# Lymphomes Folliculaires:

## Prise en charge optimale en première ligne en 2017

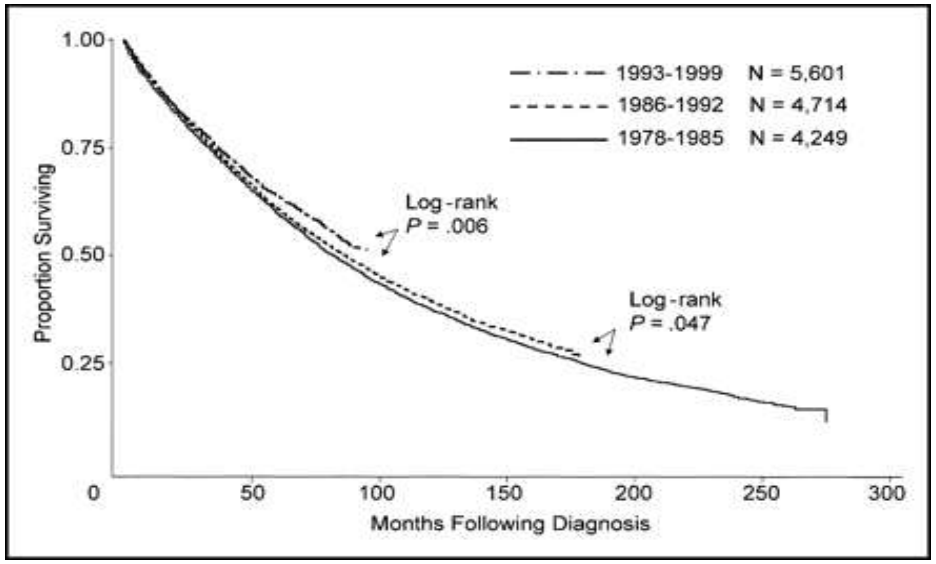
*Société Algérienne d'Hématologie*

*Le 26 Octobre 2017*

*Réda Bouabdallah*

*Institut Paoli-Calmettes, Marseille, France*

# LF: histoire naturelle



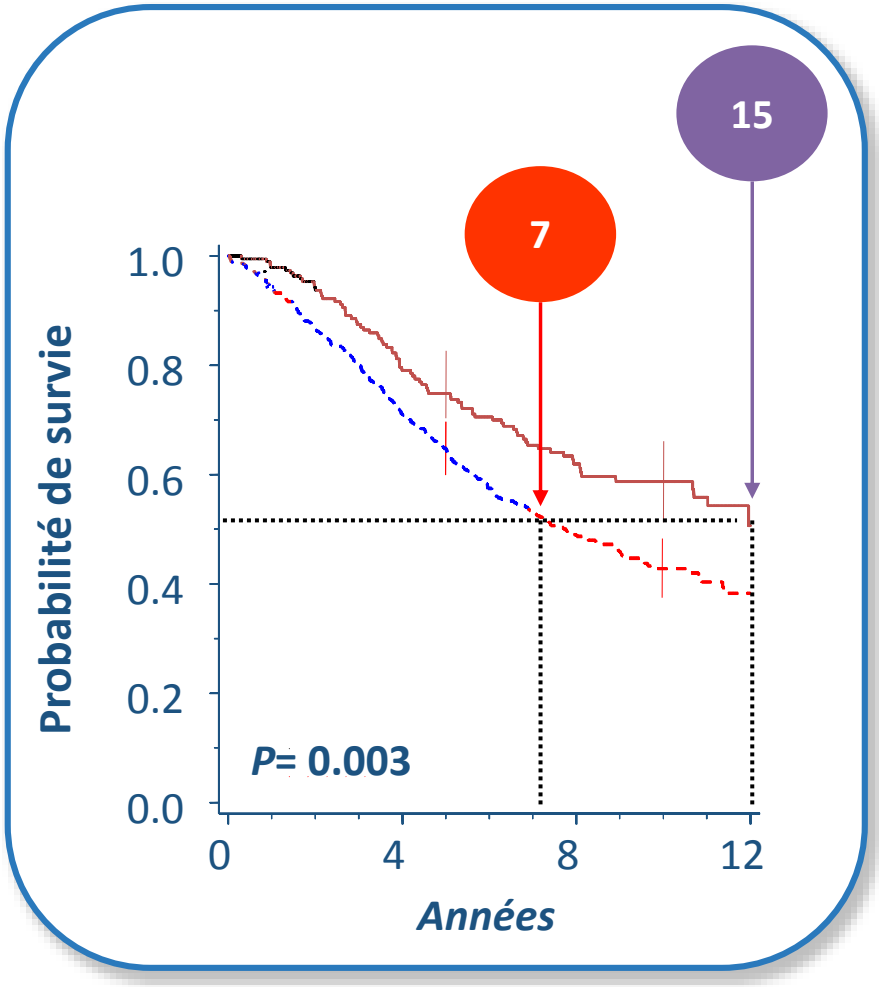

| Statut Maladie | N patients | Réponse % | Durée Médiane Réponse, mois | Survie Médiane, années |
|---|---|---|---|---|
| Diagnostic | 204 | 88 | 31 | 9,2 |
| 1ère Rechute | 110 | 78 | 13 | 4,6 |
| 2nde Rechute | 63 | 76 | 13 | 3,5 |
| ≥ 3ème Rechute | 37 | 68 | 6 | 2,0 |

*Horning SJ. Semin Oncol 1993; Swenson WT et al. J Clin Oncol 2005; Lister TA et al. J Clin Oncol 2005*

# LF: Qui Traiter?

## Critères GELF 86

- Masse > 7 cm
- ≥ 3 sites envahis (chacun > 3 cm)
- Symptôme(s) B
- Syndrome compressif urétéral, orbitaire ou gastro-intestinal
- Épanchement séreux pleural ou péritonéal (quelque soit le contenu cellulaire)
- Cytopénie : PNN < 1.0 G/L et/ou plaquettes < 100 G/L
- Leucémie (cellules malignes circ > 5 G/L)
- Splénomégalie avec limite inférieure sous la ligne ombilicale




*Solal-Céligny P et al. J Clin Oncol. 1998 Jul;16(7):2332-8.*

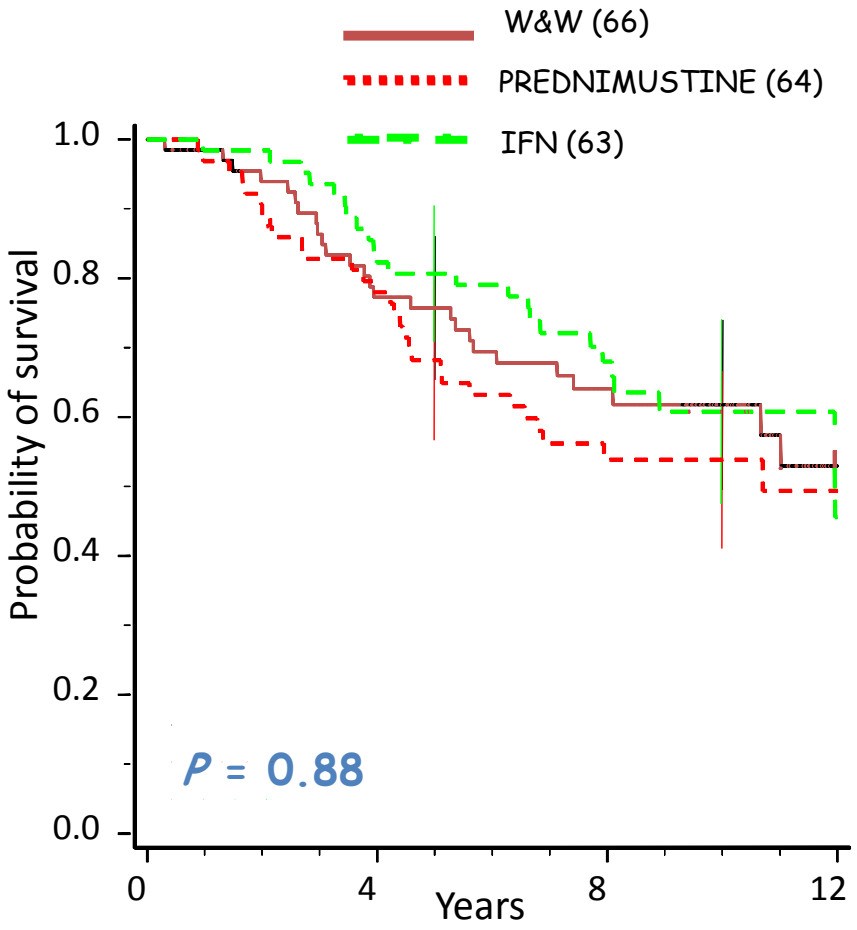
# LF & Masse Tumorale : Définition

| MASSE TUMORALE FAIBLE | MASSE TUMORALE FORTE |
| --- | --- |
| Critères GELF 86 : 0 | Critères GELF 86 ≥ 1 |
| Ou | Ou |
| Score FLIPI : 0, 1 | Score FLIPI ≥ 2 |
| Ou | Ou |
| Score FLIPI 2 : 0 | Score FLIPI 2 ≥ 1 |

# Lymphomes Folliculaires À Faible Masse Tumorale : Doit-on traiter en 2017 ?

# LF à Faible Masse Tumorale

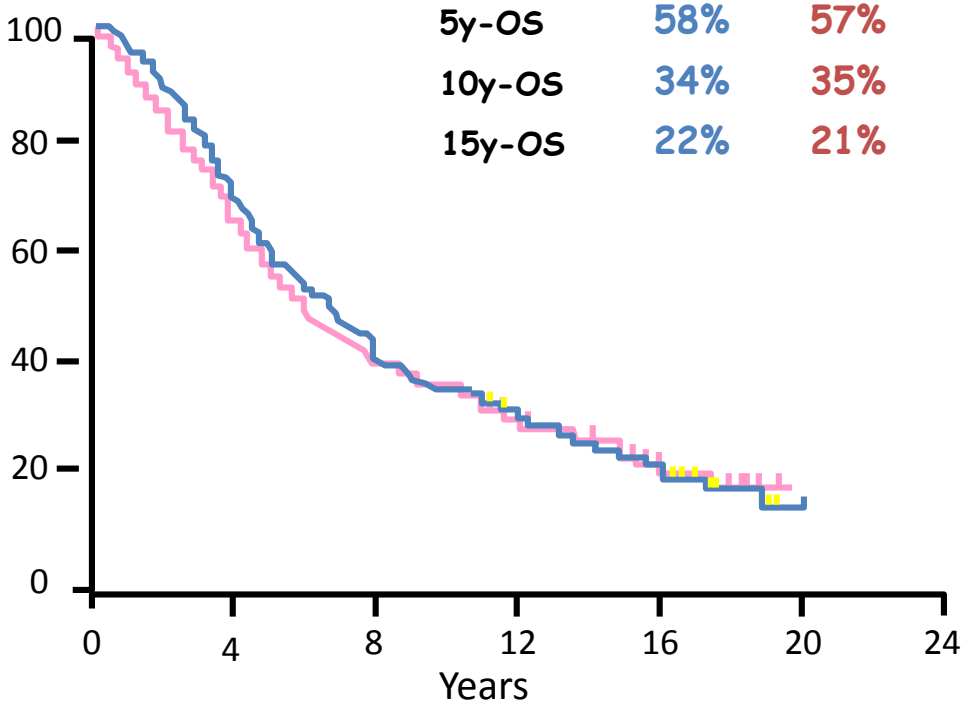
## GELF 86 Trial




*Brice P et al., J Clin Oncol 1997;15(3):1110-7*

## BNLI Trial

| | WW (151) | CLB (153) |
|---|---|---|
| Mediane | 6.7 y | 5.9 y |
| 5y-OS | 58% | 57% |
| 10y-OS | 34% | 35% |
| 15y-OS | 22% | 21% |




