  - Lourdeurs / contraintes des traitements répétés

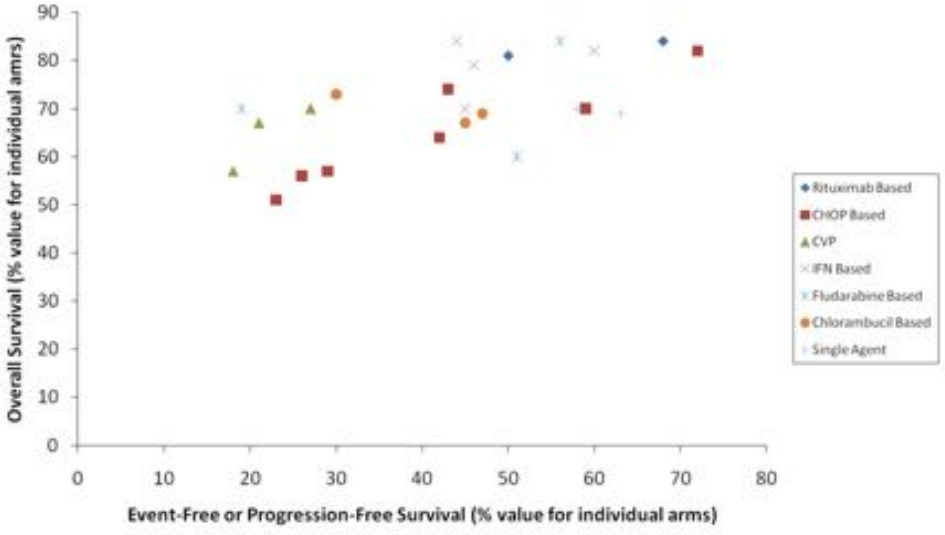
→ **Bien analyser les données,**

→ **Éviter les déductions trop intuitives**

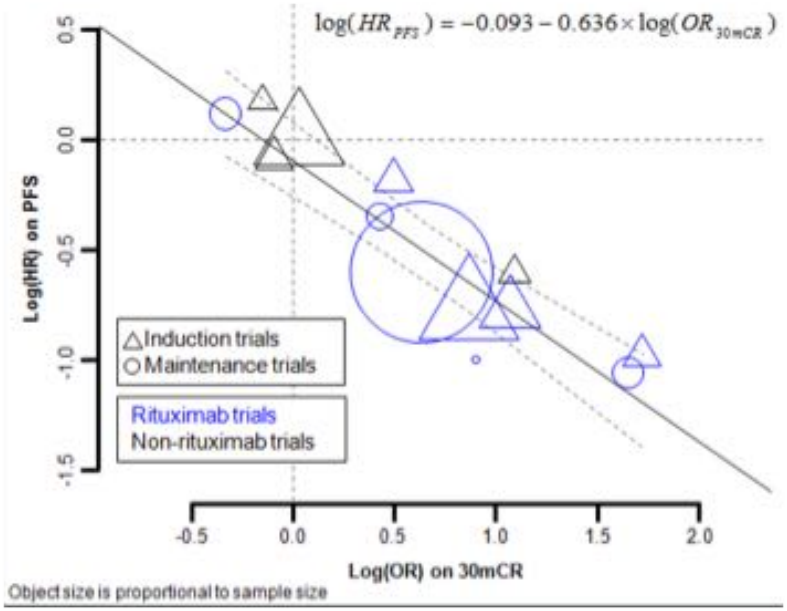
→ **…mais savoir interpréter le contexte médical**

RC à 30 mois: critère de substitution de la PFS

Absence de corrélation entre RC et EFS[1]



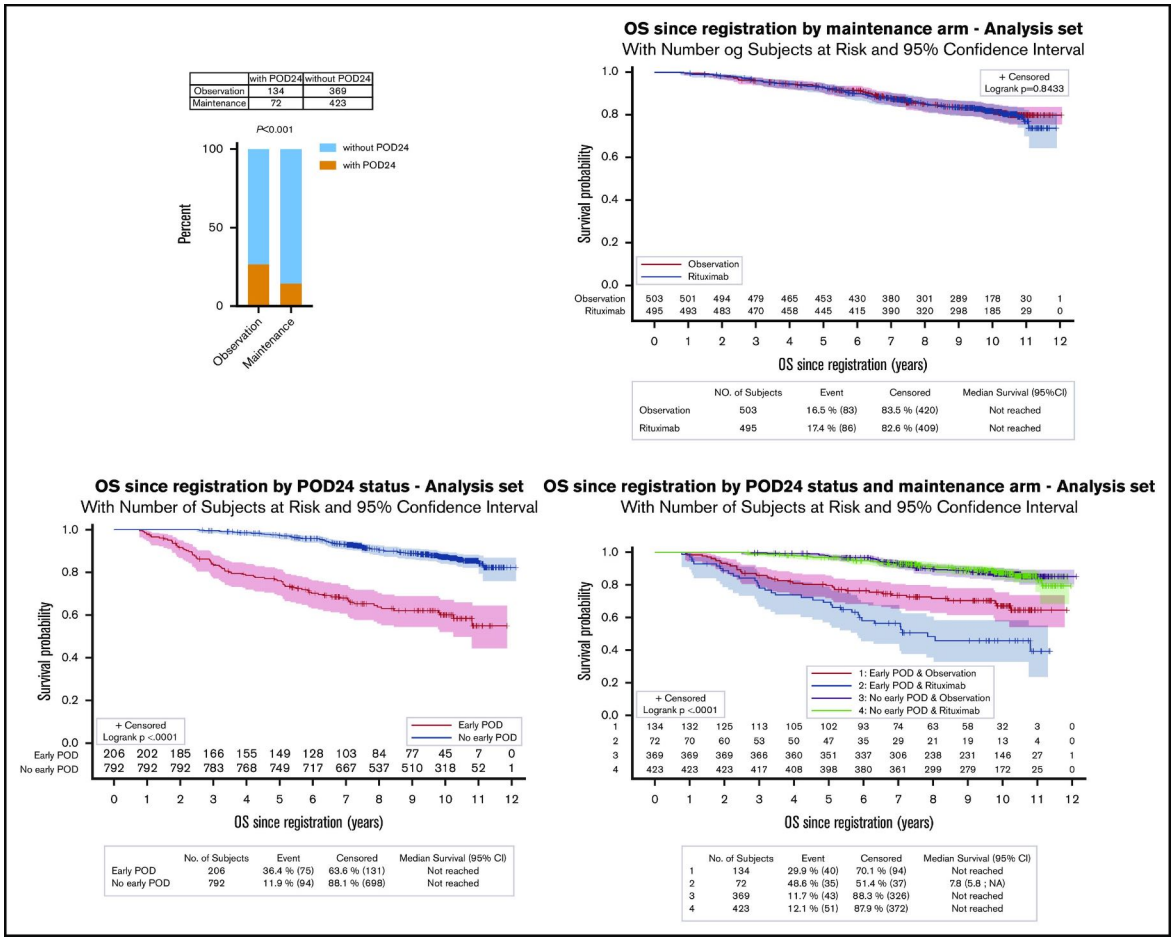
Réponse à 30 mois et EFS (Projet FLASH)[2]



30 months complete response rate
met the prespecified surrogacy qualification criteria for PFS

1. Lee et al, Ann Oncol 2011; 2. Shi et al., JCO 2017

POD24: vraiment un critère de substitution de l'OS ?



PRIMA 9 ans

Bras RM: moindre OS que obs. (maladie agressive, FLIPI3-5)

Ne pas comparer deux traitements sur leurs % de POD24 en déduisant que l'OS des LF va augmenter…

Bachy E, Blood Adv 2021

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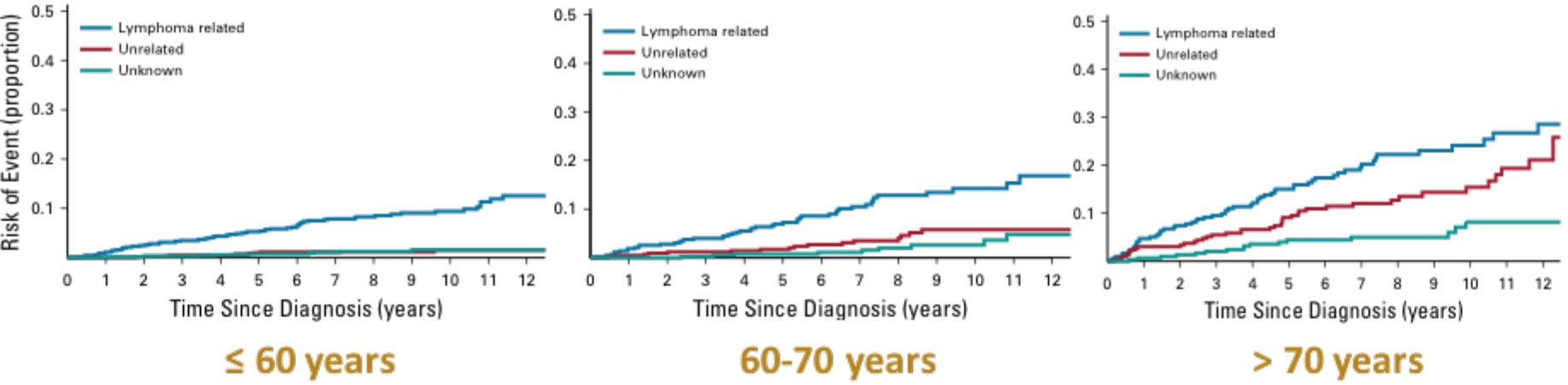
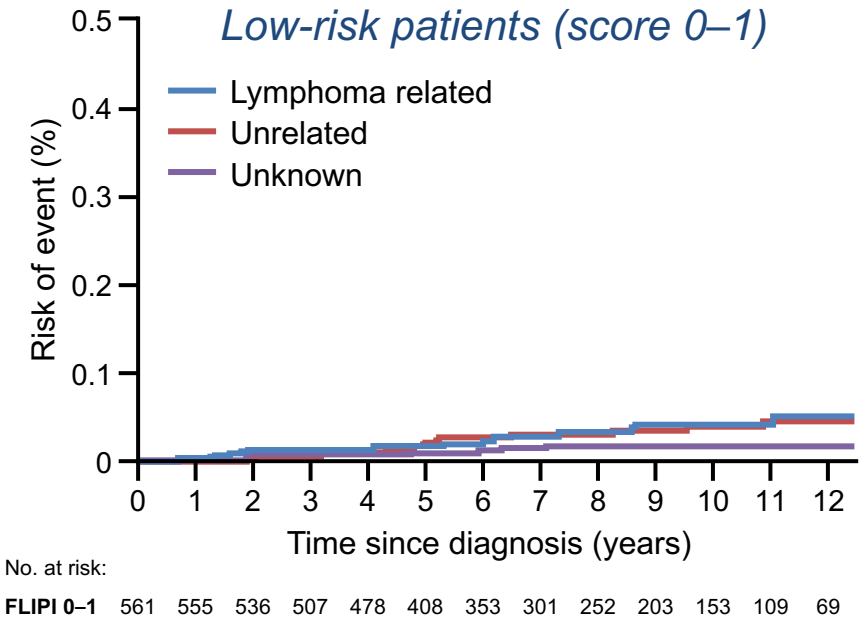
Mortalité selon la tranche d'âge

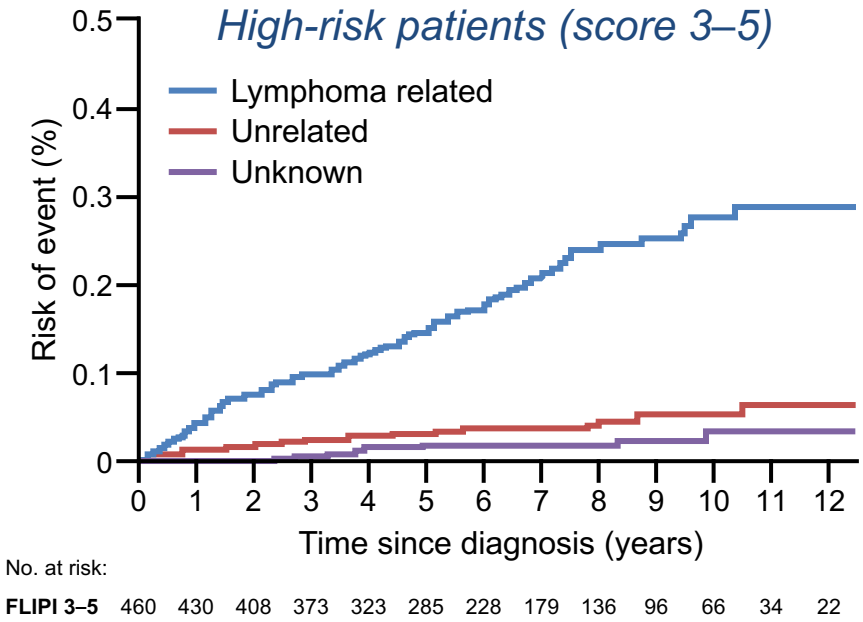


- Sarkozy C, et al. J Clin Oncol 2019;37:144–52

Le score FLIPI est corrélé à la *mortalité spécifique par LF*

US and French Cohorts (vrai quel que soit l'âge…)

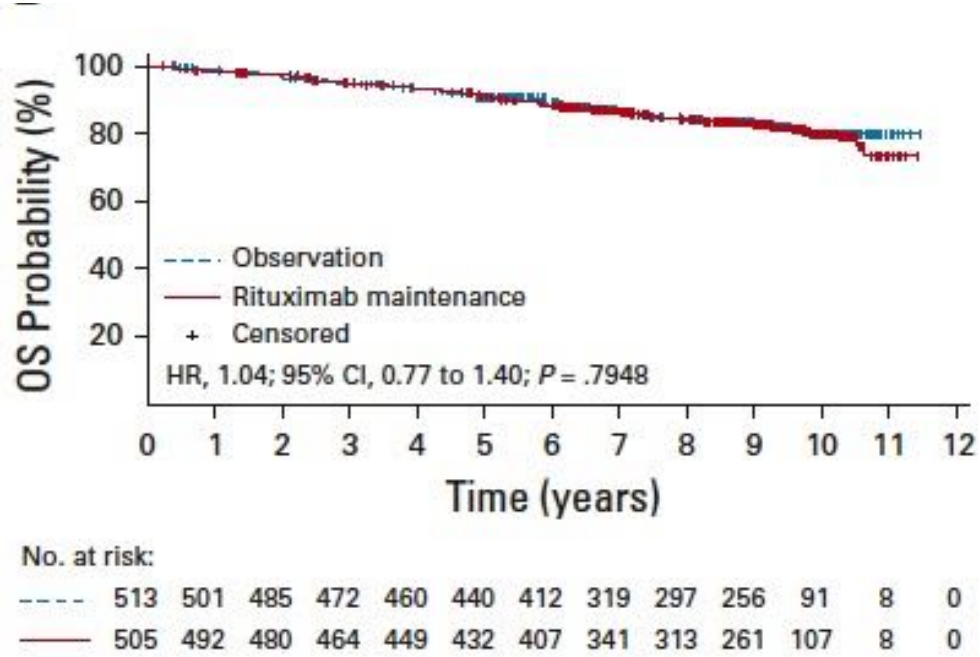




- Sarkozy C, et al. J Clin Oncol 2019;37:144–52

Nous avons amélioré la survie des patients: *meurt-on d'un LF ?*

PRIMA study (9 ans de suivi)