*Ardeshna KM, et al. Lancet 2003; 362:516–522*

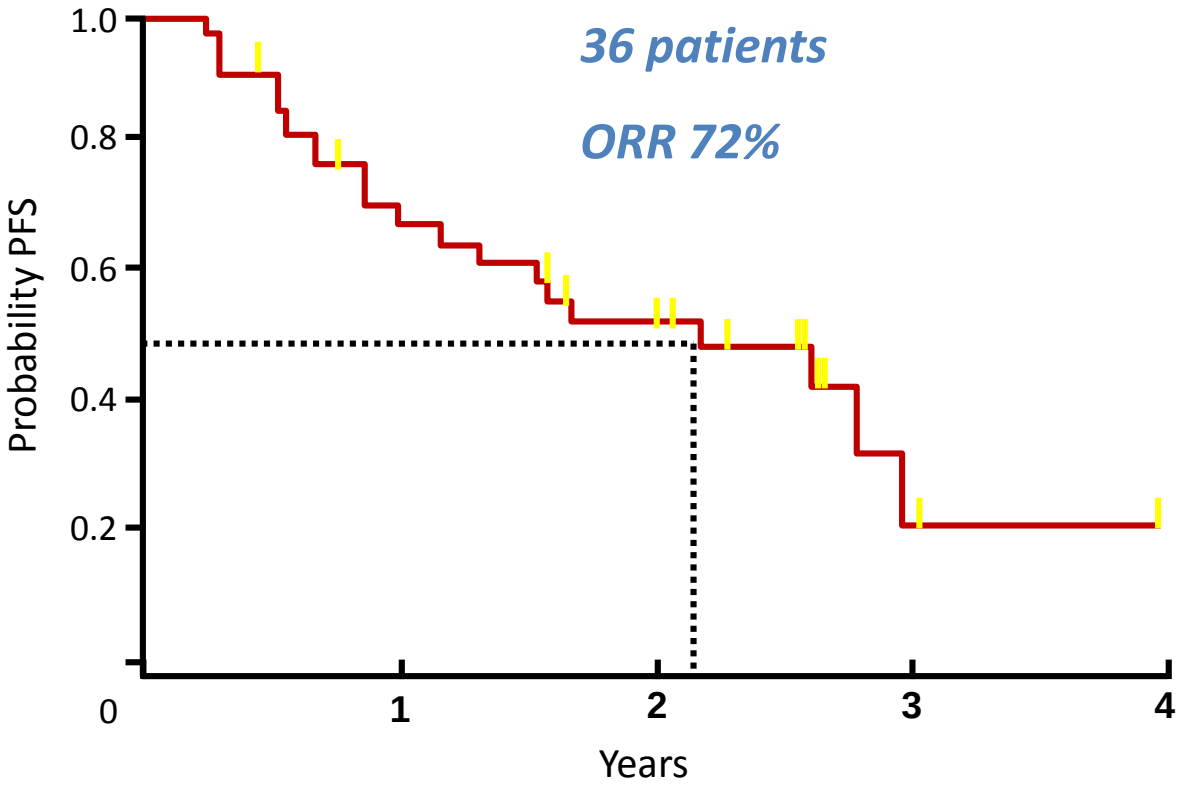
# LF à Faible Masse Tumorale

- With a median Follow-up of 10 years, 20% of patients in the WW arm will never need treatment or die from other cause than lymphoma (40% for patients >70 years)
- No survival benefit in treated patients group
- Median time to start treatment: 2,6 years
- No benefit to treat patients with FL and low tumor burden using alkylating agents or interferon
- Median time to start treatment is not influenced by initial policy (WW or treatment)
- No significant difference in Richter's occurence between the two groups

*Ardeshna KM, et al. Lancet 2003; 362:516–522*

# LF à Faible Masse Tumorale

## RITUXIMAB MONOTHERAPY, 4 doses



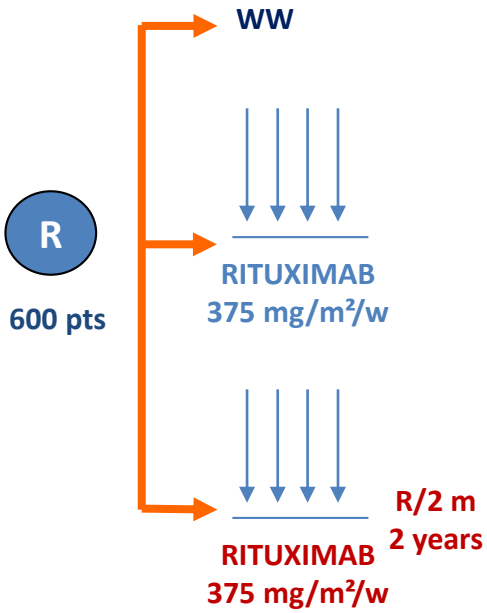

**PFS similar to that observed with:**

- **Chlorambucil**
- **WW**

*Witzig TE, et al. J Clin Oncol 2005; 23:1103–1108*

# LF à Faible Masse Tumorale

## The RWW Trial




*Main Objective*:
**Time to start Treatment (ie: CT and/or RT)**

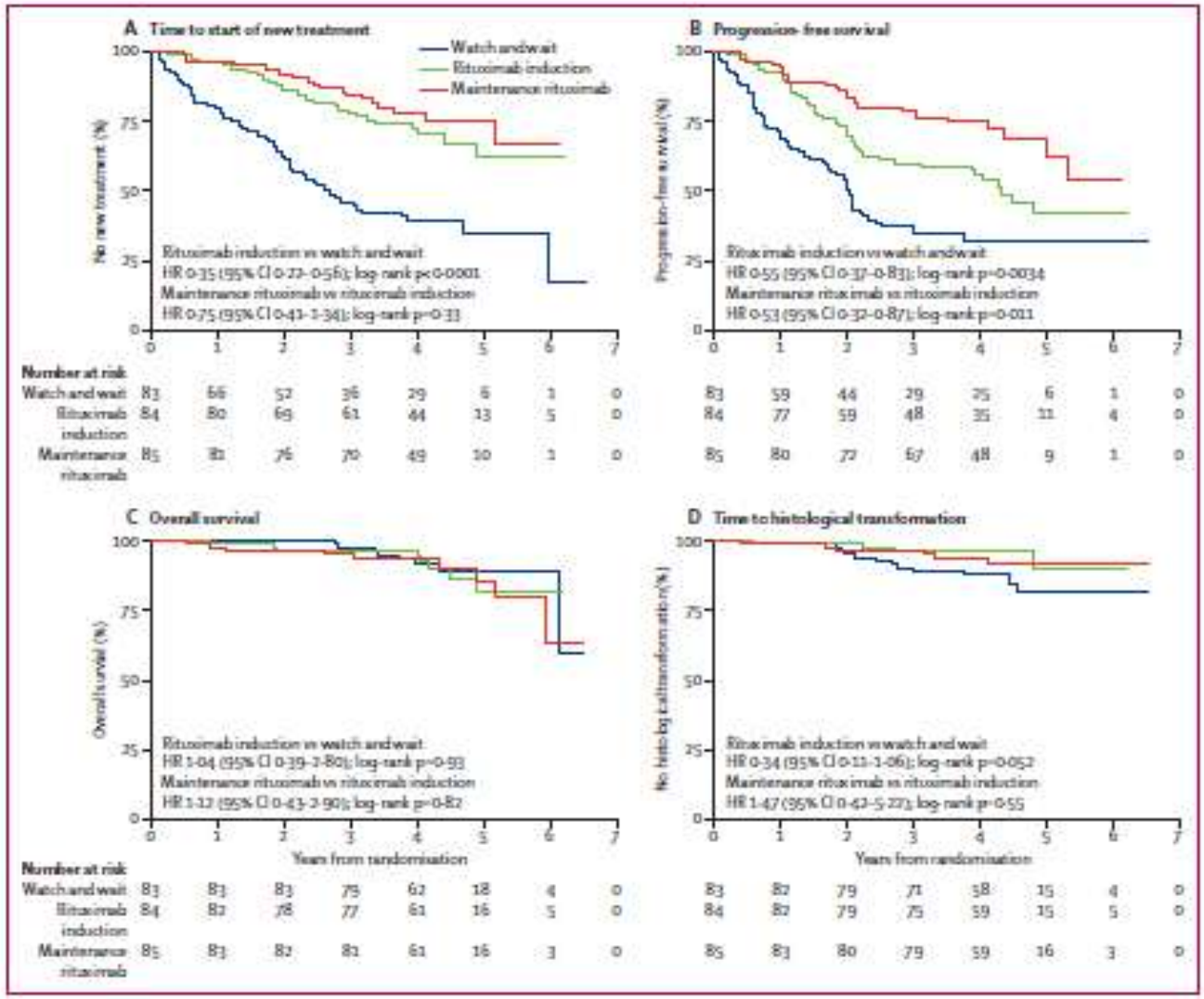



Figure 3: Kaplan-Meier curves for the 252 patients randomly assigned in the initial three-arm study
(A) Time to start of new treatment, (B) progression-free survival, (C) overall survival, and (D) time to histological transformation. HR=hazard ratio.

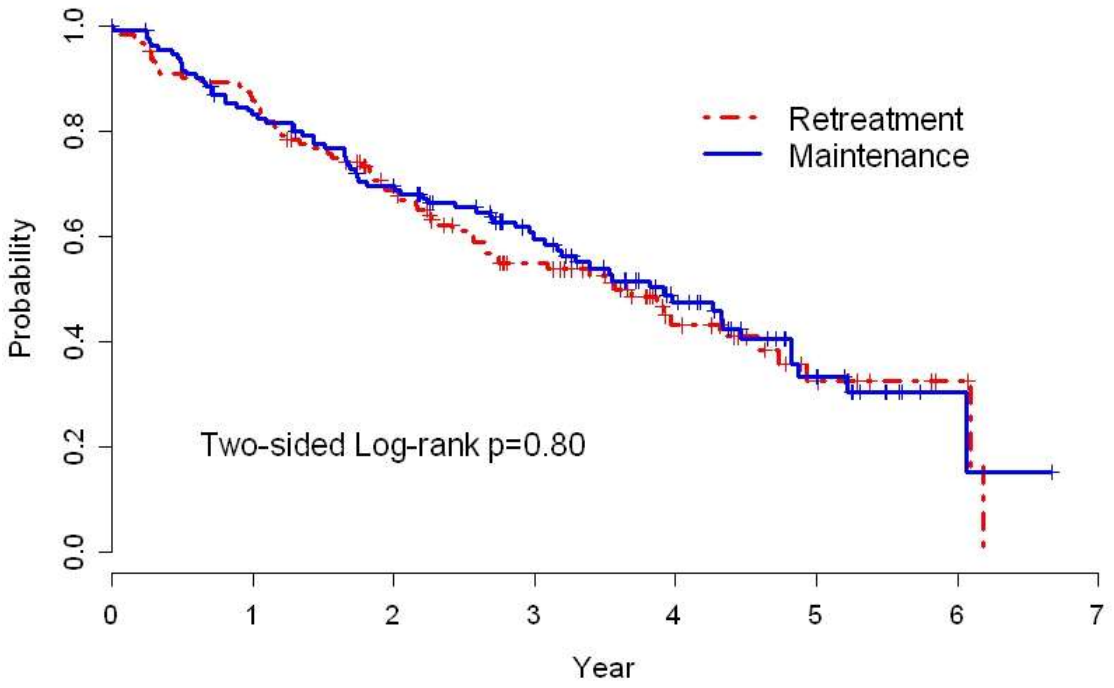
# LF à Faible Masse Tumorale

## RESORT Trial

Rituximab
375 mg/m$^2$ qw × 4

→ Rituximab Maintenance
375 mg/m$^2$ Q3 months

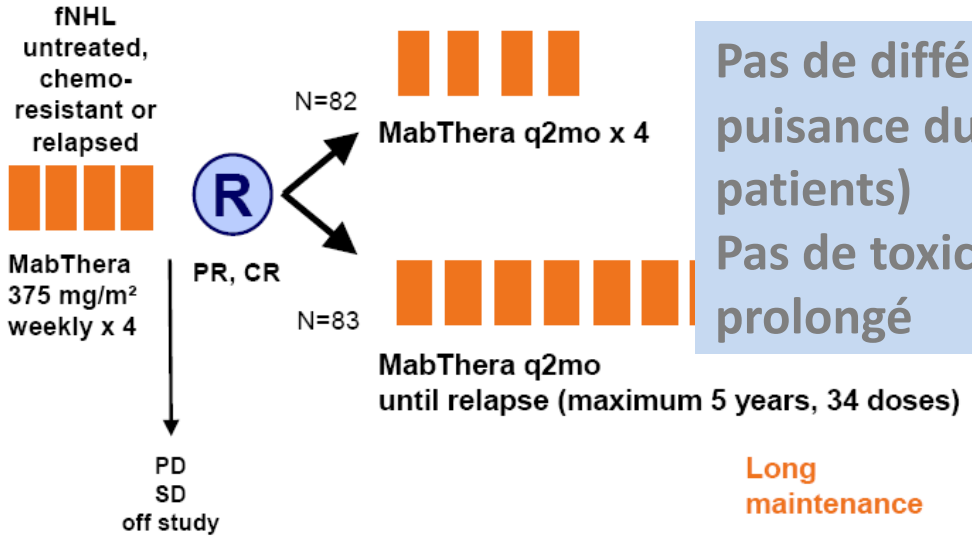
→ Rituximab Re-Treatment at Progression
375 mg/m$^2$ QW x 4



# LF à Faible Masse Tumorale

## SAKK 35/03 Trial: Prolonged Mabthera Maintenance

SAKK 35/03 study design: Prolonged MabThera maintenance therapy in FL




Pas de différence significative (manque de puisance du fait d'un nombre faible de patients)
Pas de toxicité imprévue du traitement prolongé

Taverna CJ, *et al. J Clin Oncol* 2009; 27:Abstract 8534.
Taverna CJ, *et al. Blood* 2010; 116:Abstract 1802.

# LF à Faible Masse Tumorale

## Conclusions

1. Delaying treatment initiation remains an acceptable option in 2017

2. The clinical benefit of prolonged rituximab treatment in FL patients is not established

3. Other approaches should be investigated:
   - radioimmunotherapy
   - short combination of R + chemotherapy
   - new agents (immunomodulation, new antibodies, kinase inhibitors, …)

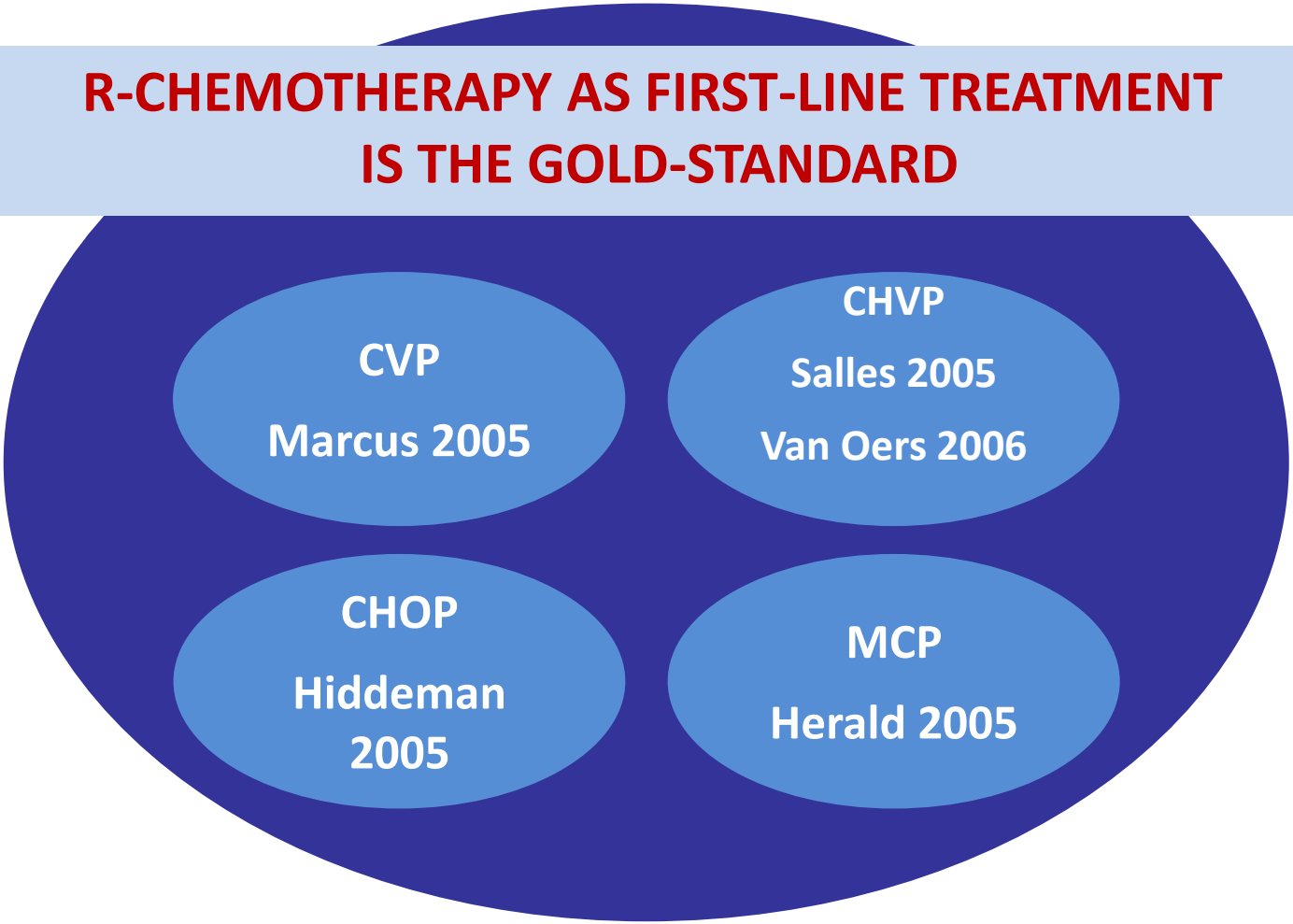
# Lymphomes Folliculaires Localisés: La Radiothérapie a-t-elle encore une place en 2017 ?

# RADIOTHERAPIE

| | N patients | Median age (years) | Treatment | 10y-OS |
|---|---|---|---|---|
| Stanford | 177 | 53 | 35-50 Gy | 64% |
| Princess Margaret | 596 | 56 | 20-35 Gy | 58% |
| BNLI | 82 | 59 | 35 Gy | 64% |
| Royal Marsden | 58 | 55 | 30-54 Gy | 79% |
| Advani | 43 | 58 | - | 86% |

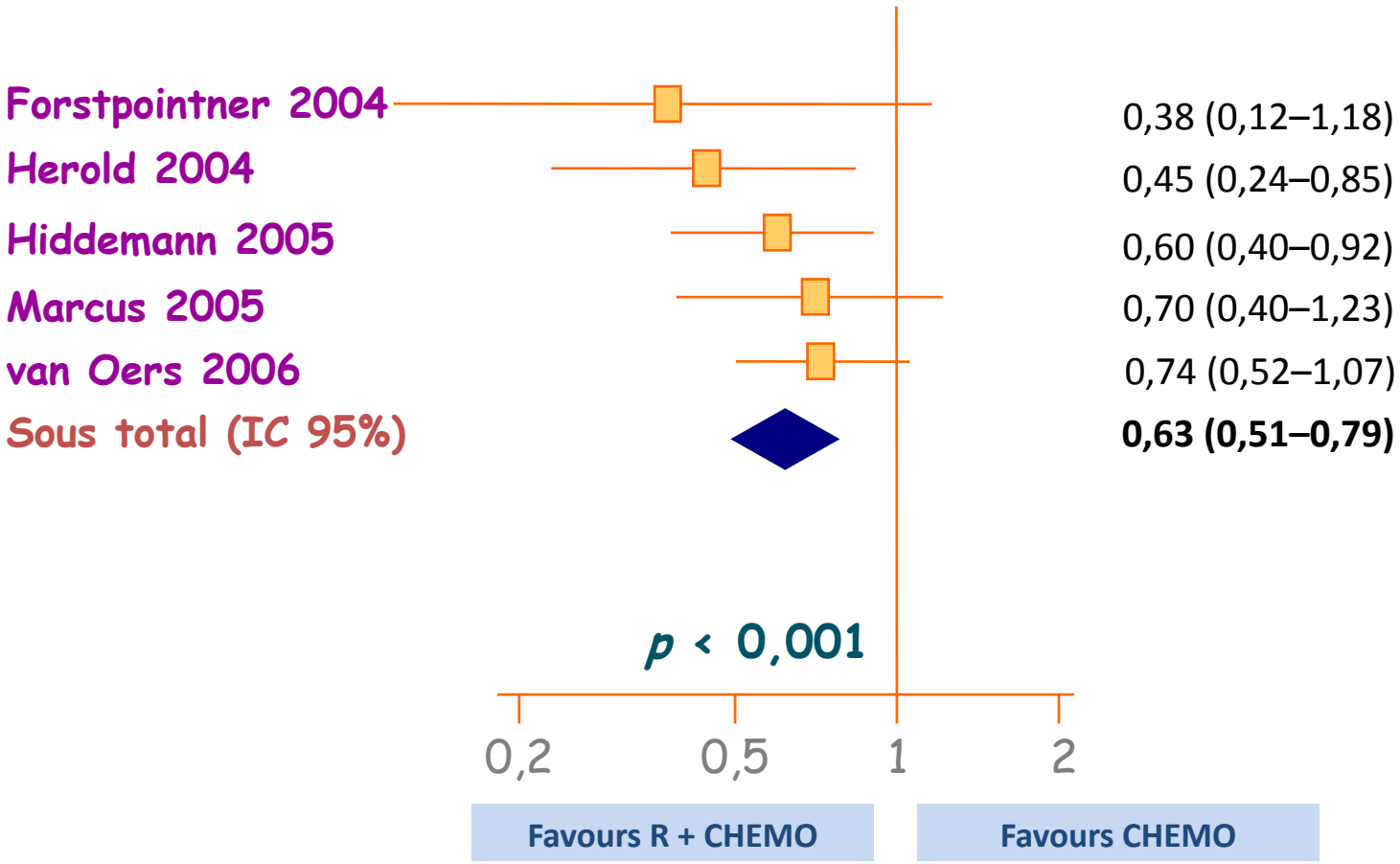
# Lymphomes Folliculaires À Forte Masse Tumorale : Comment traiter en 2017 ?