Causes de décès: observation *vs* maintenance

Progression du LF:	47,6%	51.1%
Cancer solide:	20%	5.7%
MDS/LAM:	8.3%	4.6%
Infection:	6%	12.5%
Cardiovasculaire:	6%	10%

Bachy E, et al. J Clin Oncol 2019

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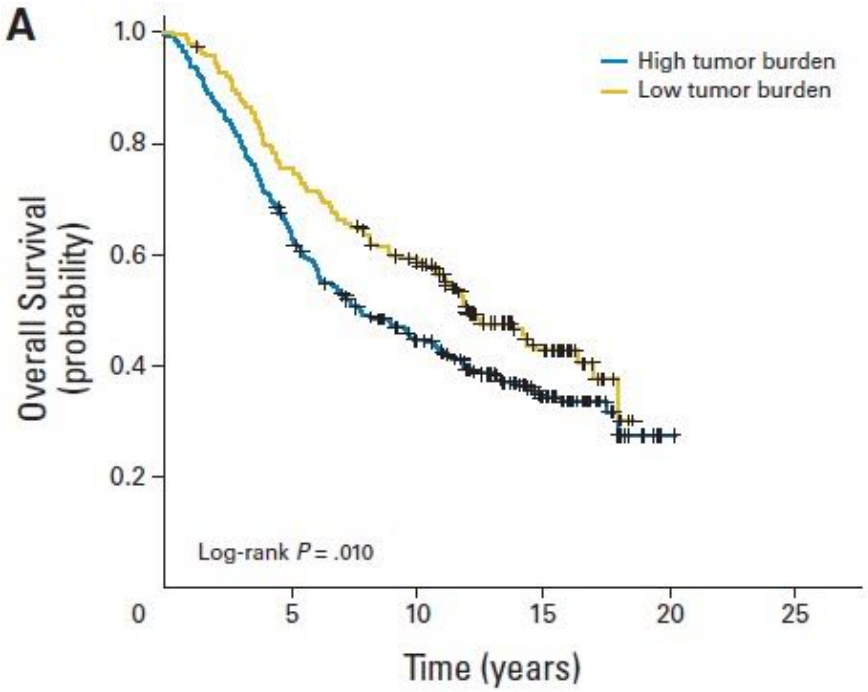
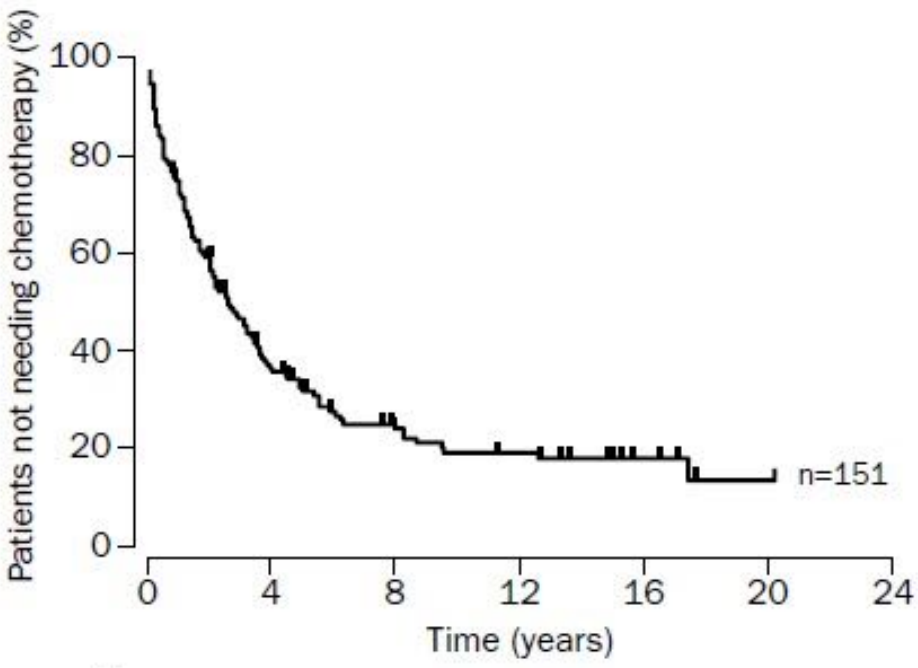
- What are the questions in the therapy of 1L high tumor burden FL ?

What are the questions – 1L Low Tumoral Burden (GELF=0)

- A different disease? What if we do nothing….
- Which options ?

20% jamais traités, et de longues durées d'OS





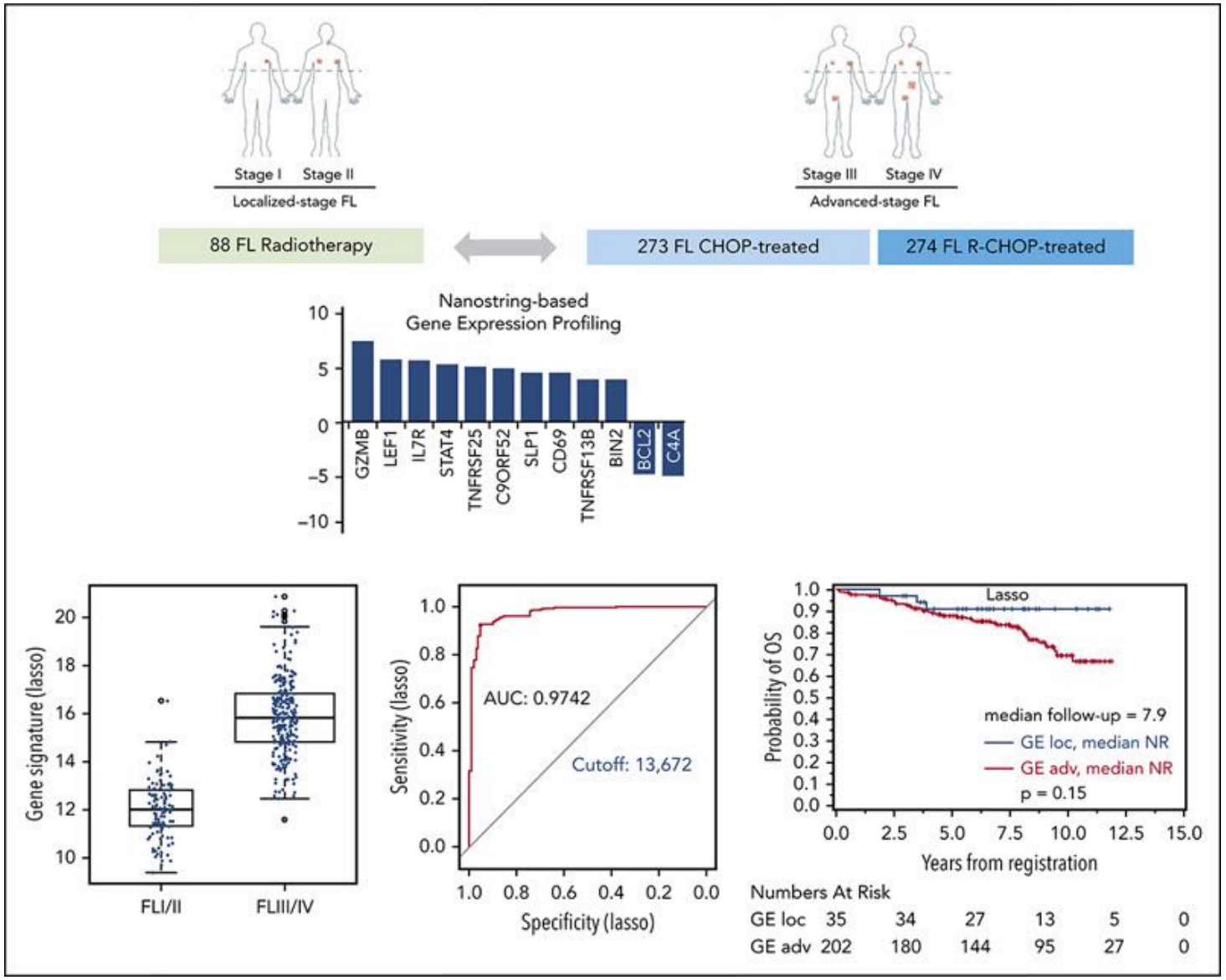
GELF 86:
Median follow-up: 9.8 y
OS: 45% at 10 years

Figure 3: **Time to first systemic treatment for patients in the observation group**
At 10 years, 19% (95% CI 13–27) of patients either did not need chemotherapy or died of lymphoma (non-lymphoma deaths were censored).

Alrdeshna KM, et al. Lancet. 2003;362:-516-522

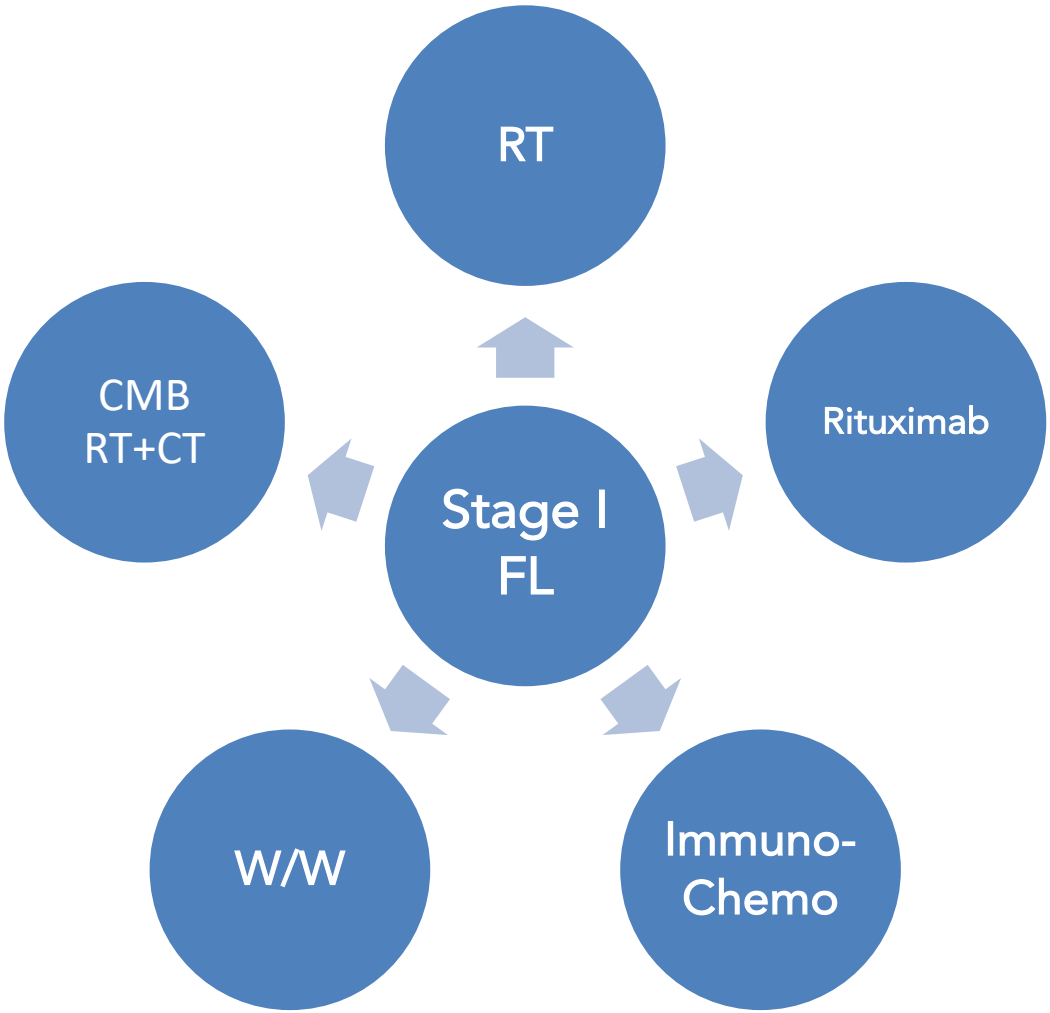
Bachy E et al, J Clin Oncol 2010,28: 822-828

Profil génomique des LF faible masse



Staiger A, Blood 2020

Pas de consensus…



Radiothérapie

Radiation for Follicular Lymphoma/Pugh et al[5]

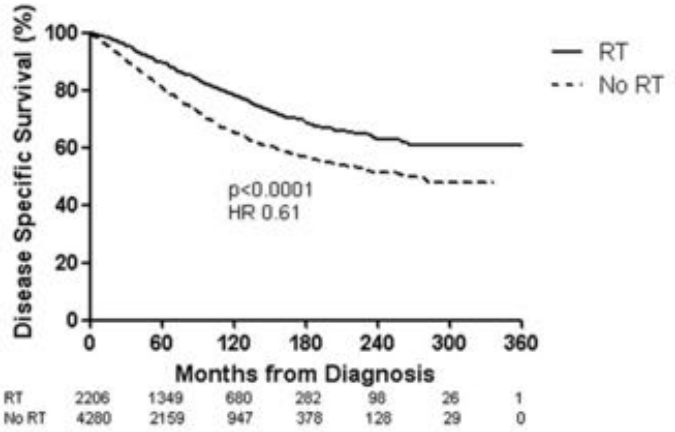


Figure 1. Non-Hodgkin lymphoma-specific survival with or without upfront external beam radiation therapy (RT) is shown. HR indicates hazard ratio.