# LF à Forte Masse Tumorale



# LF à Forte Masse Tumorale

## OS: Meta-analysis

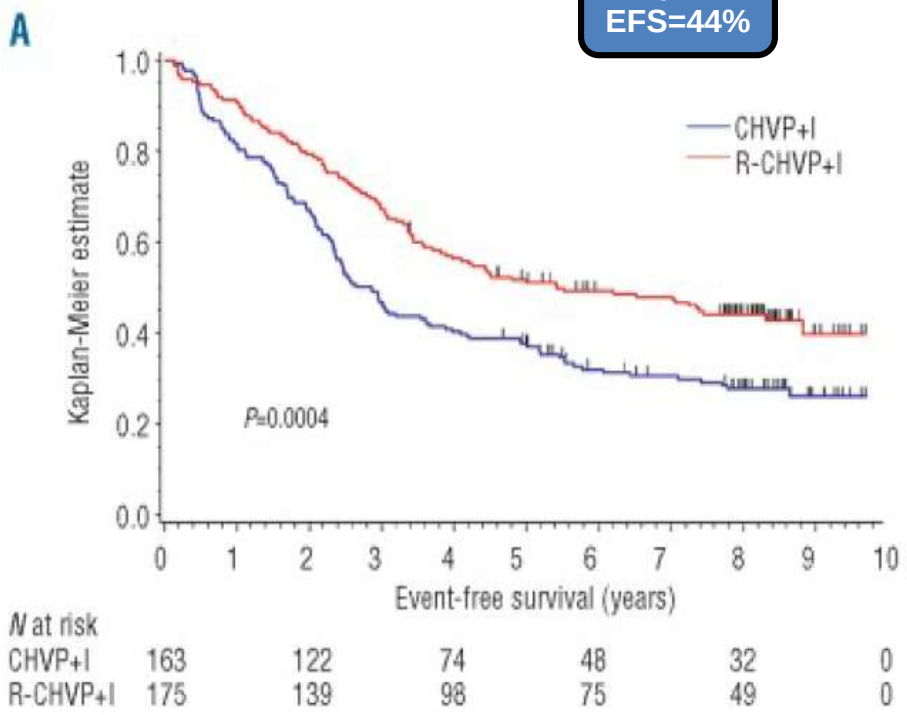



*Schulz H et al., J Natl Cancer Inst. 2007; 99(9): 706-714*

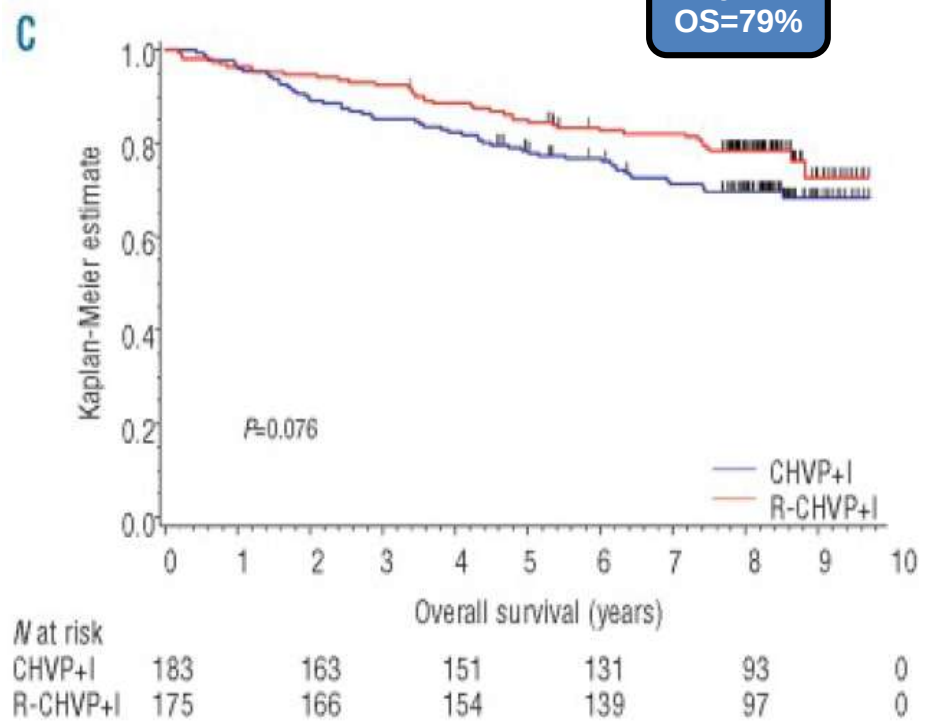
# LF à Forte Masse Tumorale

## FL 2000 GELA-GOELAMS Study: Ph III, Multicentric

**8-year EFS=44%**




**8-year OS=79%**

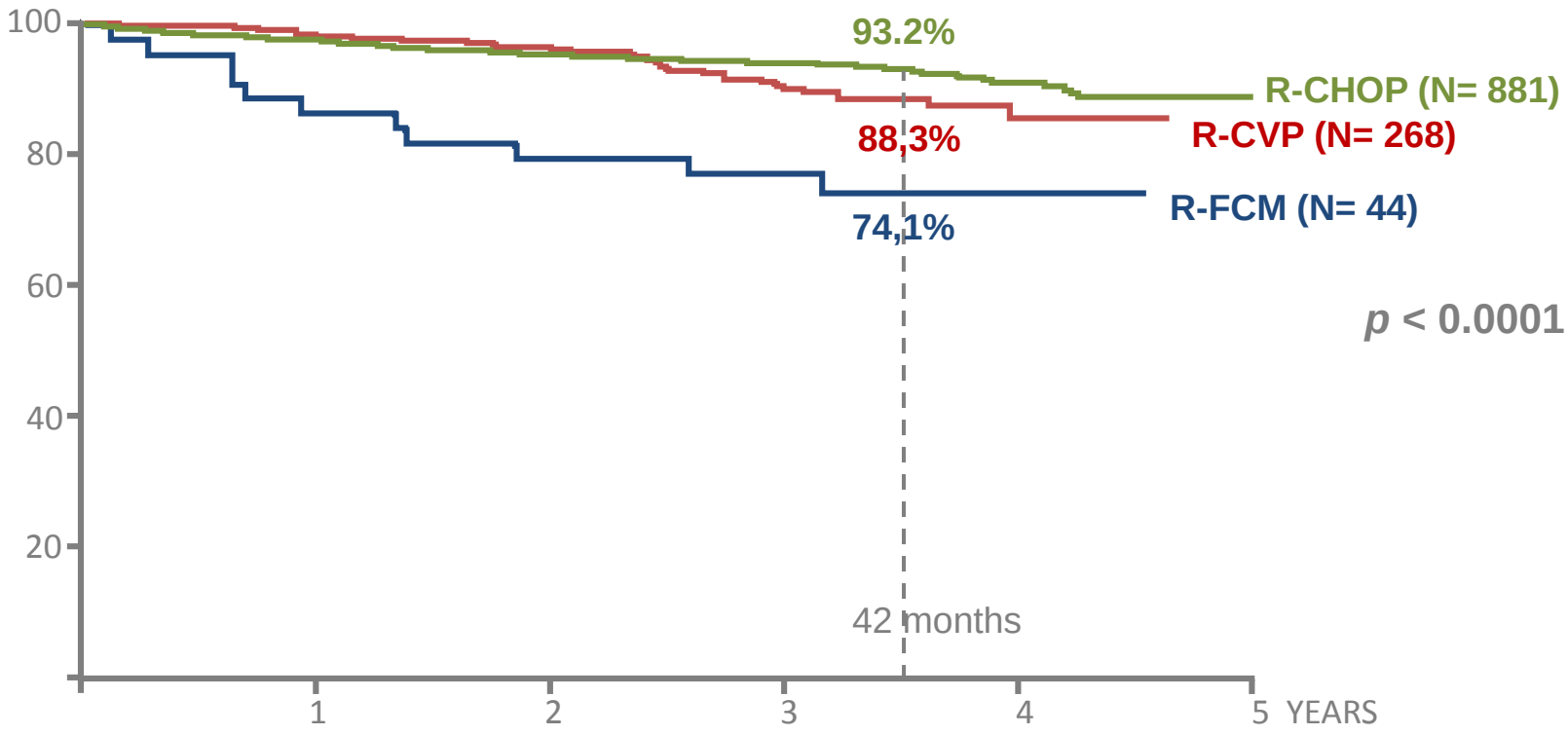



**Median follow-up = 8.3 years**

*Bachy et al, Haematologica 2013*

# LF à Forte Masse Tumorale

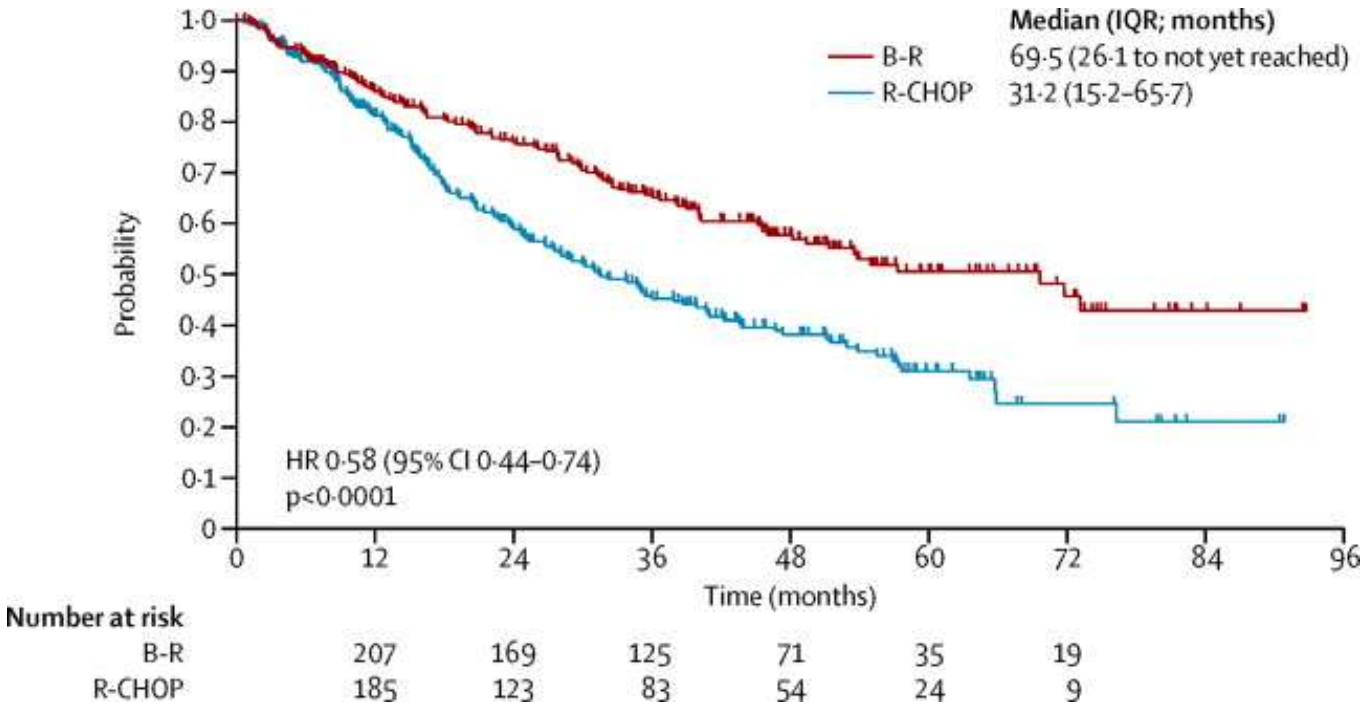
## All chemo regimen are not equal: PRIMA Study
## OS from registration by induction regimen




*Morschhauser et al., ICML 2011*

# LF à Forte Masse Tumorale

## All chemo regimen are not equal: R-Benda vs R-CHOP
## PFS from registration by induction regimen




*Rummel MJ et al., The Lancet 2013*

# LF à Forte Masse Tumorale

## How to consolidate response after Induction Regimen?

**1980's: INTERFERON ALPHA**

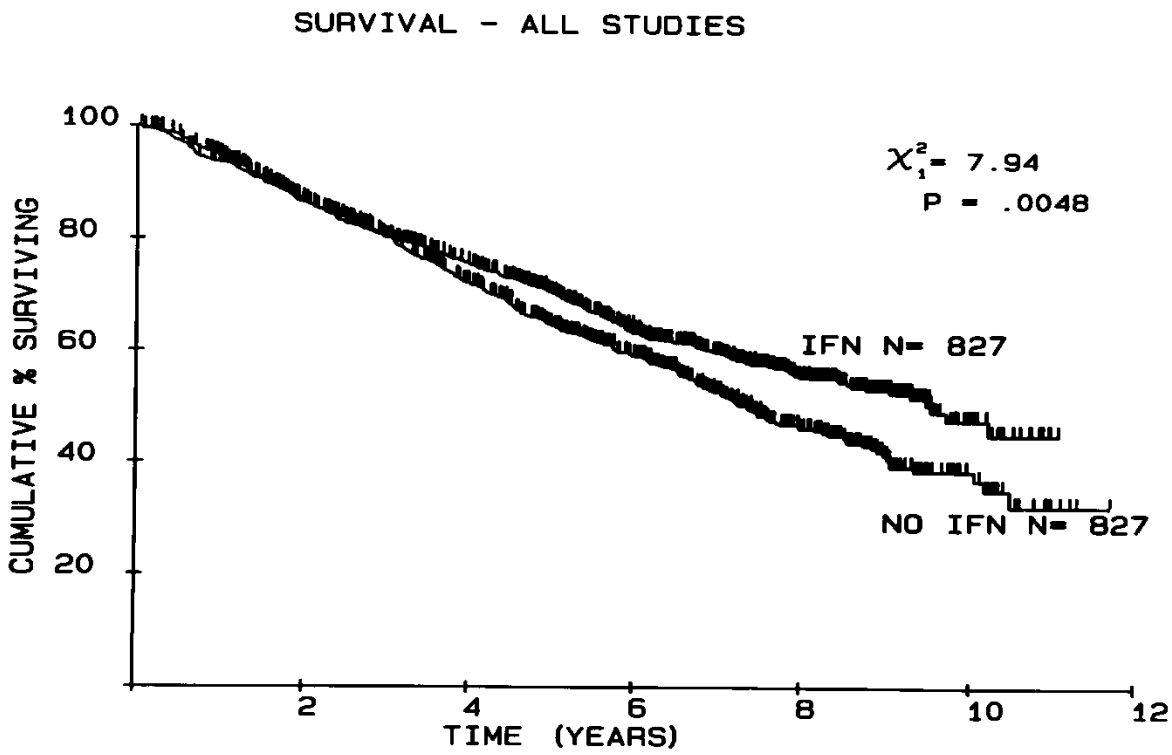
**1990's: AUTOLOGOUS STEM CELL TRANSPLANTATION**

**2000's: MONOCLONAL ANTIBODIES**
- **RADIO IMMUNO CONJUGATES**
- **RITUXIMAB**

**2010's: FUTURE DIRECTIONS**

# LF à Forte Masse Tumorale

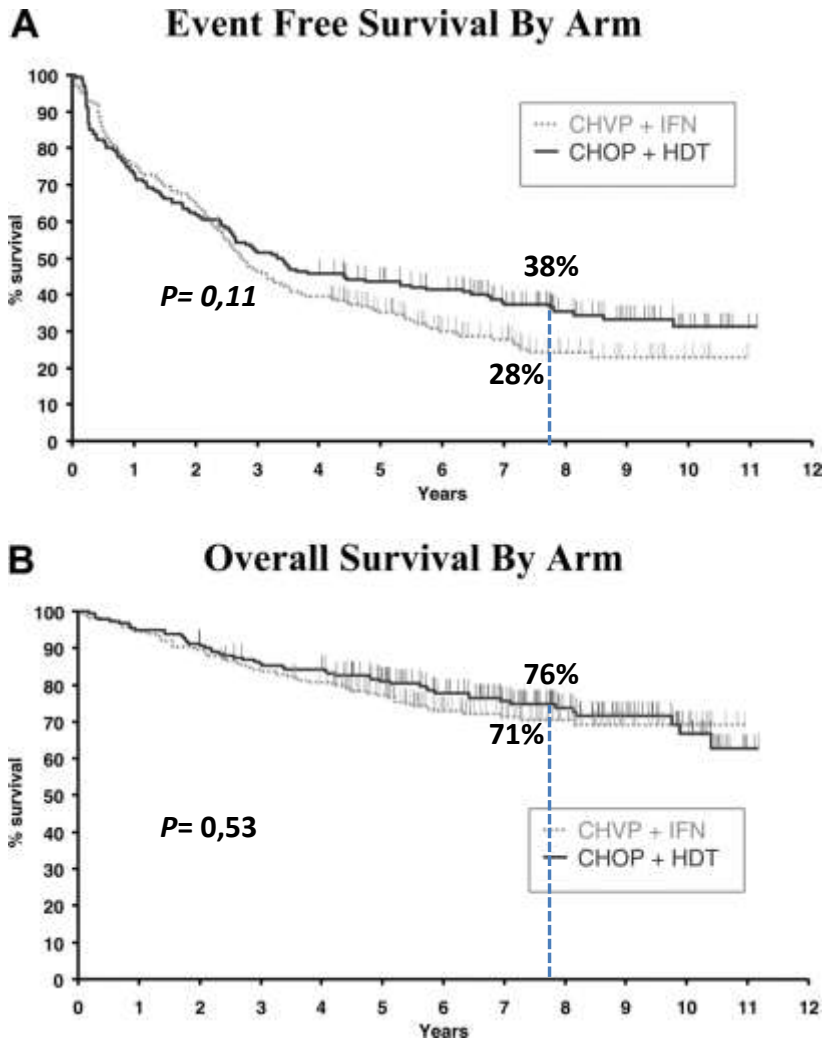
## IFNα Treatment maintenance: Meta-analysis




*Rohatiner et al, JCO 2005, 23: 2215-2223*

# LF à Forte Masse Tumorale

## ASCT: GELF 94 Results

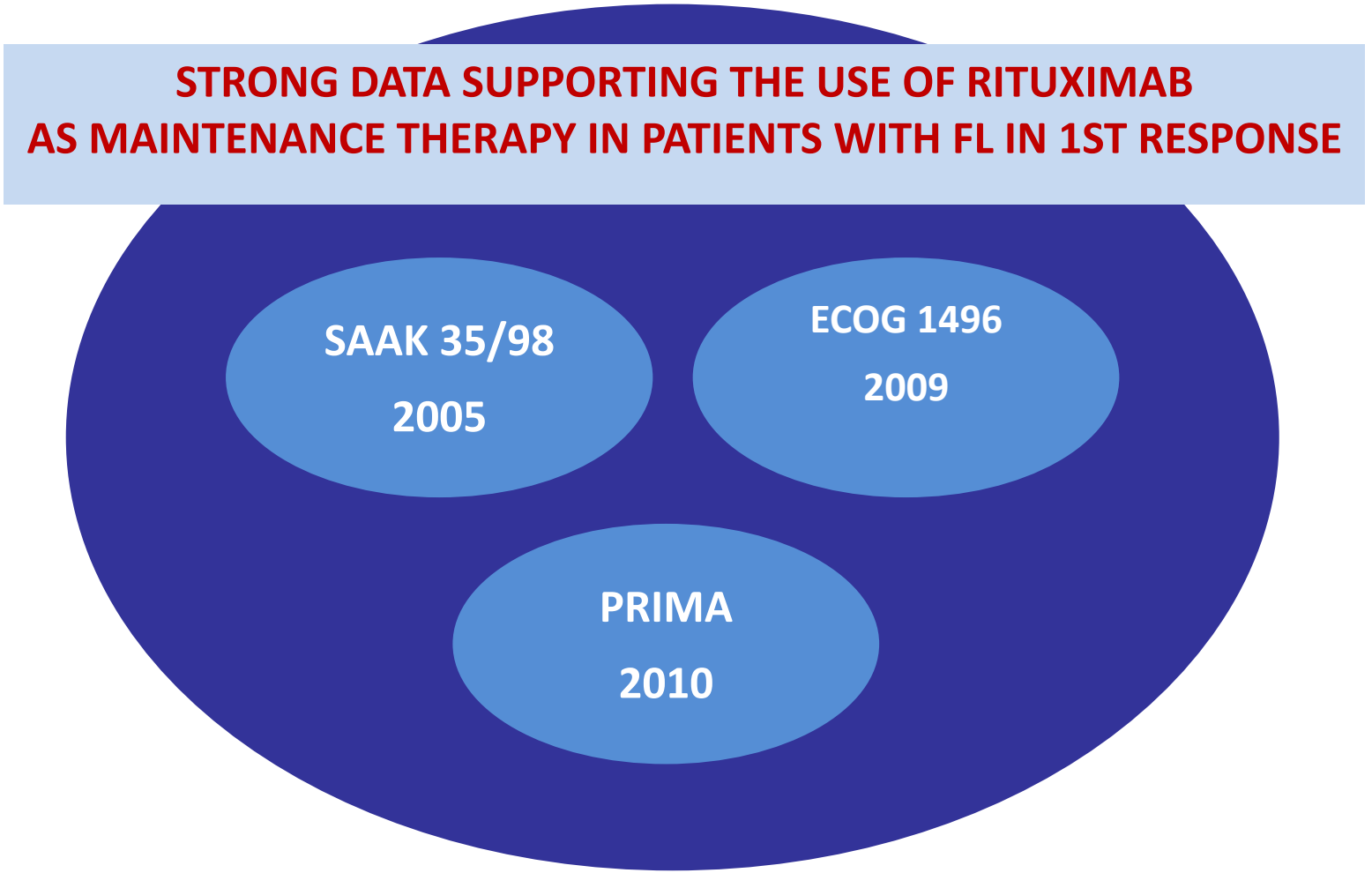



blood



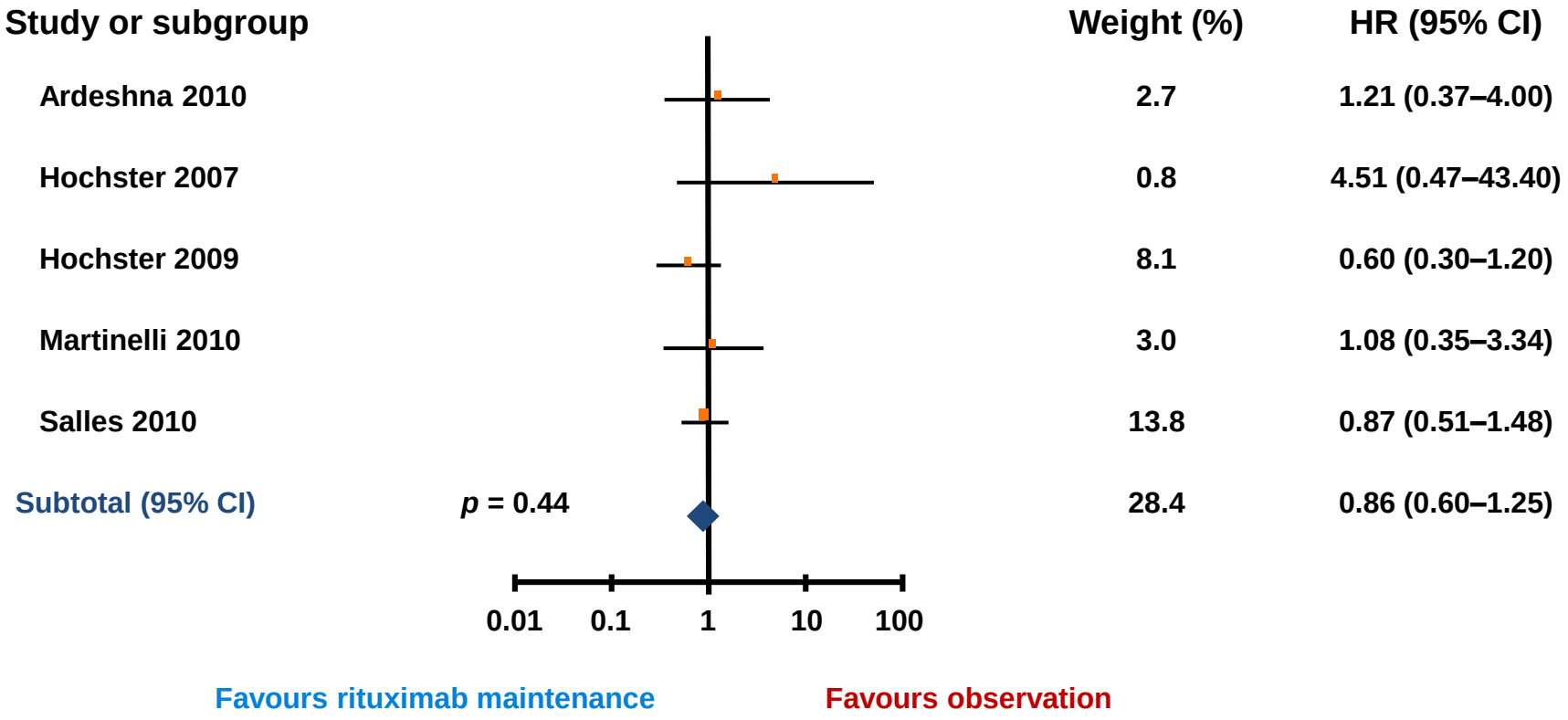
*Sebban C et al. Blood 2006;108:2540-2544*