- ✓ A 24 Gy XRT dose provides equivalent results to 40-45 Gy [1]
- ✓ In patients with high risk features (bulk, high LDH, grade 3), other options are recommended [2]
- ✓ Staging using PET-CT and BM is recommended [3]
- ✓ Relapses are not infrequent [1, 3, 4]

1. Lowry et al. Radiother Oncol, 2011
2. NCCN & ESMO Guidelines
3. Friedberg , et al. JCO 2012
4. Plancarte et al. Eur J Haematol. 2006
5. Pugh et al. Cancer 2010

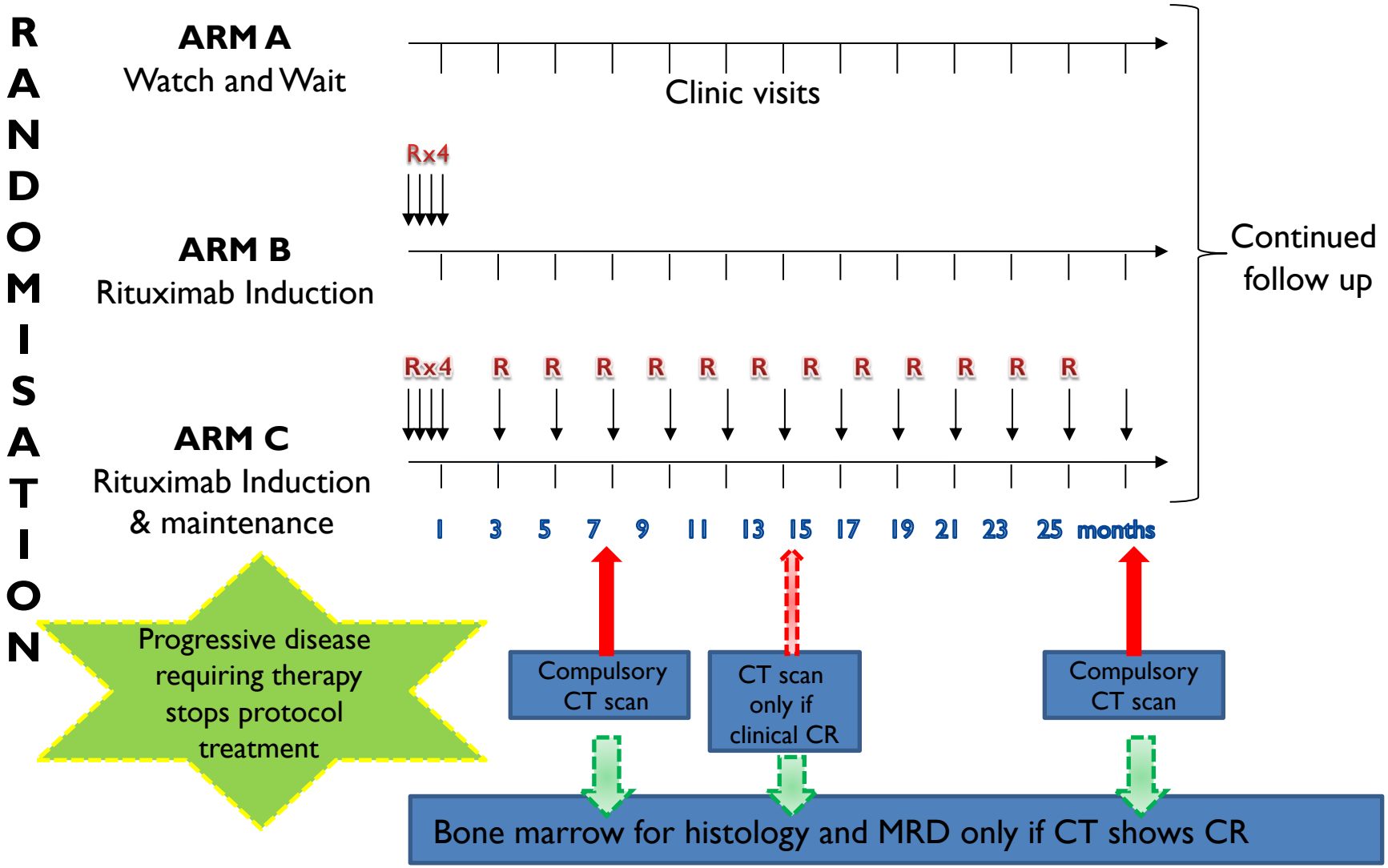
Essai « Comparison » de LymphoCare (USA)

	XRT N=56	Obs N=35	Ritux N=25	R-chemo N=57	Chemo XRT N=26
Number of PFS events (%)	18 (32%)	9 (26%)	6 (24%)	9 (16%)	1 (4%)
Unadjusted HR (95% CI) [relative to radiotherapy]	---	0.93 (0.42, 2.08)	0.65 (0.26, 1.63)	0.39 (0.18, 0.87)	0.09 (0.01, 0.67)
Adjusted* HR (95% CI) [relative to radiotherapy]	---	1.02 (0.45, 2.34)	0.56 (0.21, 1.48)	0.36 (0.16, 0.82)	0.11 (0.01, 0.83)

*Adjusted for: grade, LDH, and B-symptoms

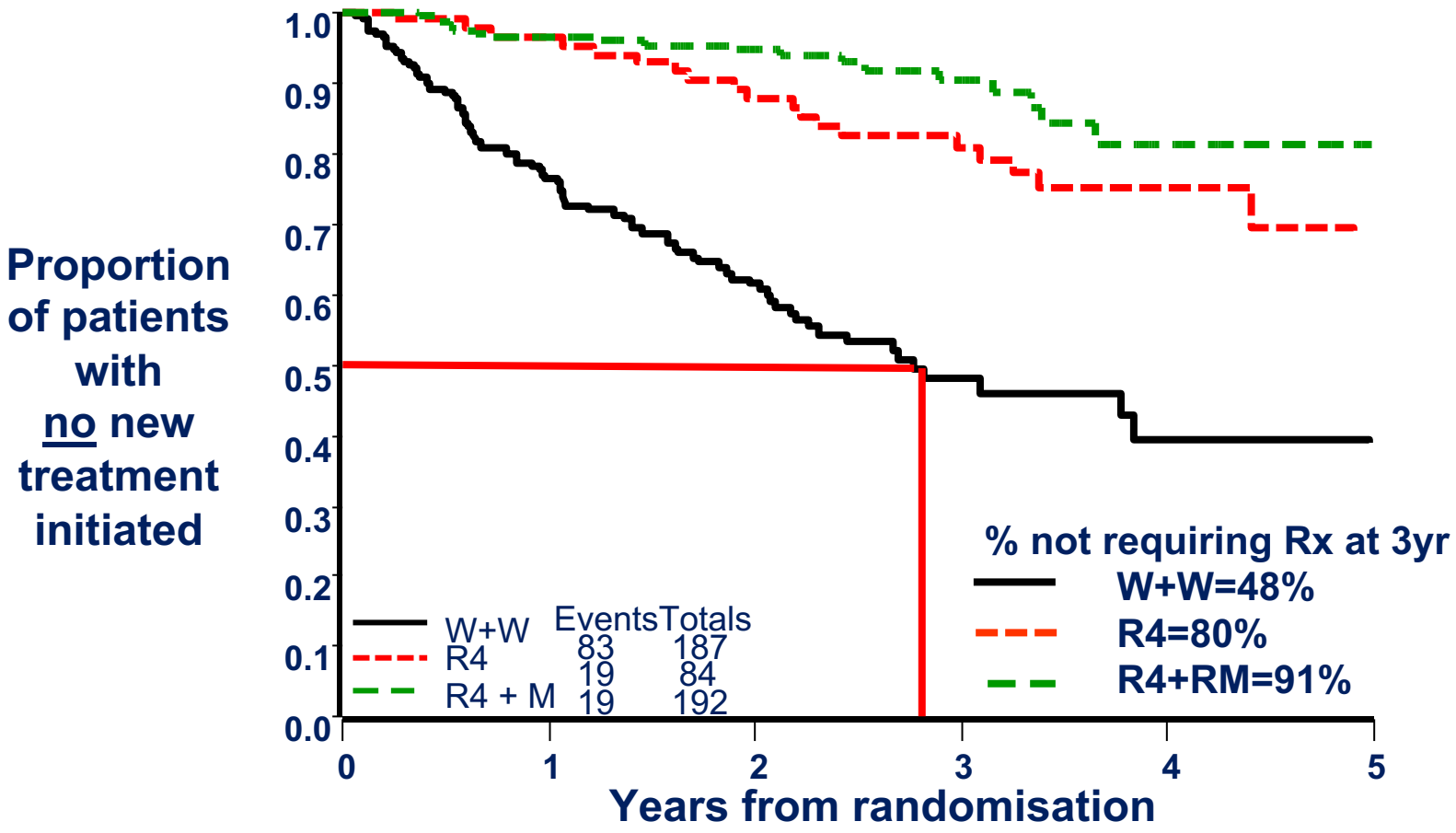
Friedberg JW, J Clin Oncol. 2012 Sep 20;30(27):3368-75.

Essai RWW



Ardeshna *et al. Lancet Oncol*, 2014; 14: 424-435

Essai RWW



HR (Rituximab vs W+W) = 0.37, 95%CI = 0.25, 0.56, p<0.001

HR (Rituximab + M vs W+W) = 0.20, 95% CI = 0.13, 0.29, p <0.001

HR (Rituximab + M vs Rituximab) = 0.57, 95% CI = 0.29, 1.12, p =0.10

Ardeshna *et al. Lancet Oncol*, 2014; 14: 424-435

Essai RESORT

Experimental arms

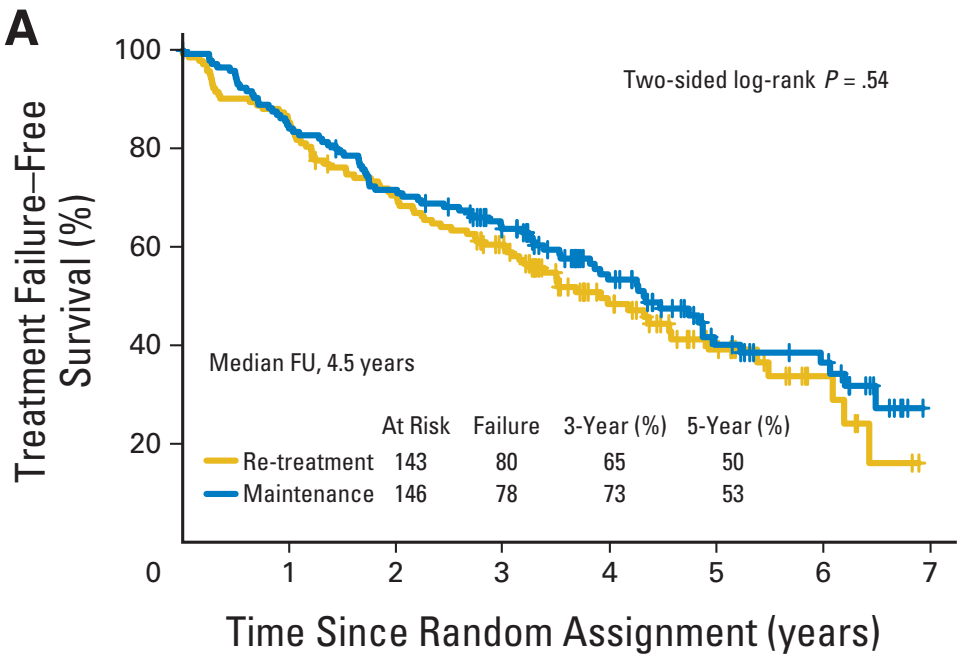
Induction therapy

Rituximab (375 mg/m²)
4 × once weekly cycles
(N = 384)

Responders
(n = 274)
randomized

Rituximab maintenance
Rituximab single dose q3mo
(n = 140)

Rituximab retreatment
Rituximab (375 mg/m² 4 × once weekly cycles at disease progression) (n = 134)



Conclusions des essais RWW et RESORT

- **W/W est le standard**
- Mais
  - Rituximab est sécure
  - Rituximab augmenteTTNT and PFS
  - Rituximab Retraitment à la progression vs maintenance : même TTNT avec moins de dépenses/sélection clonale
- Selon le choix du patient/médecin, **W/W ou RTX x 4 sont des options acceptables**

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What are the questions – 1L HTB

- Induction phase:
  - What is the best chemo backbone ?
  - What is the best MoAb backbone ?
- Which maintenance ?
- Chemo-sparing options: an ideal candidate would:
  - Be *more effective* than R-chemo (and RM) in high risk disease
  - Be *less toxic* in patients with good outcome
  - Be *targeted* on a vital pathway for a dedicated FL/TME

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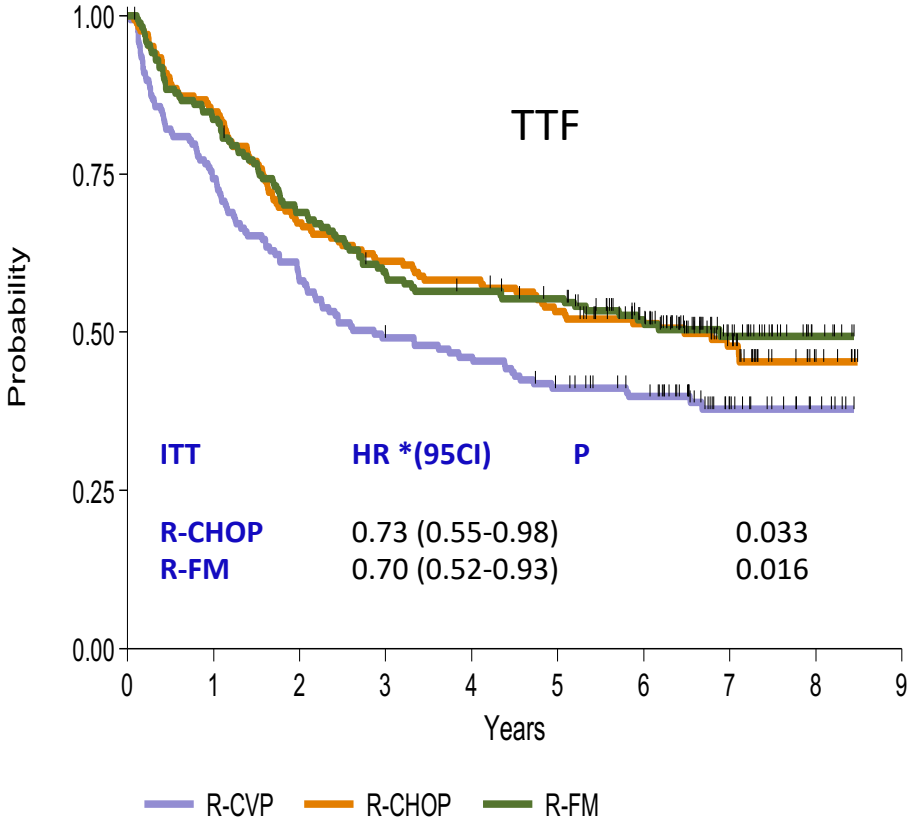
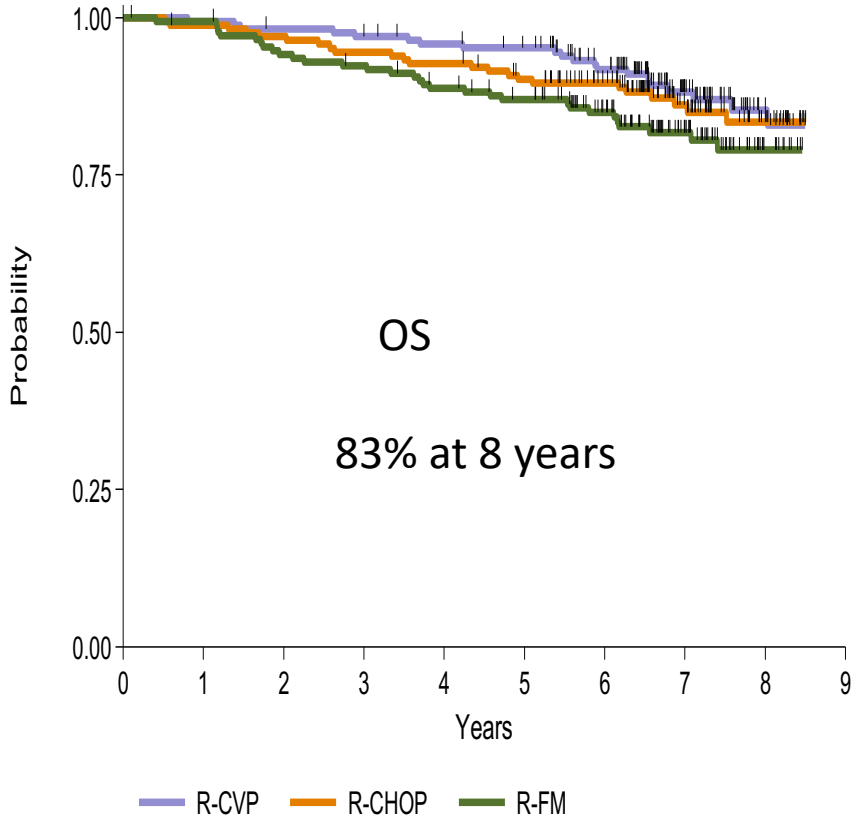
FOLL05 Study
R-CVP vs R-CHOP vs R-FM