# LF à Forte Masse Tumorale



# LF à Forte Masse Tumorale

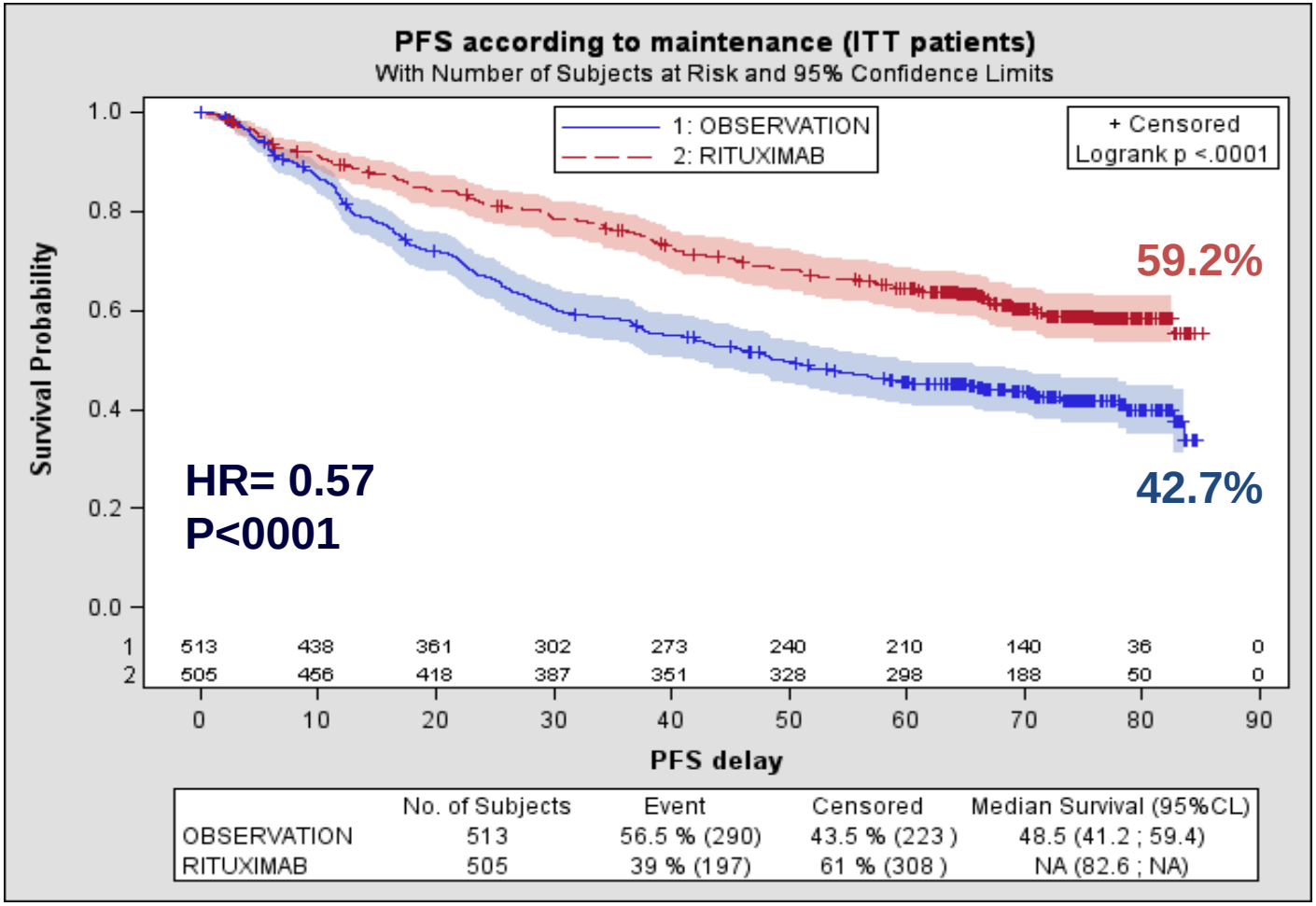
## Rituximab maintenance and OS: Meta-analysis




*Vidal L, et al. JNCI 2011.*

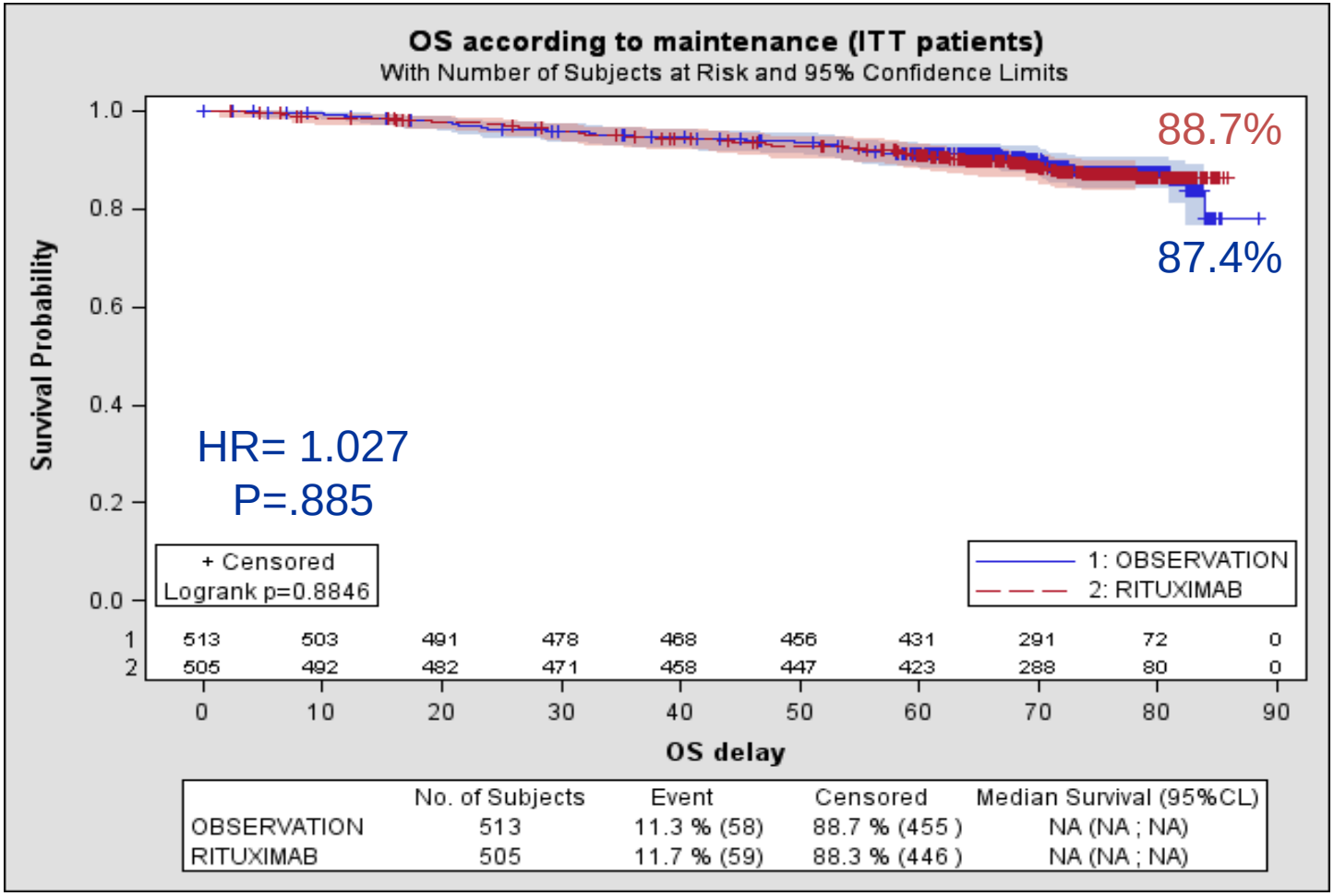
# LF à Forte Masse Tumorale

## PRIMA Study 6 years FU



# LF à Forte Masse Tumorale

## PRIMA Study 6 years FU



# Lymphomes Folliculaires:

## Traitement de 1ière ligne
## Futures directions

*Société Algérienne d'Hématologie*

*Le 26 Octobre 2017*

*Réda Bouabdallah*

*Institut Paoli-Calmettes, Marseille, France*

# OBITITUZUMAB-BENDAMUSTINE

Non-Hodgkin Lymphoma

ARTICLE

## Safety and efficacy of obinutuzumab with CHOP or bendamustine in previously untreated follicular lymphoma

Andrew Grigg,[1] Martin J.S. Dyer,[2] Marcos González Díaz,[3] Martin Dreyling,[4] Simon Rule,[5] Guiyuan Lei,[6] Andrea Knapp,[7] Elisabeth Wassner-Fritsch[7] and Paula Marlton[8]

EUROPEAN HEMATOLOGY ASSOCIATION

Ferrata Storti Foundation

**GA101 + BENDAMUSTINE 4-6 cycles**

**GA101 + CHOP 6-8 cycles**

**CR PR**

**GA101 1000 mg/3 months 2 years**

**GA101 1000 mg/3 months 2 years**

***Primary Objective:***
**Safety**

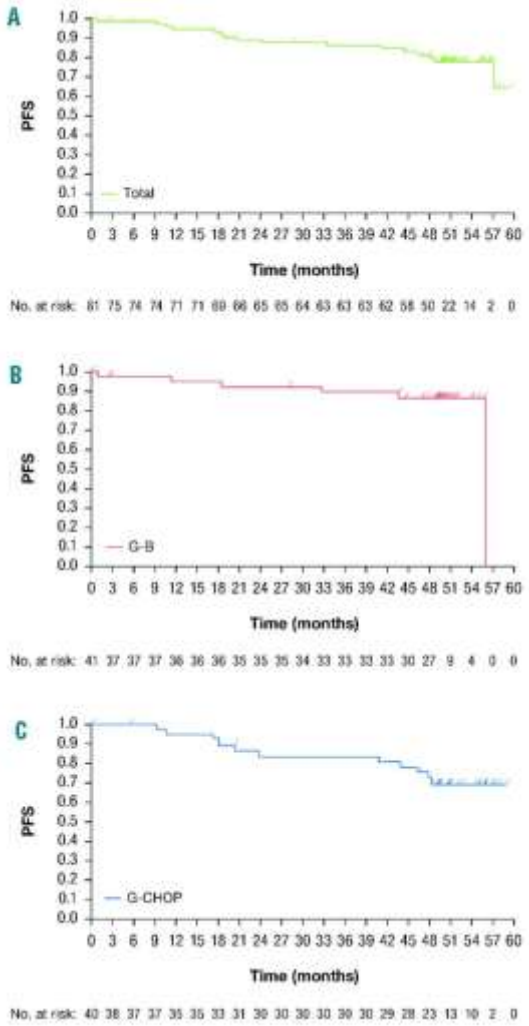
***Secondary Objectives:***
**ORR, CRR**
**PFS**

*Grigg A et al., Haematologica 2017*

# OBITITUZUMAB-BENDAMUSTINE

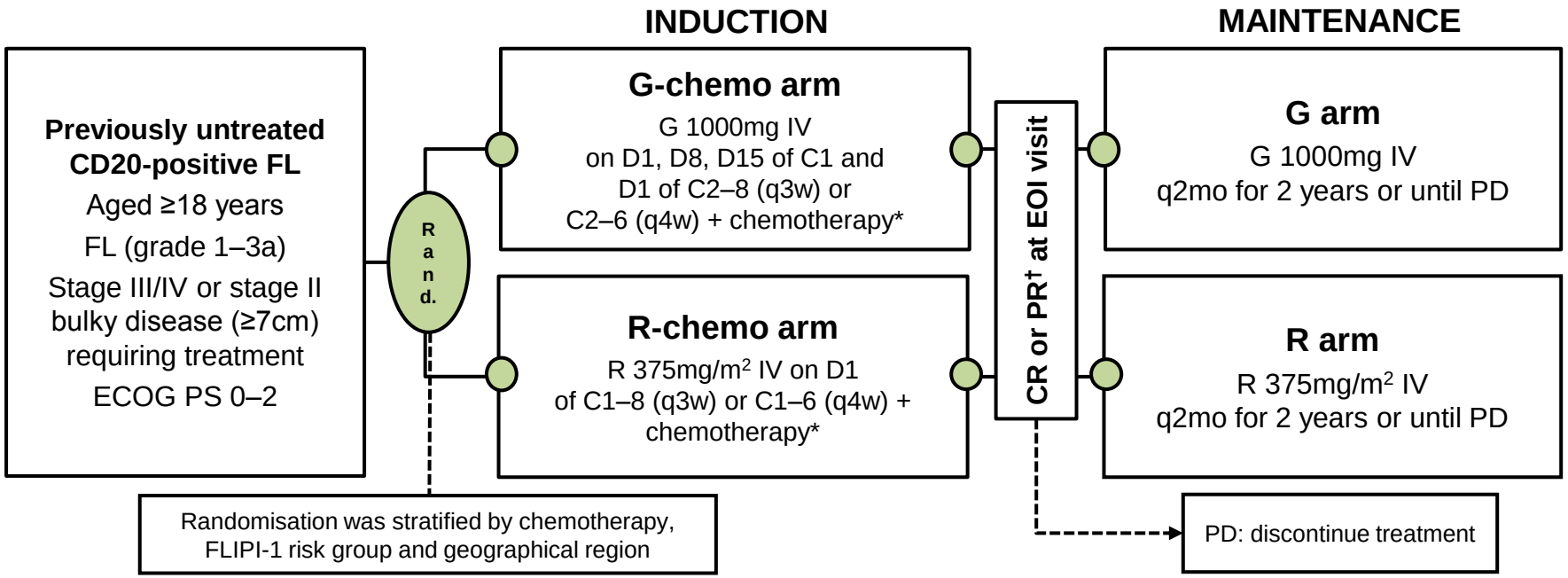
| | G-B | G-CHOP | TOTAL |
|---|---|---|---|
| N | 41 | 40 | 81 |
| Med. Age (y) | 57 | 53,5 | 55 |
| Bulky (≥ 7 cm) | 41% | 45% | 43% |
| FLIPI (IR + HR) | 80% | 83% | 82% |

| | G-B | G-CHOP | TOTAL |
|---|---|---|---|
| ORR | 93% | 95% | 94% |
| CR at end of induction | 37% | 35% | 36% |
| CR at 30 months | 63% | 58% | 61% |
| 3 –y PFS | 90% | 84% | 87% |