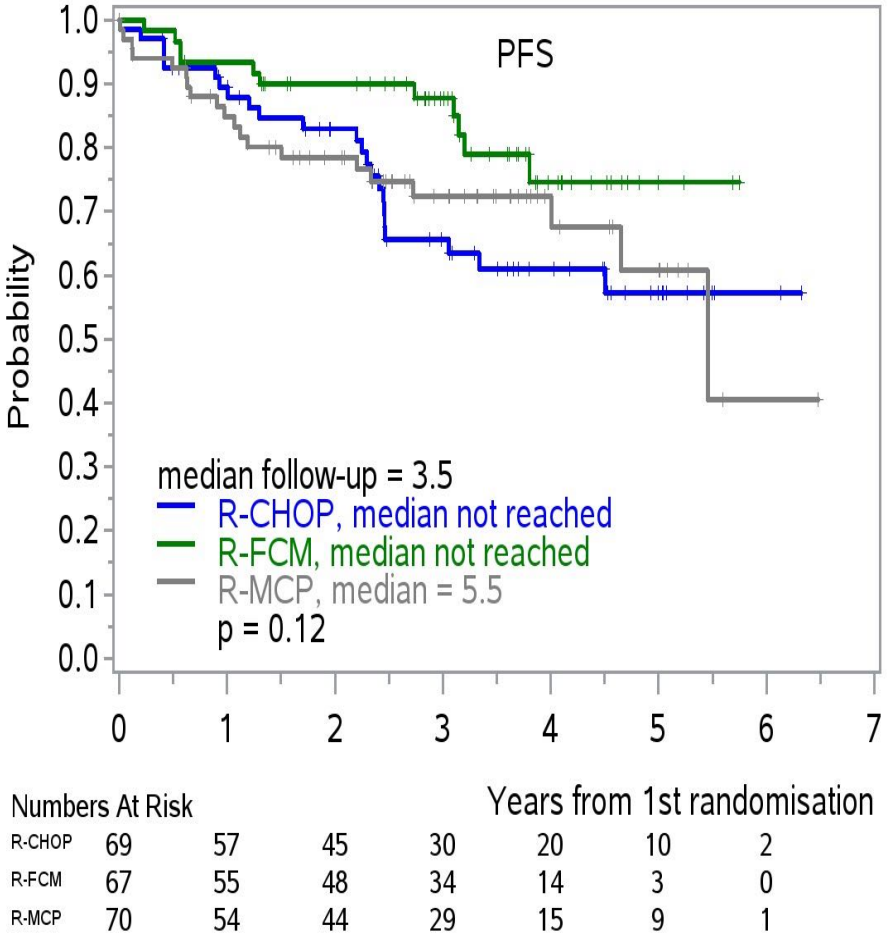
N = 500, median FU 7 years



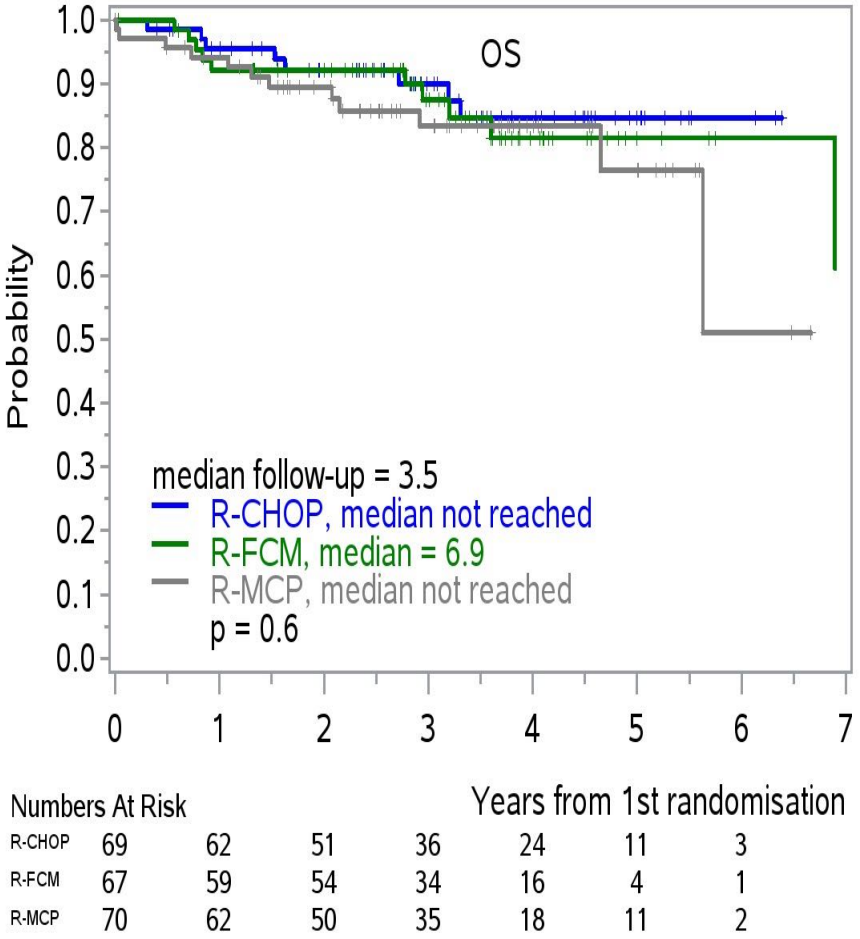


Luminari et al, JCO 2018

R-CHOP vs R-FCM vs R-MCP
GLSG and OSHO N=205 FL



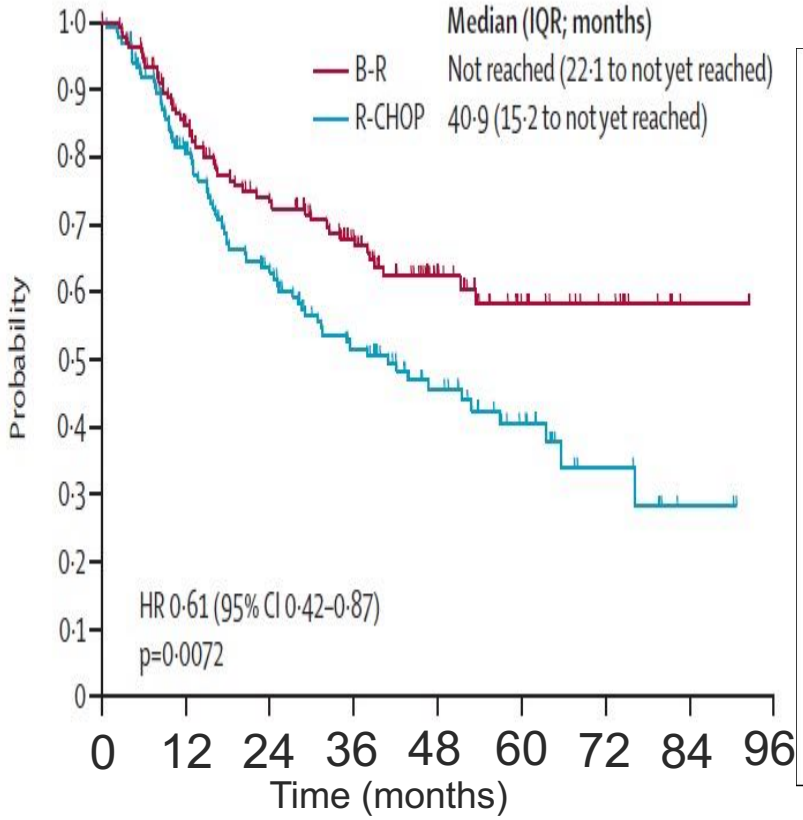
Numbers At Risk							
R-CHOP	69	57	45	30	20	10	2
R-FCM	67	55	48	34	14	3	0
R-MCP	70	54	44	29	15	9	1

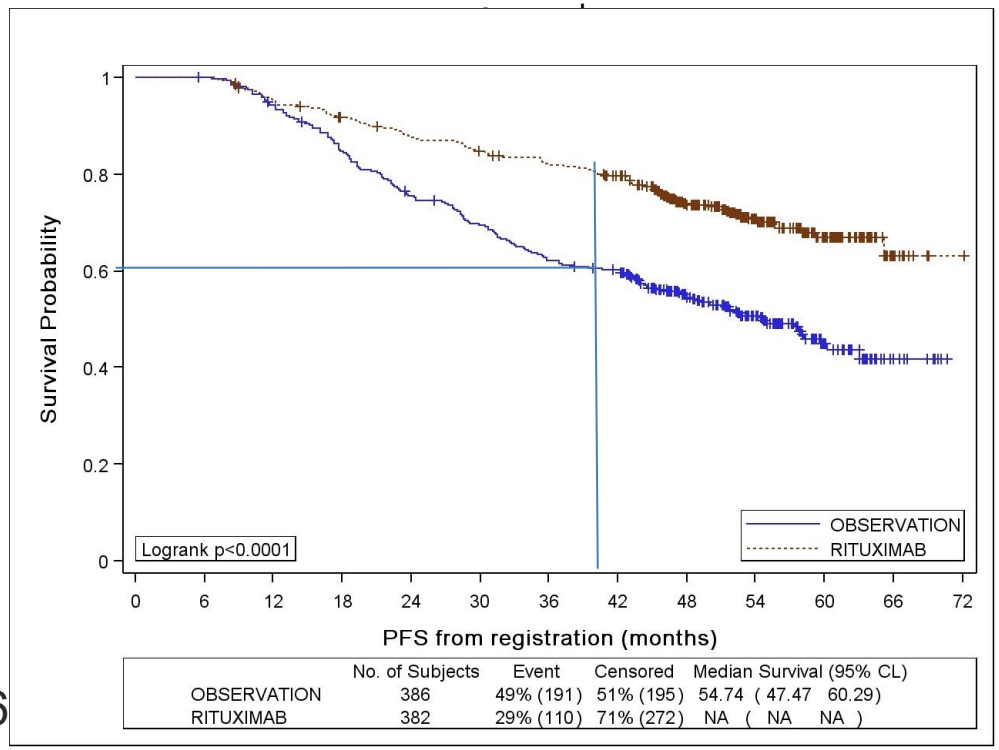


Numbers At Risk							
R-CHOP	69	62	51	36	24	11	3
R-FCM	67	59	54	34	16	4	1
R-MCP	70	62	50	35	18	11	2

Hoster et al, ICML 2017, abstr 13

R-Benda vs R-CHOP: StiL vs BRIGHT study (PFS)

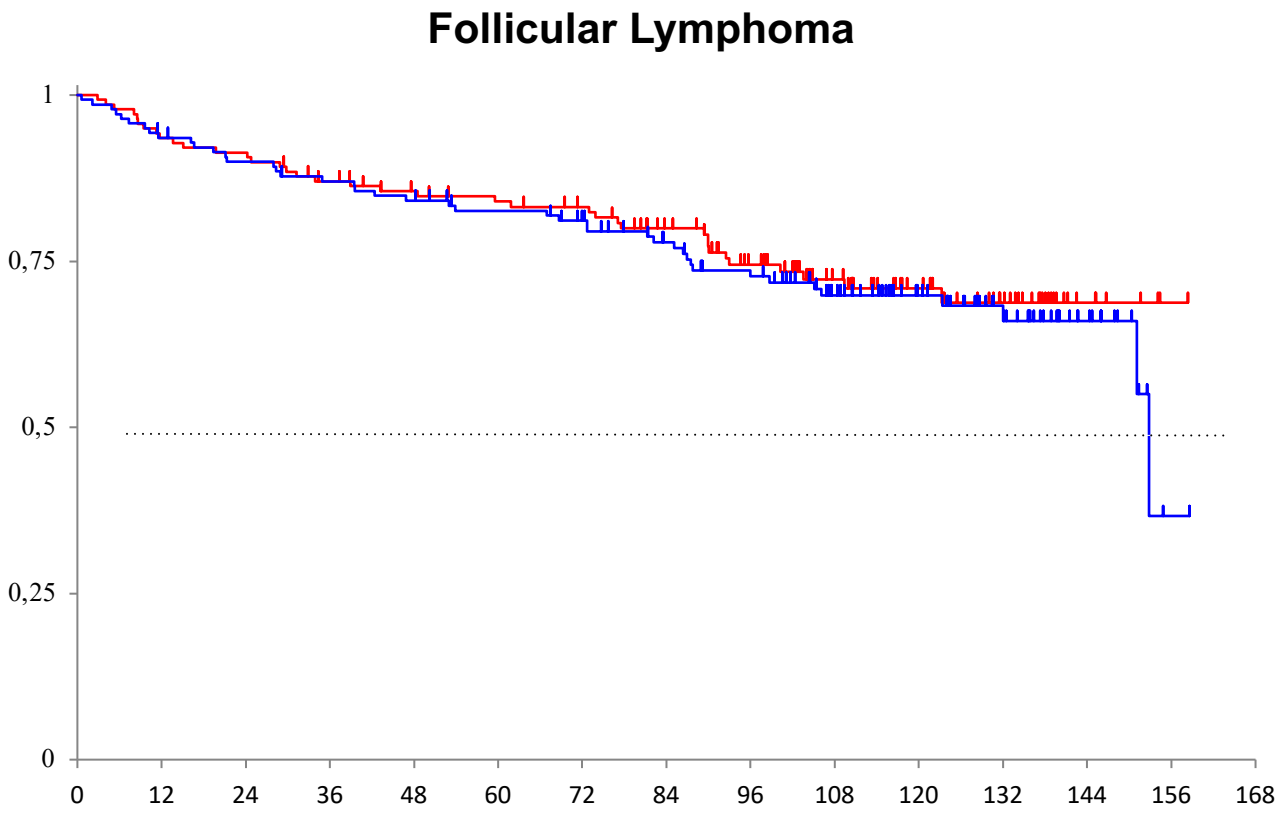




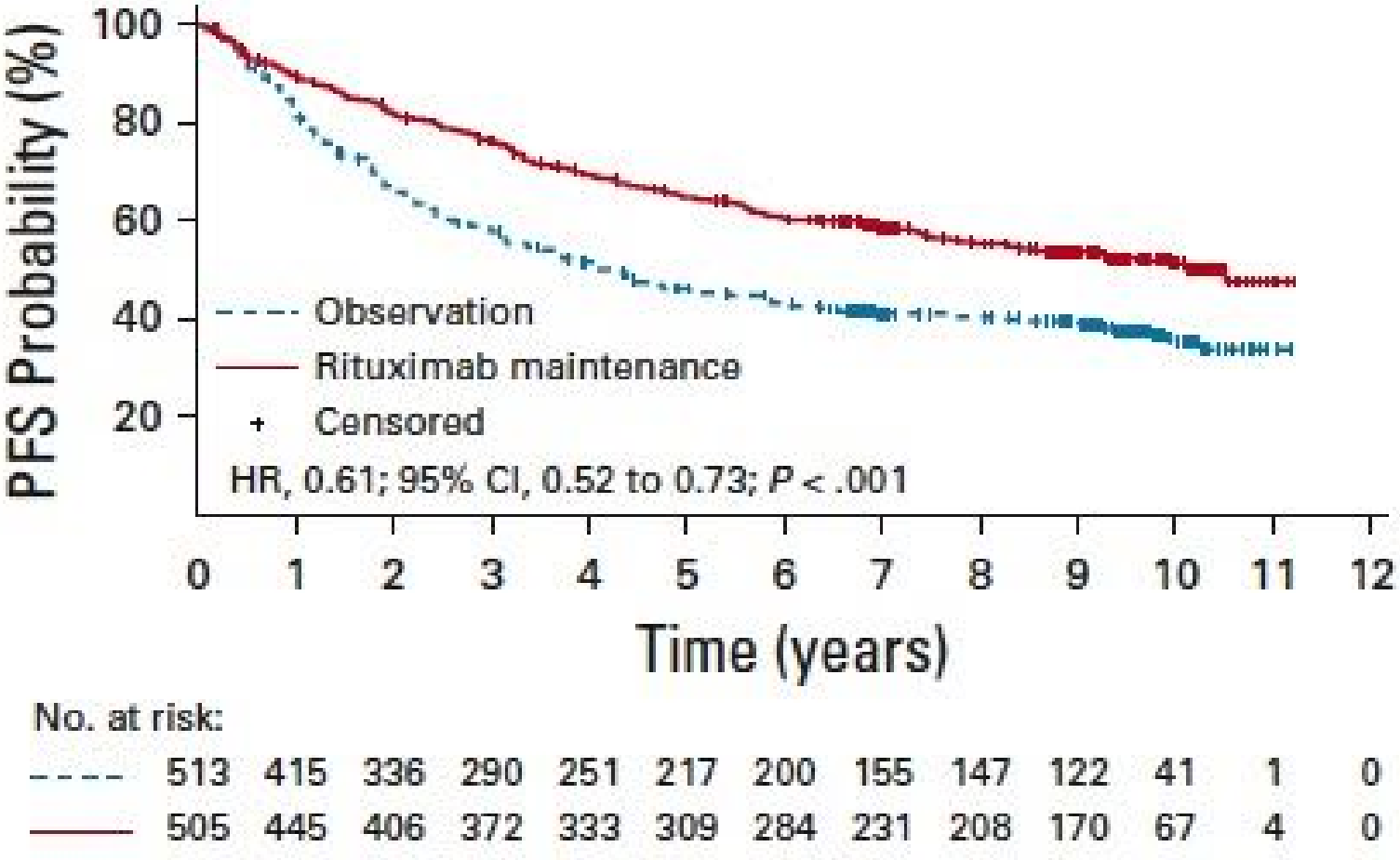
Rummel MJ, et al. Lancet 2013.

Hawkins et al. ICML 2017; abstract 131.

R-Benda vs R-CHOP: StiL vs BRIGHT study (OS)



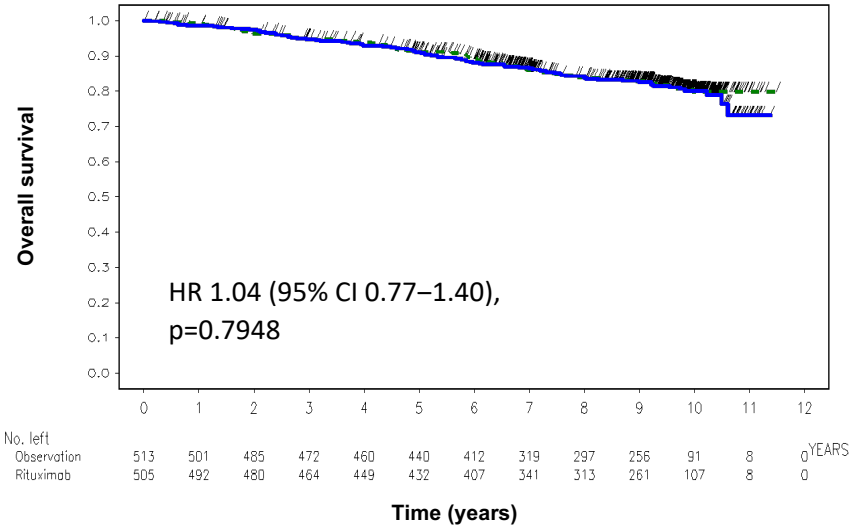
PRIMA: RCHOP obs. vs RCHOP+RM 2 ans (9y FU)



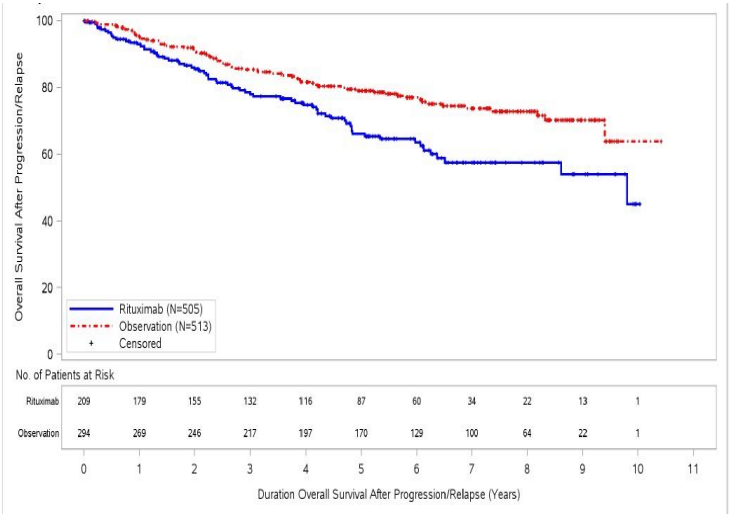
Bachy E, J Clin Oncol 2019

PRIMA: RCHOP obs. vs RCHOP+RM 2 ans (9y FU)

OS 1L



OS 1st salvage



HT at relapse: 9.2% vs 7.7%

RTX: 42% vs 26%

autoSCT: 16% vs 7%

Increased PFS does not translate into improved OS: *not a surrogate marker*

Increased PFS, TTNT: *economic endpoints*

Bachy E, J Clin Oncol 2019

PRIMA 9y FU: safety

Causes of death

n/N (%)	Observation N=513	Rituximab maintenance N=505
Total deaths	84 (16.4)	88 (17.4)
Progressive disease	38/84 (45.2)	39/88 (44.3)
Other causes	46/84 (54.8)	49/88 (55.7)
Second neoplasia	24/84 (28.6)	6/88 (6.8)
AML/MDS	7/84 (8.3)	2/88 (2.3)
Infections	6/84 (7.1)	11/88 (12.5)
Cardiovascular	4/84 (4.8)	8/88 (9.1)

SAE

n (%)	Observation N=508	Rituximab maintenance N=501
AEs*	194 (38.2)	285 (56.9)
Grade 3–4 AEs	86 (16.9)	122 (24.4)†
SAEs	68 (13.4)	106 (21.2)
Total deaths	83 (16.3)	84 (16.8)
Grade 5 AEs	3 (<1)	8 (1.6)

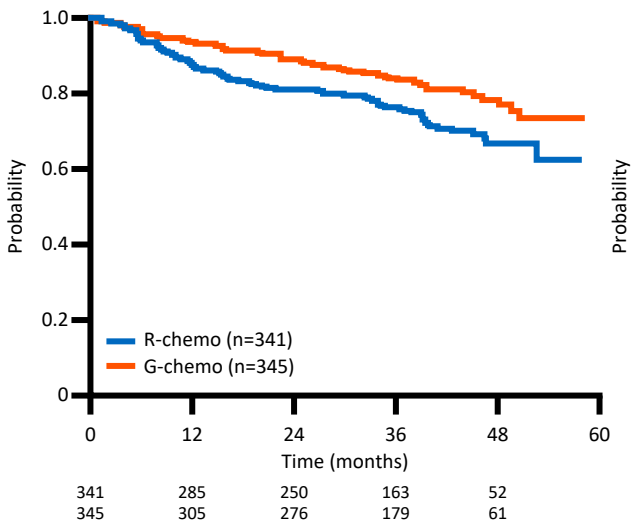
*Includes grade 3–5 toxicities, grade 2–5 infections, and SAEs;
†difference mainly represented by neutropenia and infections

Bachy E, J Clin Oncol 2019

GALLIUM: PFS OBINU > RITUX + chemo backbone

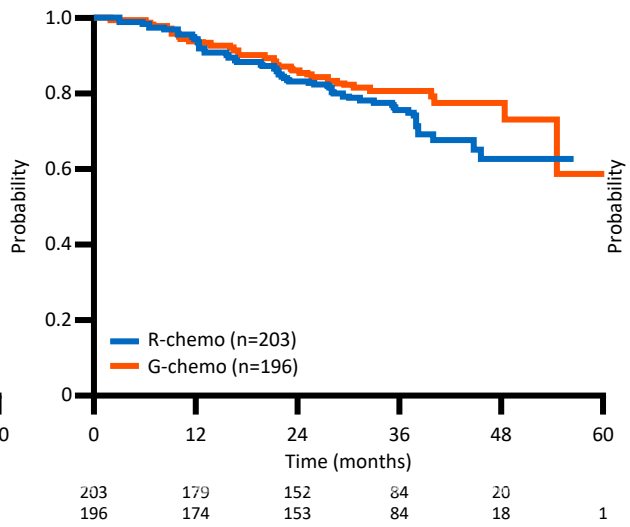
G-CVP: bonne option pour les LF âgés…

Benda



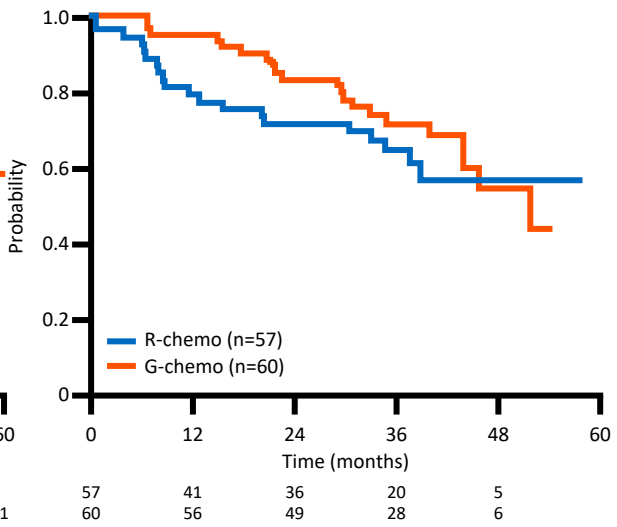
HR (95% CI)†	0.63 (0.46, 0.88)
3-yr PFS	84.1% G-B vs 76.4% R-B

CHOP



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

CVP



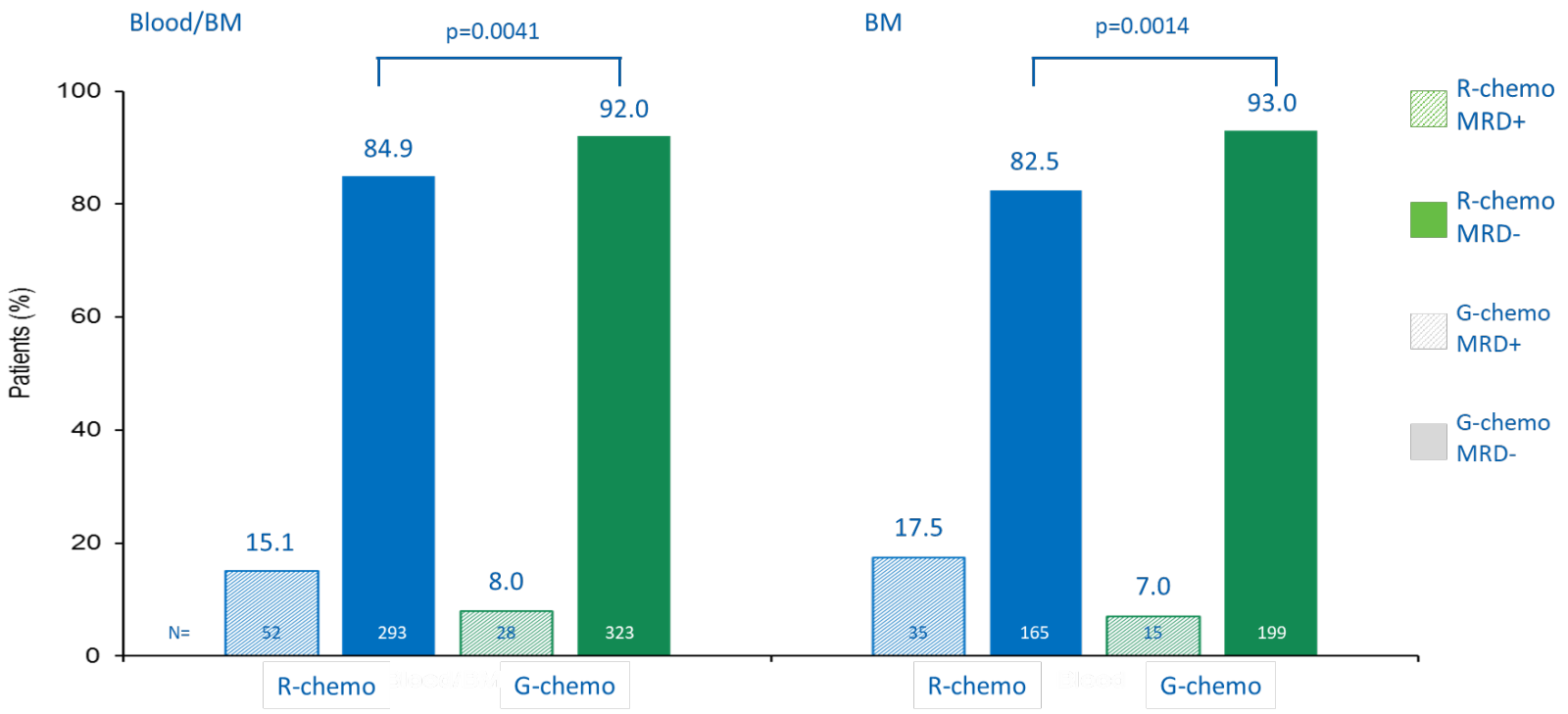
HR (95% CI)†	0.79 (0.42, 1.47)
3-yr PFS	71.3% G-CVP vs 64.2% R-CVP

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

POD24 G-chemo *vs* R-chemo: 9% vs 16%

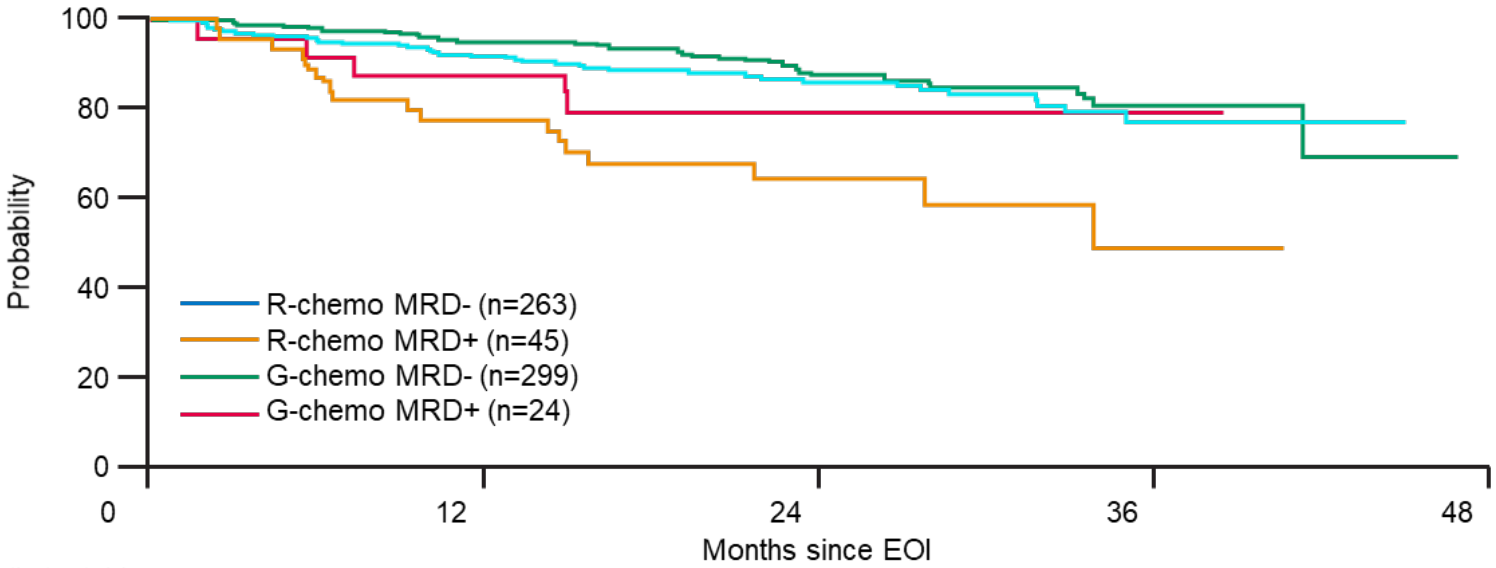
Marcus R, NEJM 2017 and Hiddeman W JCO 2018

Statut MRD sang/moelle en fin d'induction



Pott C et al. oral presentation at ASH 2016: Abstract #613

PFS selon bras de traitement et statut MRD



No. of patients at risk									
R-chemo MRD-	263	244	230	185	134	77	31	4	0
R-chemo MRD+	45	38	33	27	12	10	4	0	0
G-chemo MRD-	299	291	273	223	153	93	41	5	0
G-chemo MRD+	24	22	21	16	6	3	1	0	0

Ne pourrait-on pas éviter la maintenance chez les patients en RC MRD- ?