*Grigg A et al., Haematologica 2017*

# Obinituzumab-CT vs R-CT as 1st Line in FL: GALLIUM




***Primary Objective:*** **PFS (INV)**
***Secondary Objectives:*** **PFS (ICR), ORR, EFS, OS, Safety**

*Marcus R et al., NEJM 2017*

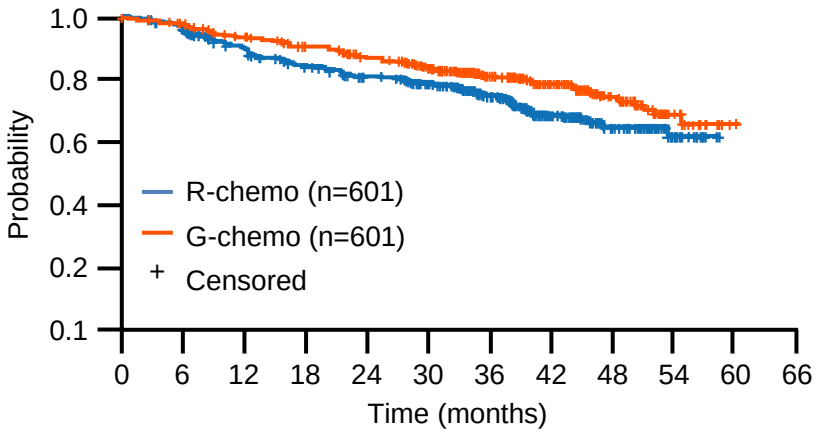
# Obinituzumab-CT vs R-CT as 1st Line in FL: GALLIUM

| n (%) | R-chemo, n=601 | G-chemo, n=601 |
|---|---|---|
| AGE, Median | 58.0 (23–85) | 60.0 (26–88) |
| FLIPI ≥ 2 | 476 (79%) | 474 (79%) |
| BM+ | 295 (49.3)‡ | 318 (53.7) § |
| EN INVOLVEMENT | 396 (65.9) | 392 (65.2) |
| BULKY (≥7cm) | 271 (45.2)¶ | 255 (42.5)¶ |
| INTERVAL DG-RANDO (Months) | 1.4 (0–168.1)‡ | 1.5 (0.1–121.6)‡ |
| CHEMOTHERAPY | | |
| BENDA | 341 | 345 |
| CHOP | 203 | 196 |
| CVP | 57 | 60 |

*Marcus R et al., NEJM 2017*

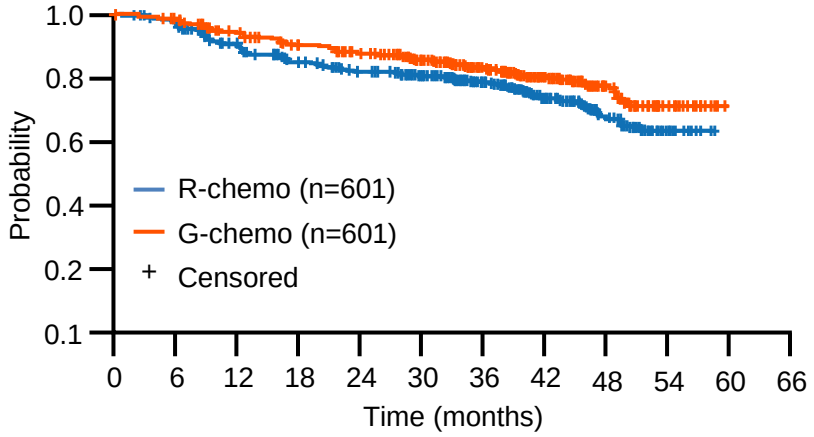
# Obinituzumab-CT vs R-CT as 1st Line in FL: GALLIUM

*INV-assessed PFS*




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

*ICR-assessed PFS*




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

*Marcus R et al., NEJM 2017*

# Obinituzumab-CT vs R-CT as 1st Line in FL: GALLIUM

## Adverse Events

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

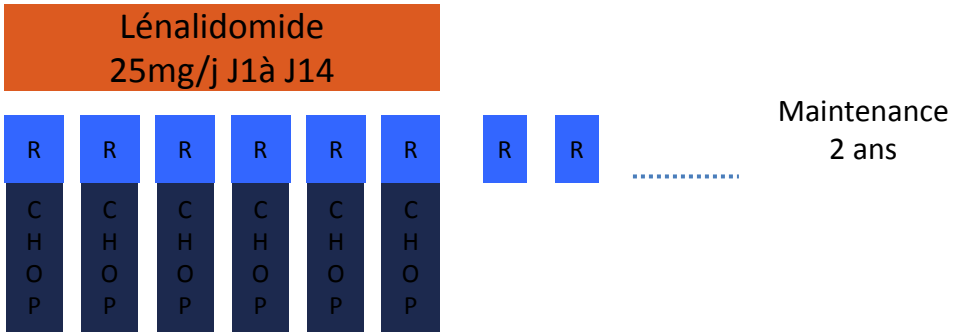
## Selected grade 3–5 AEs of particular interest (frequency >2%)

| n (%) of pts reporting ≥1 one event | R-chemo, n=597 | G-chemo, n=595 |
|---|---|---|
| Neutropenia | 236 (39.5) | 278 (46.7) |
| Infections[†] | 98 (16.4) | 121 (20.3) |
| IRR | 40 (6.7) | 74 (12.4) |
| Thrombocytopenia | 16 (2.7) | 36 (6.1) |
| 2nd malignancies | 21 (3.5) | 29 (4.9) |
| Cardiac events | 17 (2.8) | 23 (3.9) |

*Marcus R et al., NEJM 2017*

# LENALIDOMIDE-RITUXIMAB-CHOP

## Lénalinomide + R-CHOP: R2CHOP Phase II



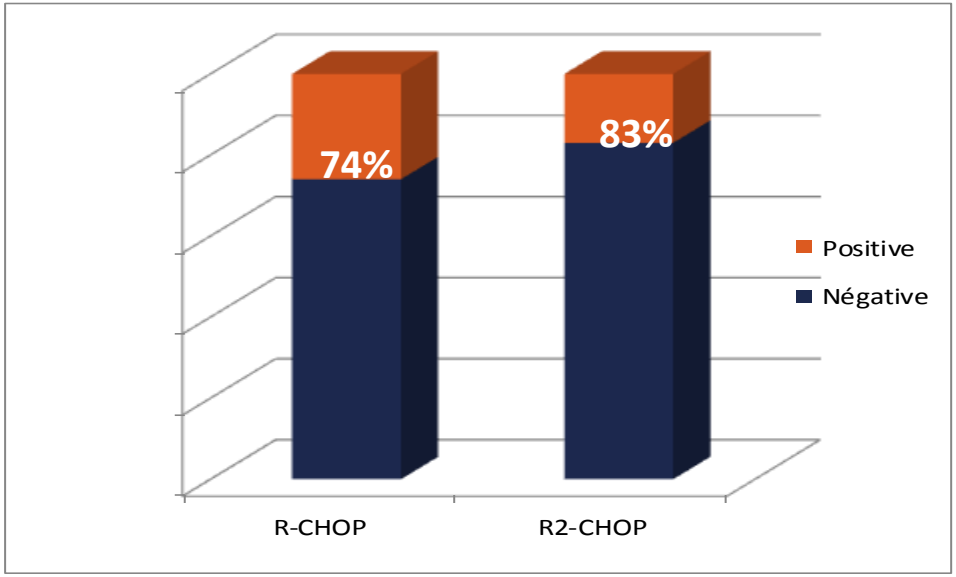

| | Patients (n = 80) |
|---|---|
| Âge | 57 ans [29-71] |
| | n (%) |
| Stade III-IV | 74 (93) |
| LDH élevées | 32 (40) |
| Masse > 10 cm | 20 (25) |
| FLIPI 3-5 | 50 (63) |

Critères de jugement

-Principal : taux de RC

-Secondaires : tolérance, SSP, SG, comparaison avec PRIMA

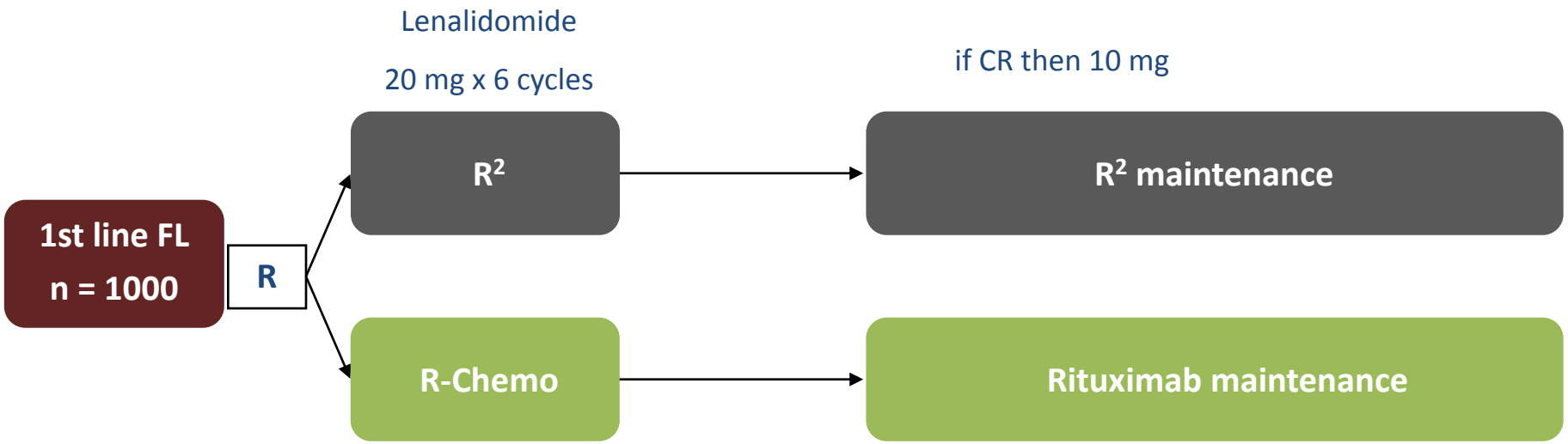
**Réponse à la fin de l'induction (Critères de Deauville)**




*ASH 2013 - D'après Tilly H et al., abstr. 248, actualisé*

# RELEVANCE: R2 vs R-CHEMOTHERAPY

## International Multicenter Randomized phase III Study




**Co-Primary End-points:** **CR/Cru at 1,5 years**
**PFS**

# CONCLUSIONS

## QUI TRAITER?

**Patients avec Forte Masse Tumorale: OUI**

***Patients avec Faible Masse Tumorale: ?***

## COMMENT TRAITER?

**R-CHIMIOTHERAPIE: R-CHOI**

***R: ? R suivi de Zevalin: ? Nouv***

**AMELIORATION SIGINIFICATIVE DE L'ESPERANCE DE VIE**

## COMBIEN DE TEMPS FAUT-IL TRAITER?

**Induction (4 m) + Maintenance (24 m): OUI**

***IS MORE BETTER ?***

# INTERROGATIONS

**De nouveaux paramètres sont à considérer**:

Longueur des intervalles sans traitement

Qualité de vie sous traitement

Toxicités des traitements à long terme …

Mais **le lymphome continue de représenter la principale cause de décès** et nous devons poursuivre l'évaluation des innovations thérapeutiques…

en évaluant soigneusement la qualité de la réponse

en s'efforçant d'améliorer la survie ..