Pott C et al. oral presentation at ASH 2016: Abstract #613

GALLIUM: Selected grade 3–5 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*
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

Hiddeman W JCO 2018

What are the questions – 1L HTB

- Induction phase:
  - What is the best chemo backbone ?
  - What is the best MoAb backbone ?

- Which maintenance ?

- Chemo-sparing options: an ideal candidate would:
  - Be *more effective* than R-chemo (and RM) in high risk disease
  - Be *less toxic* in patients with good outcome
  - Be *targeted* on a vital pathway for a dedicated FL/TME

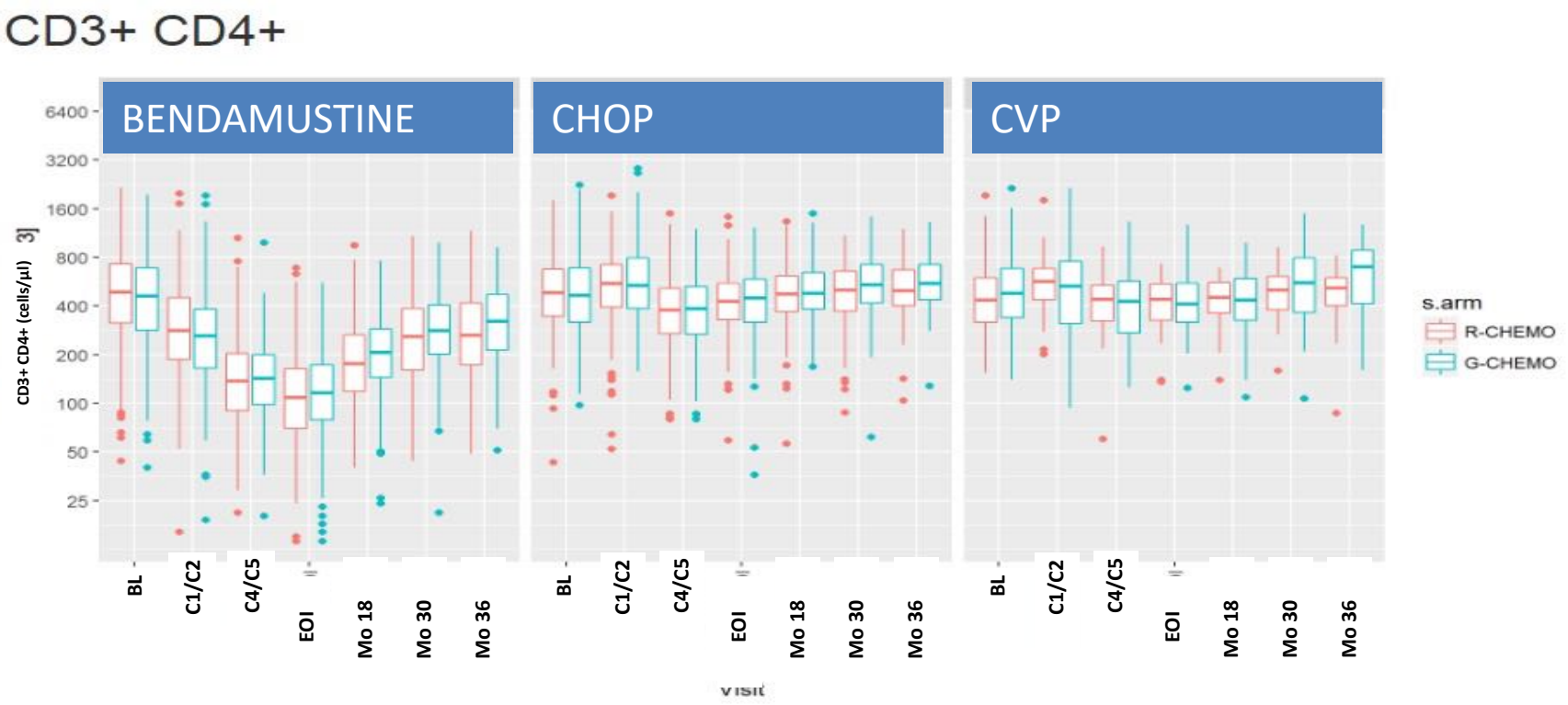
Grade 3–5 infections by chemo and by phase

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)

Hiddeman W JCO 2018

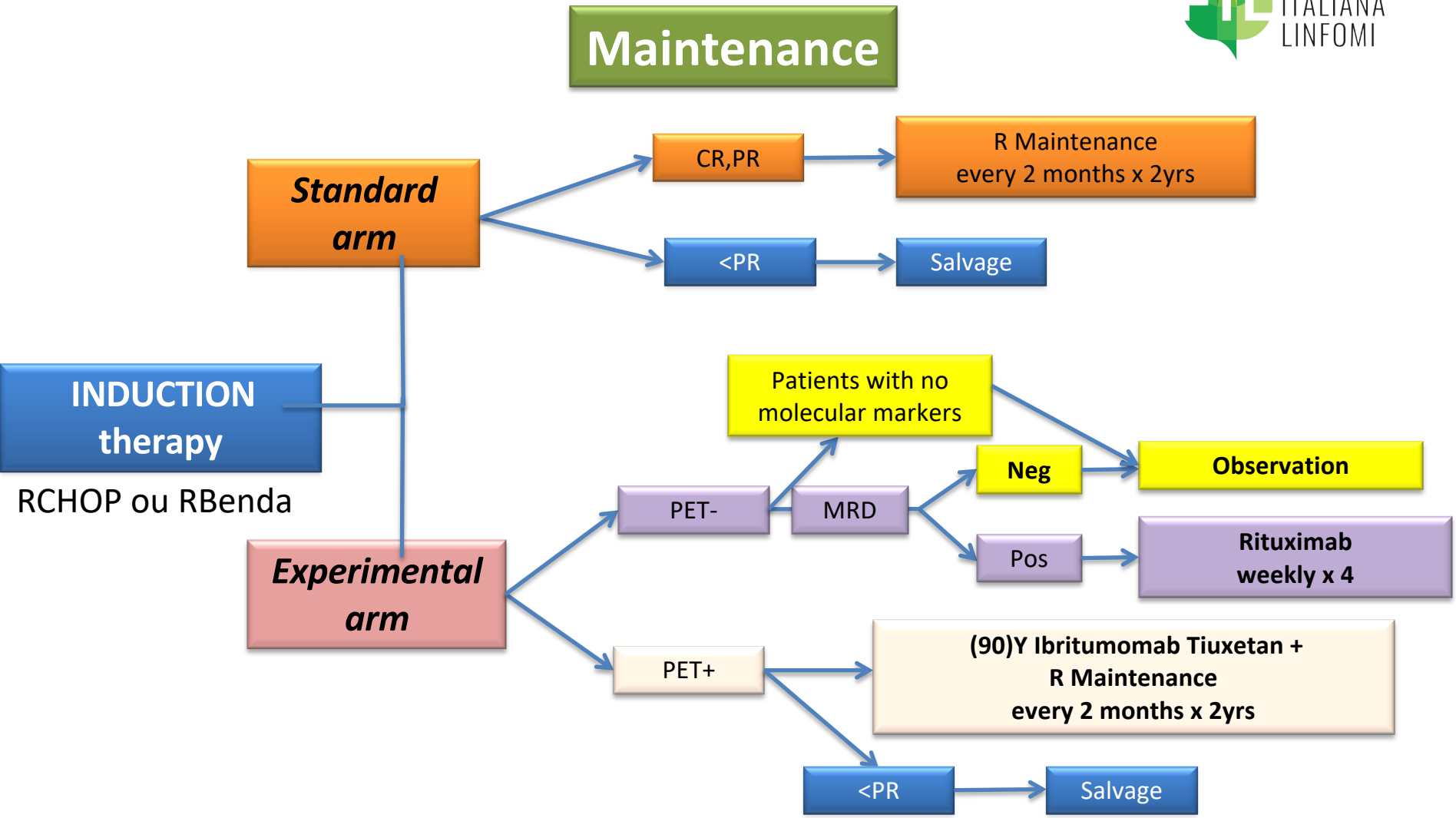
*Safety population

CD4 T-cell counts over time



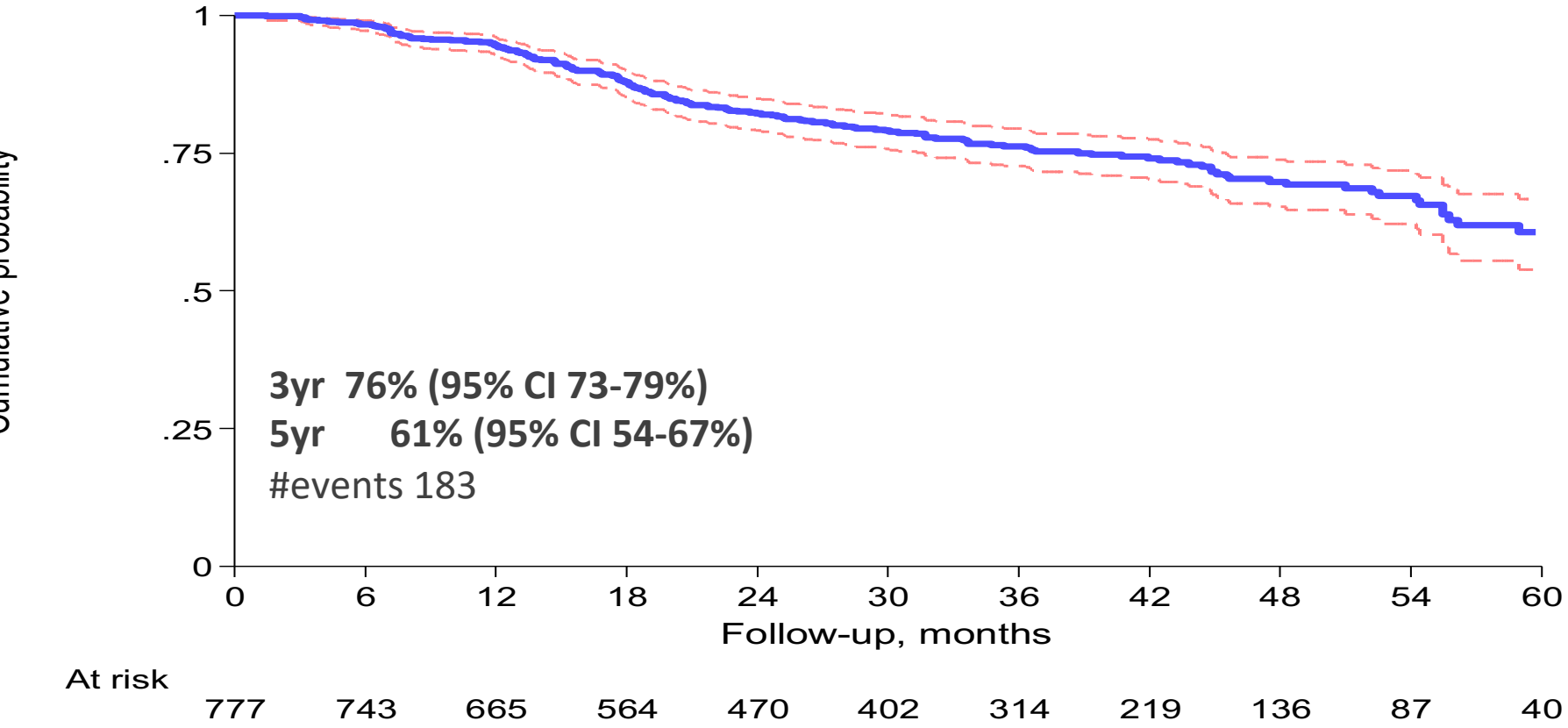
Hiddeman W JCO 2018

FOLL12 study: rando maintenance ou pas si RCM MRD-



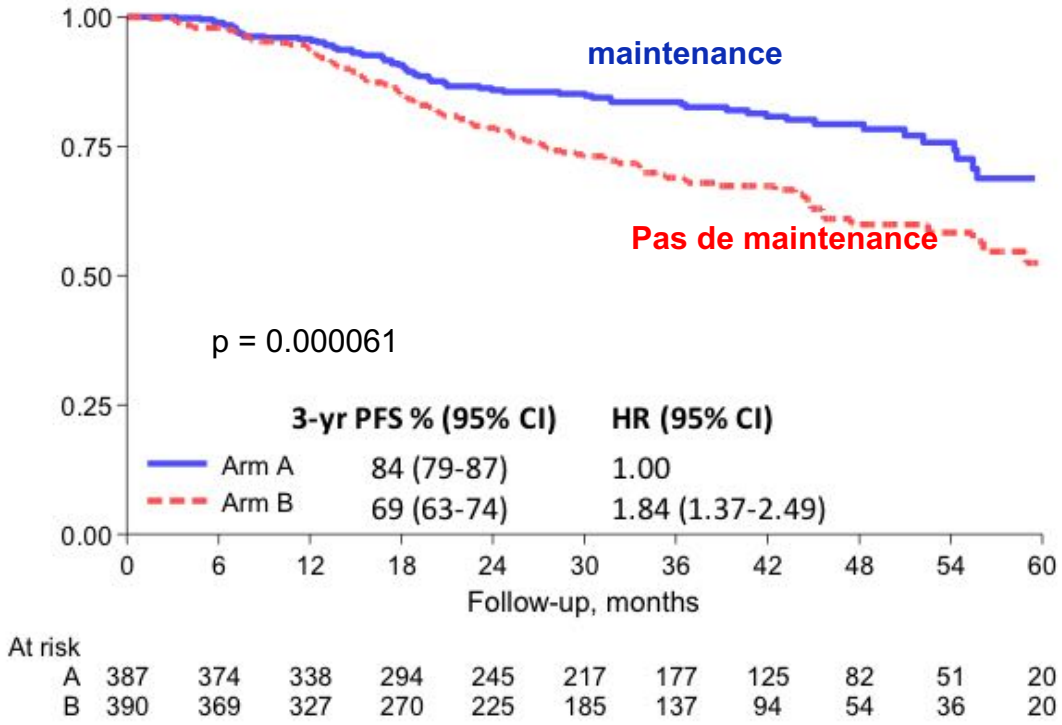
- Luminari S, J Clin Oncol 2021

FOLL12 study: rando maintenance ou pas si RCM MRD-



- Luminari S, J Clin Oncol 2021

FOLL12 study: rando maintenance ou pas si RCM MRD-



- A Complete Metabolic Response is good news
- A Complete Molecular Response is good news
- However, not enough to omit a 2 years rituximab maintenance

- Luminari S, J Clin Oncol 2021

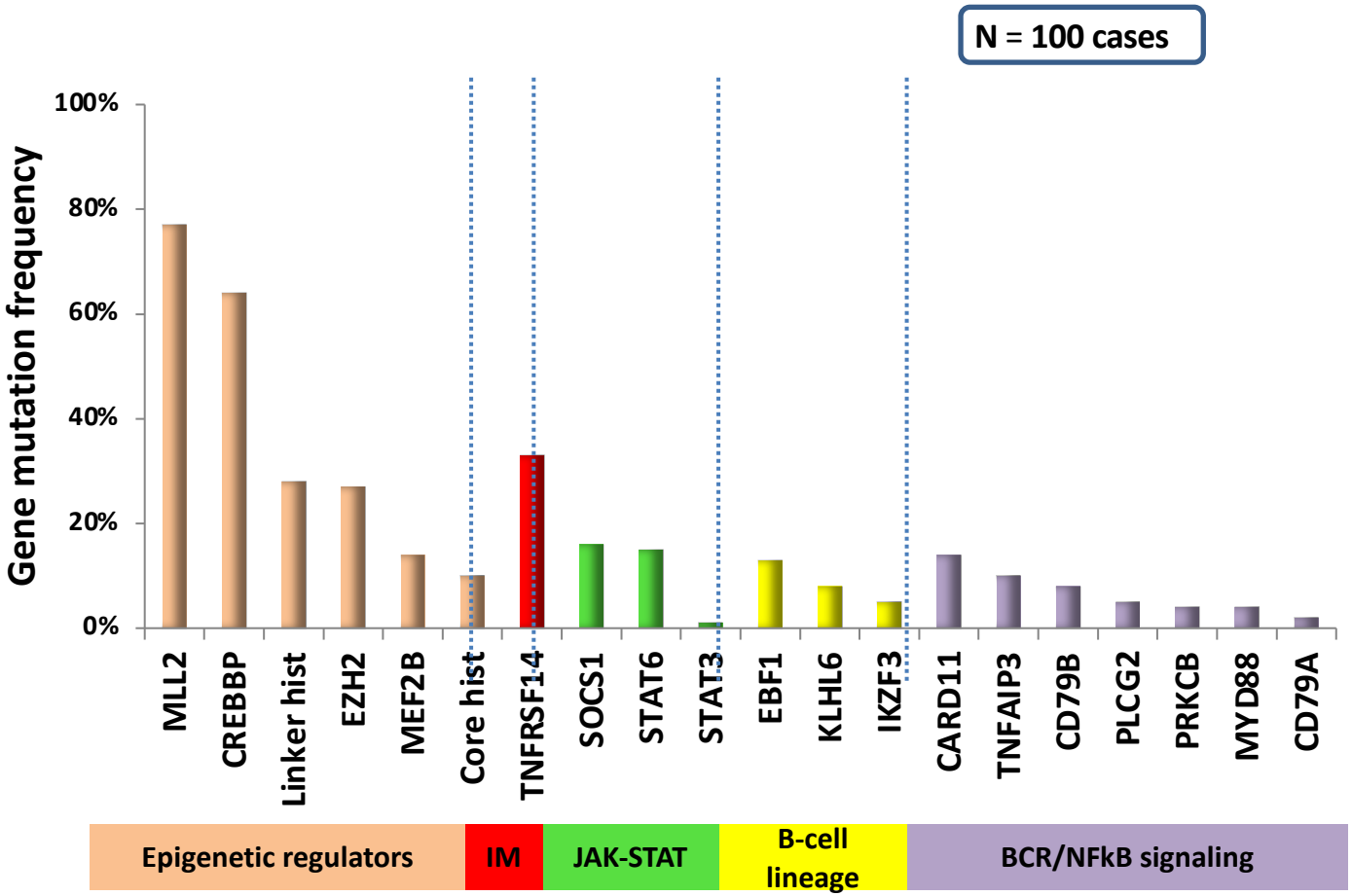
What are the questions – 1L HTB

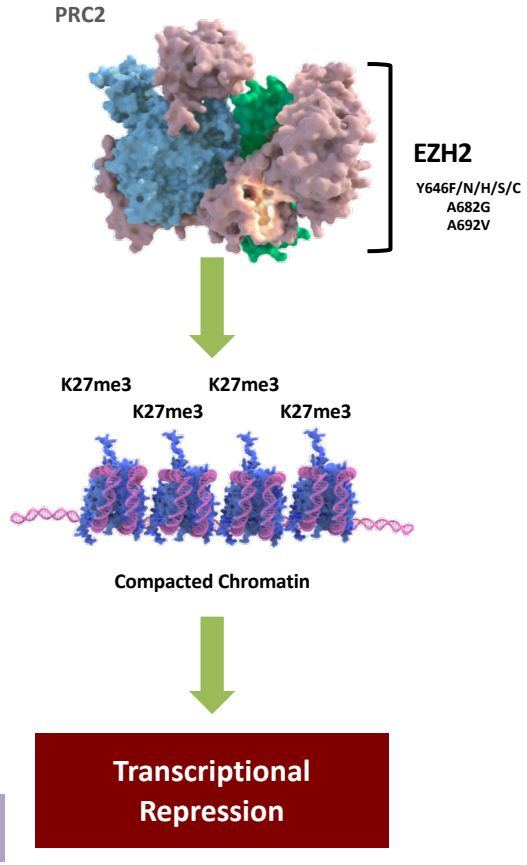
- Induction phase:
  - What is the best chemo backbone ?
  - What is the best MoAb backbone ?

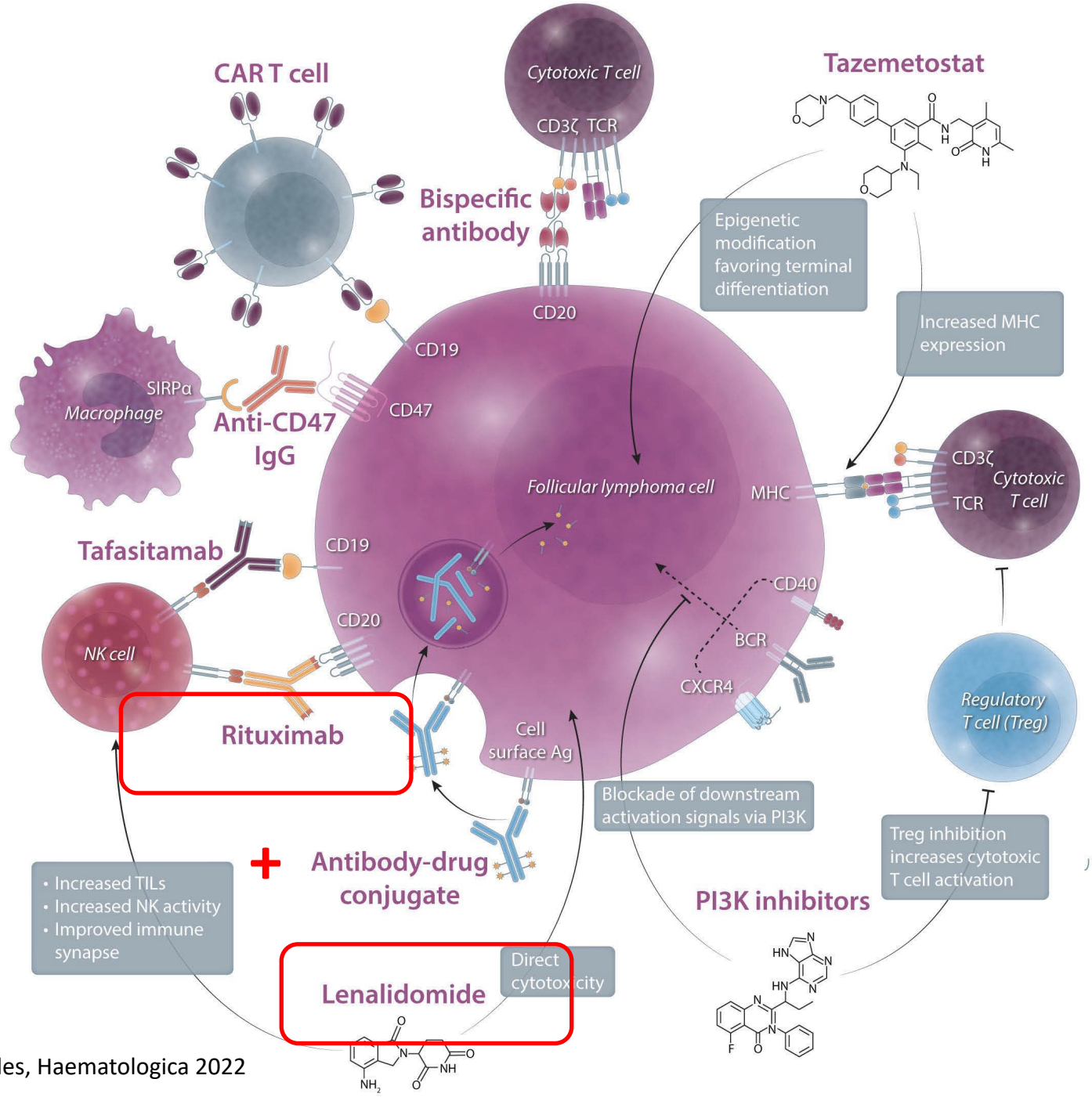
- Which maintenance ?

- Chemo-sparing options: an ideal candidate would:
  - Be more effective than R-chemo (and RM) in high risk disease
  - Be less toxic in patients with good outcome
  - Be *targeted* on a vital pathway for a dedicated FL/TME

Time to awake silenced genes and immune cells !

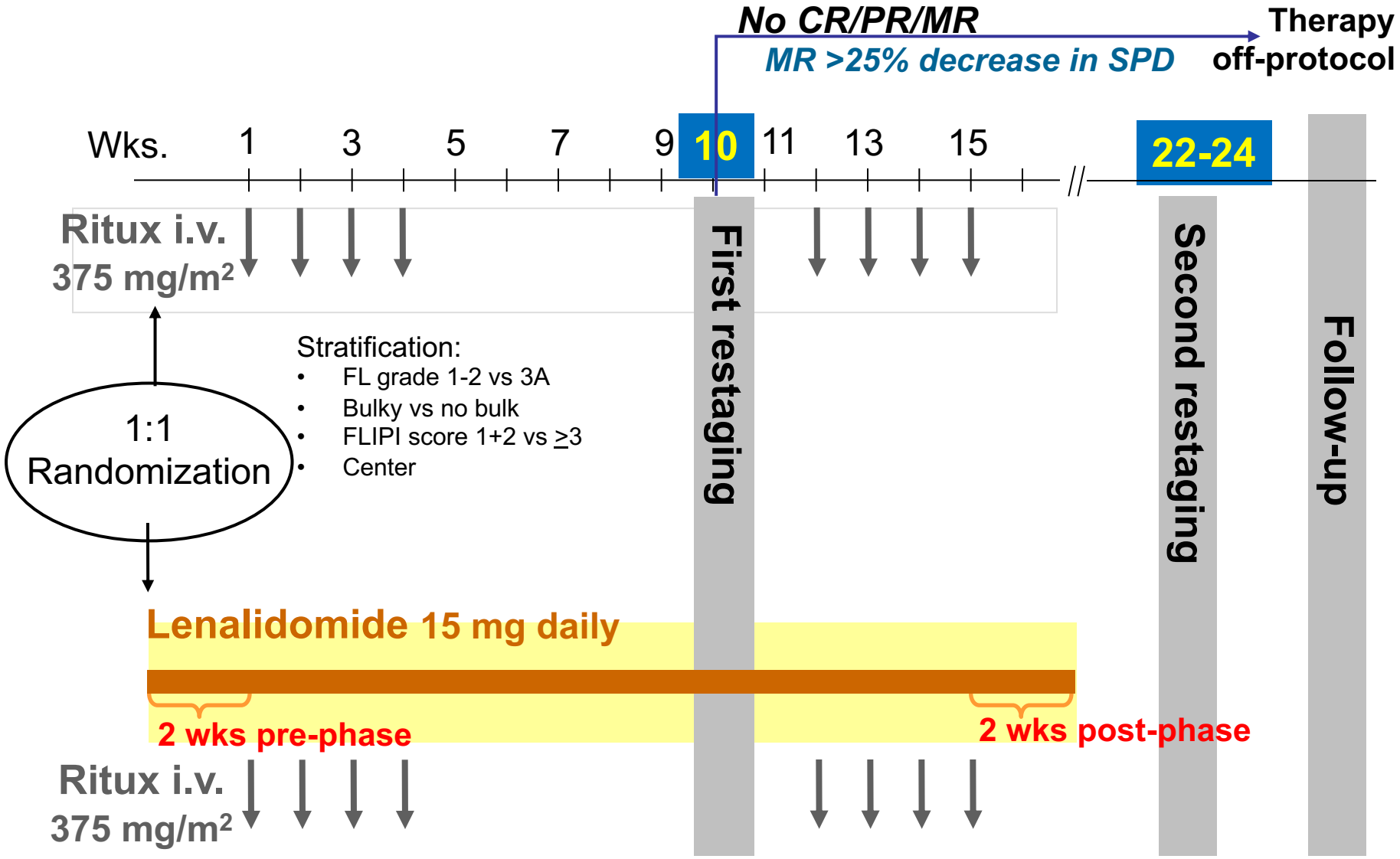






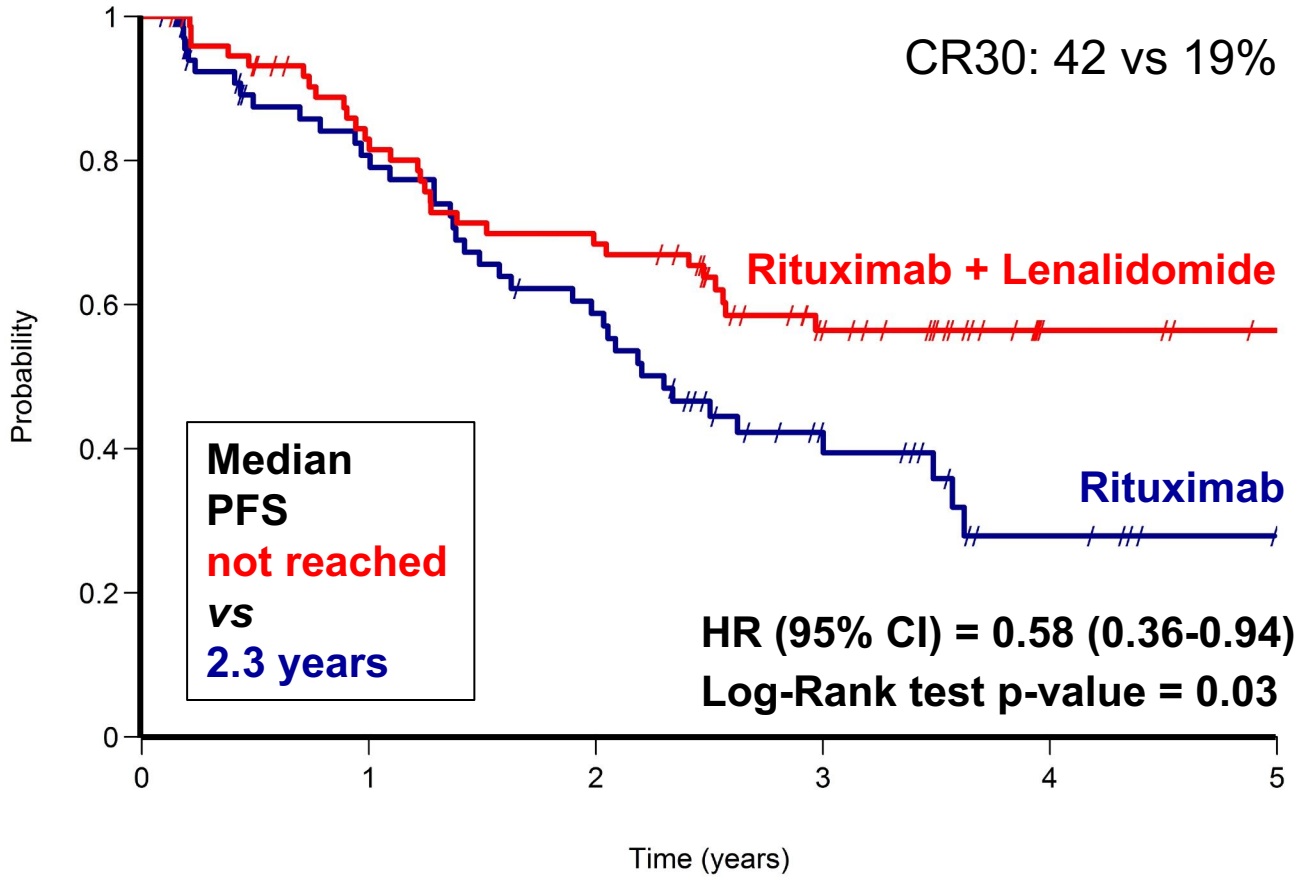
D.Qualls and G.Salles, Haematologica 2022

LEN : SAKK-Nordic 35/10 Trial design



Zucca E, Blood 2019

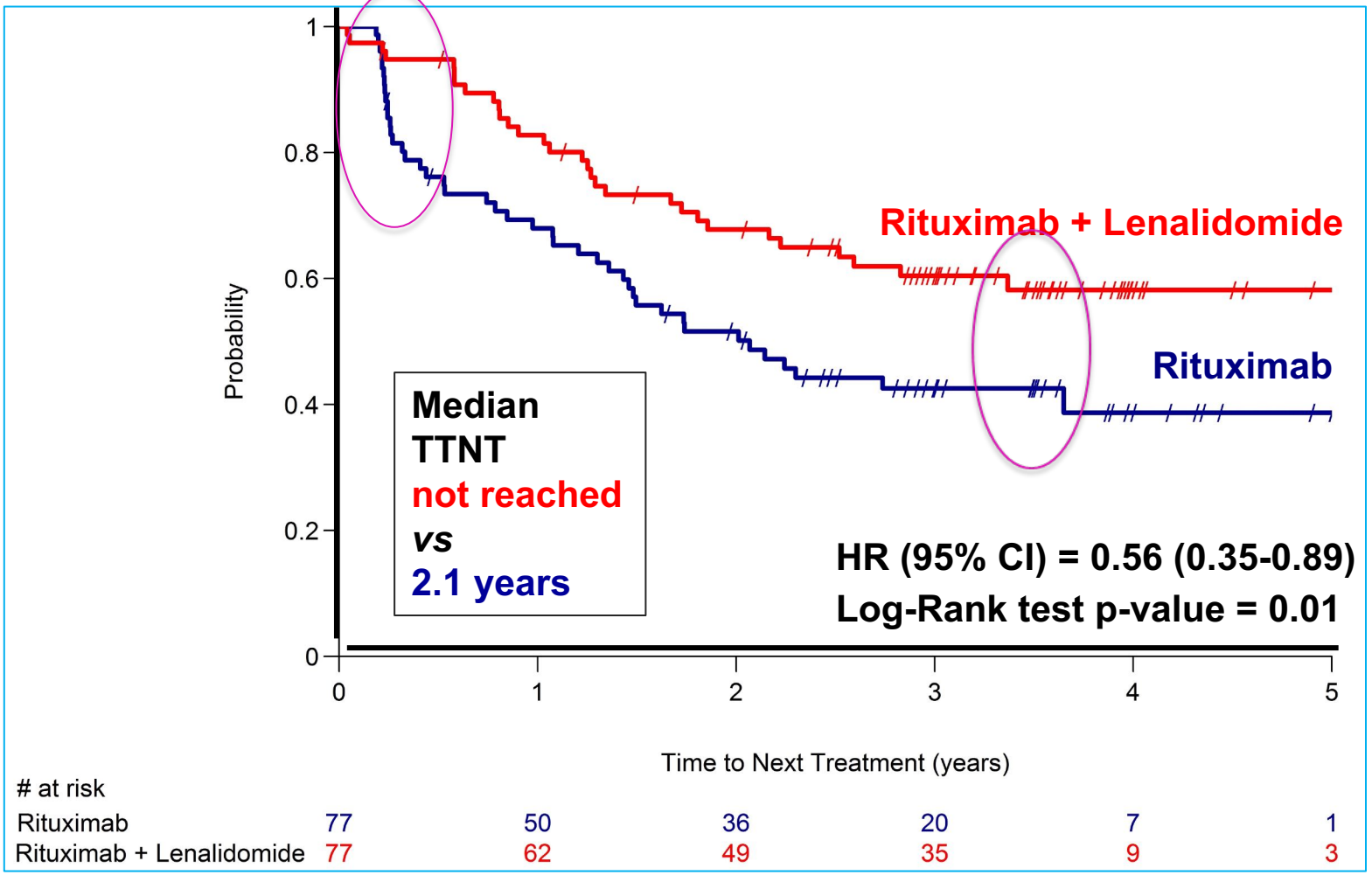
SAKK-Nordic 35/10 Trial : PFS



# at risk						
Rituximab	77	48	34	15	5	0
Rituximab + Lenalidomide	77	57	47	26	6	3

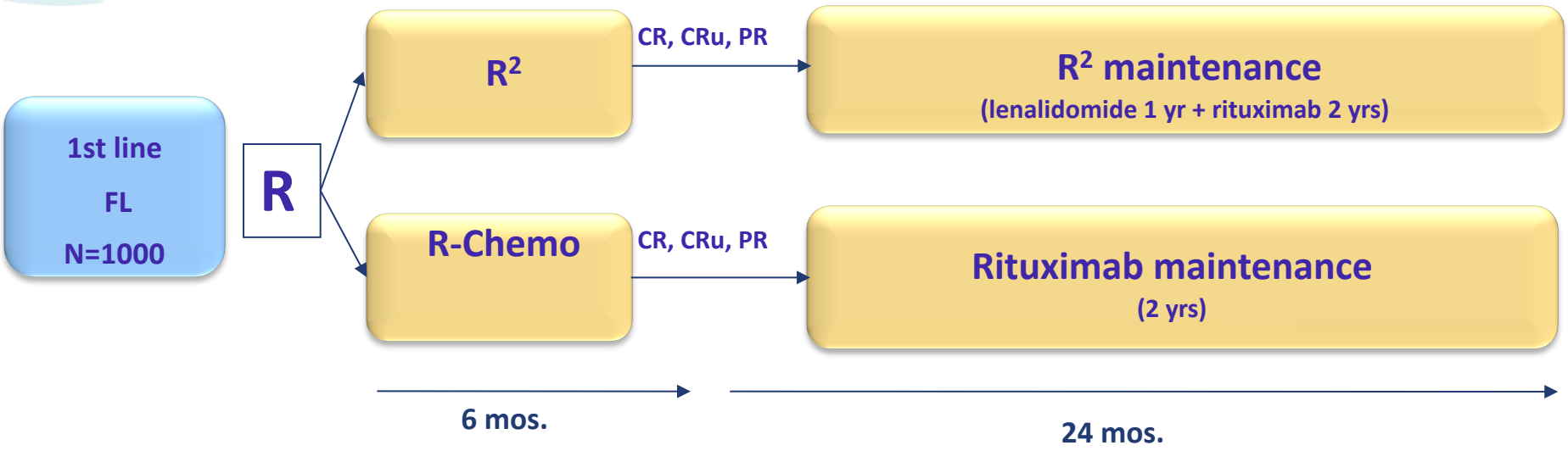
Zucca E, Blood 2019

SAKK-Nordic 35/10 Trial : TTNT



Zucca E, Blood 2019

The "RELEVANCE" Trial



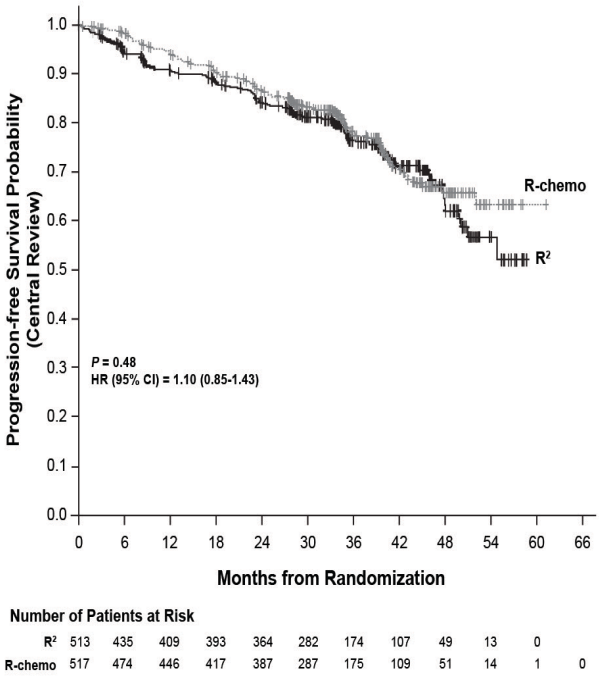
- **R-Chemo**: Investigator choice of R-CHOP, R-CVP, or R-B
- **Eligibility:** Patients who need treatment (GELF criteria)
- **Stratification**: FLIPI (0-1 v 2 v 3-5), Age (>60 v ≤ 60), diameter of largest node (> 6 v ≤ 6 cm)
- **Endpoints:** PFS, CR/CRu? At 30 months
- **R² Regimen:**
  - **Rituximab** 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

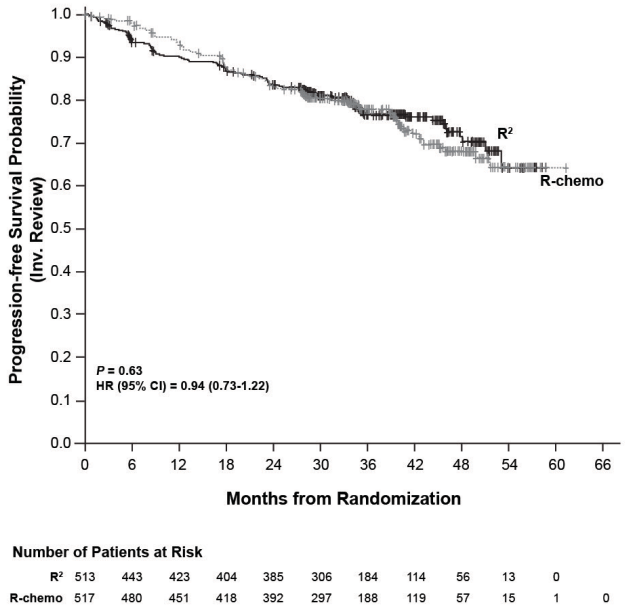
RELEVANCE™
RITUXIMAB LENALIDOMIDE VERSUS ANY CHEMOTHERAPY

Relevance: R-LEN = R-CHOP

20% CR *vs* 20% CR

PFS **PFS2y 84%** **83%** **OS**





513 rituximab-revlimid (R2) and 517 R-chemo
= 16% of POD24 (again…)

Morschhauser F, NEJM 2018

Relevance: R-LEN = R-CHOP

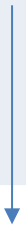
Table 3. Adverse Events during the Treatment Period in the Safety Population.

Adverse Event	Rituximab–Lenalidomide Group (N = 507)		Rituximab–Chemotherapy Group (N = 503)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Neutropenia*	381 (75)	160 (32)	386 (77)	252 (50)
Anemia*	333 (66)	0	446 (89)	0
Thrombocytopenia*	268 (53)	11 (2)	266 (53)	8 (2)
Cutaneous reactions†	220 (43)	36 (7)	120 (24)	5 (1)
Diarrhea	187 (37)	10 (2)	95 (19)	6 (1)
Constipation	178 (35)	1 (<1)	167 (33)	5 (1)
Rash	146 (29)	20 (4)	39 (8)	1 (<1)
Fatigue	115 (23)	1 (<1)	147 (29)	4 (<1)
Nausea	100 (20)	0	209 (42)	8 (2)
Abdominal pain	78 (15)	4 (<1)	46 (9)	4 (<1)
Myalgia	73 (14)	0	29 (6)	1 (<1)
Arthralgia	71 (14)	3 (<1)	70 (14)	1 (<1)
Peripheral edema	69 (14)	0	47 (9)	1 (<1)
Muscle spasms	68 (13)	0	21 (4)	0
Infusion-related reaction	66 (13)	7 (1)	56 (11)	1 (<1)
Upper respiratory tract infection	47 (9)	0	55 (11)	0
Vomiting	34 (7)	2 (<1)	94 (19)	7 (1)
Peripheral neuropathy	35 (7)	1 (<1)	79 (16)	3 (<1)
Tumor flare reaction	30 (6)	7 (1)	1 (< 1)	0
Leukopenia	21 (4)	8 (2)	48 (10)	30 (6)
Febrile neutropenia	11 (2)	11 (2)	34 (7)	33 (7)
Tumor lysis syndrome	7 (1)	6 (1)	5 (1)	3 (<1)
Alopecia	5 (1)	0	45 (9)	3 (<1)

Morschhauser F, NEJM 2018

Conclusions – 1L

	Localisés	Disséminés
Faible masse	1/ W&W 2/ RTX seul x4 3/ RTE 24Gy ou 2x2Gy	1/ W&W 2/ RTX seul x4
Forte masse	1/ R/G-chimio +/- M 2/ RTX (au cas par cas)	1/ R/G-chimio +/- M



Identifier POD24

Comment améliorer la 1L HTB ?

- GALLIUM met la barre haut…
  - 3y PFS = 80%, améliorer à 85% (mPFS 11.9 ans, HR 0.78): 517 events, >2000 pts à inclure !
  - Améliorer le % de CMR des FLIPI3-5: new drug + R-CHOP
- Faire aussi bien mais moins toxique, non inferiority design:
  - Echec de Relevance R^2+RM = RCHOP+RM
  - Ga-Len: 3y PFS 82% (OR 94%, 80% de CMR)
  - Privilégier les FLIPI 0-2 pour une désescalade
- Biomarker-based therapy ou POD24-high risk therapy:
  - FLIPI2+TEP (TMTV)
  - *Nouveaux modéles basés sur le ML*
- Privilégier des options qui préservent les fonctions médullaires, améliorent la QDV, évitent les pb cardio-vasculaires, les autres cancers, l'efficacité vaccinale…

Merci de votre attention