… pour essayer de guérir les patients

# Lymphomes Folliculaires:

## Traitement des Rechutes/Réfractaires

*Société Algérienne d'Hématologie*

*Le 26 Octobre 2017*

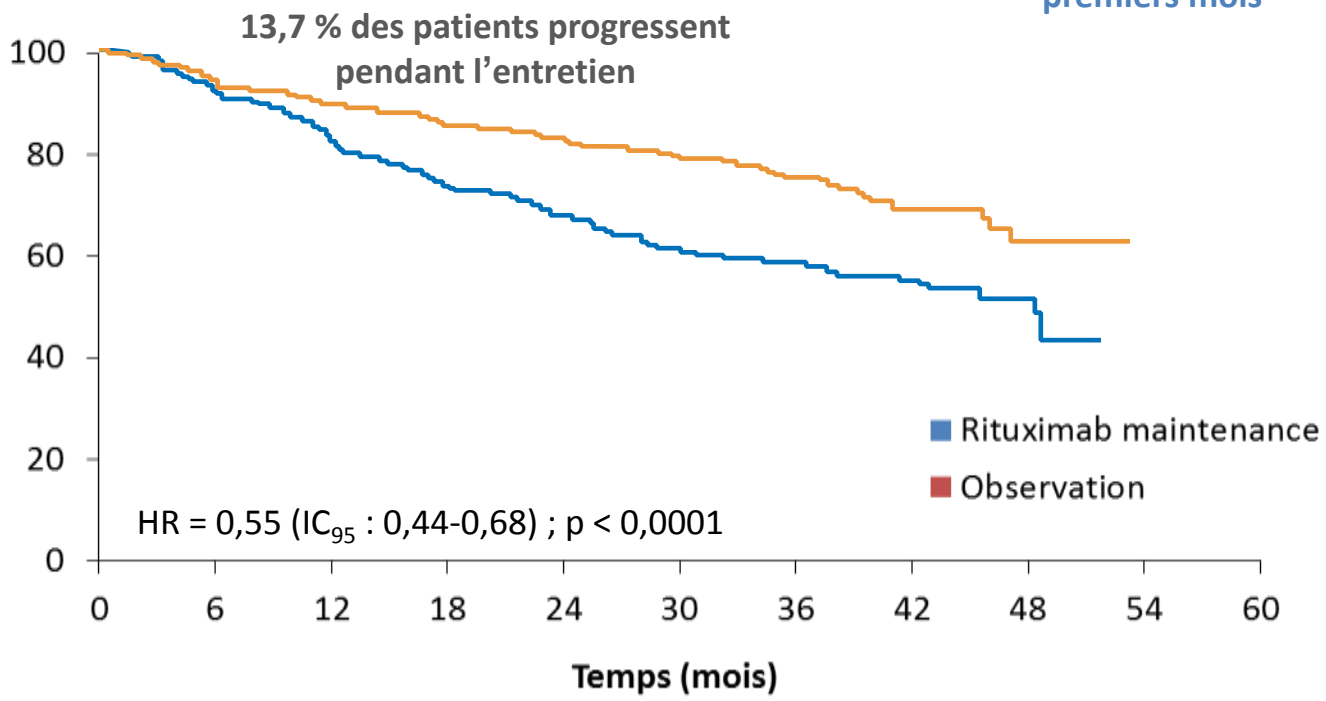
*Réda Bouabdallah*

*Institut Paoli-Calmettes, Marseille, France*

# Etude Prima: Survie sans Progression

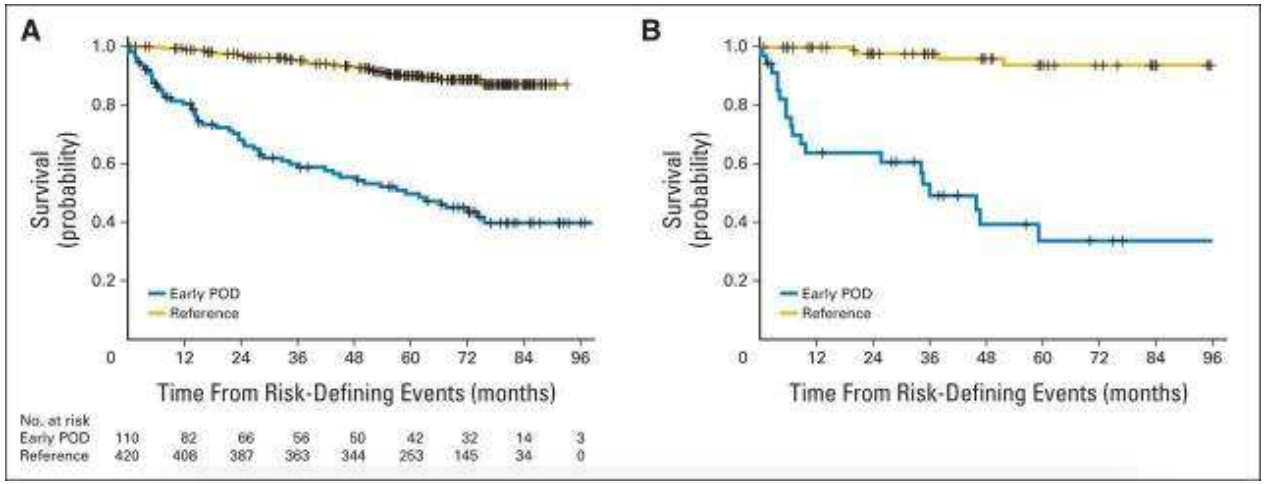
**2,7 % des patients progressent pendant l'induction**

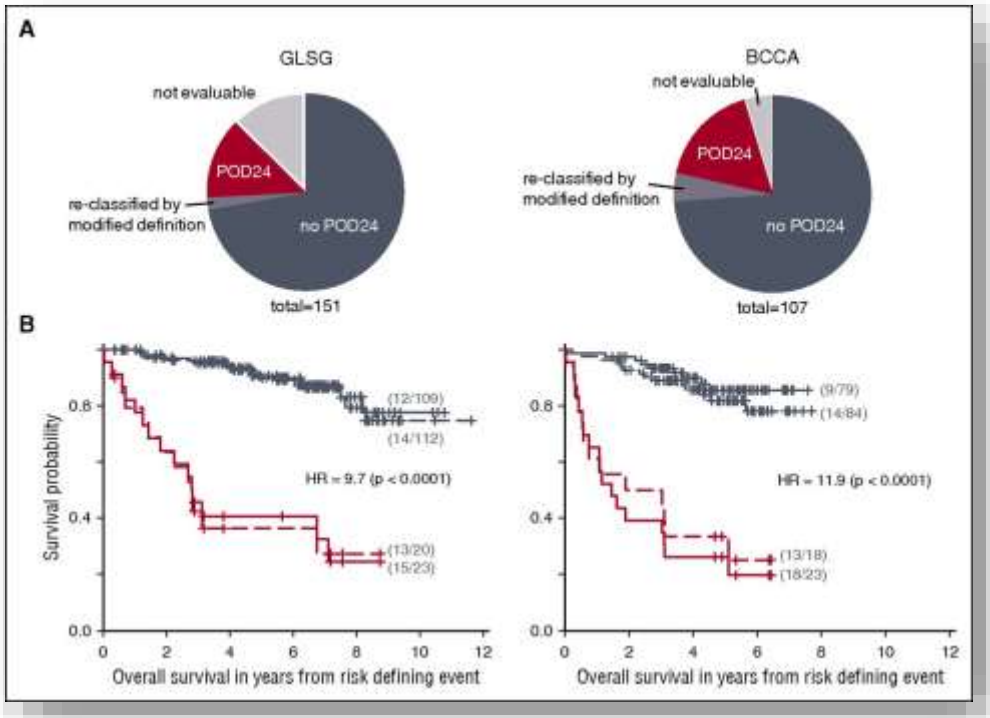
**20 % des patients auront rechuté/progressé dans les 24 premiers mois**




*Salles G et al. Lancet 2010 ; Salles G et al. ASH 2013.*

# Early relapse after R-CHOP= poor outcome

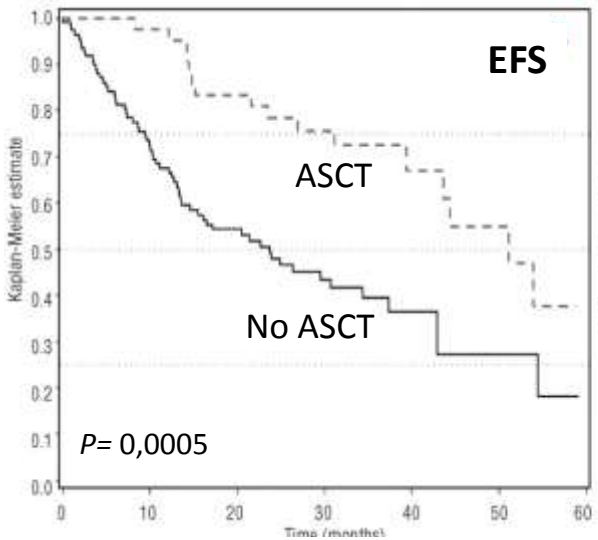


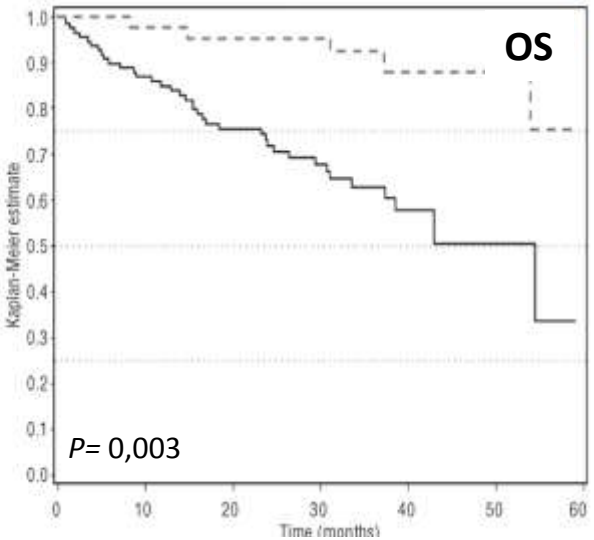



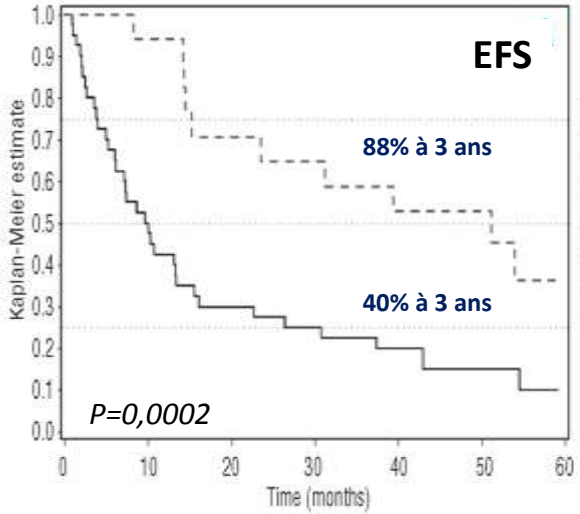

*Casulo C, et al. J Clin Oncol 2015;*
*Jurinovic V, et al. Blood 2016*

# Place de l'Autogreffe en Rechute/Réfractaire

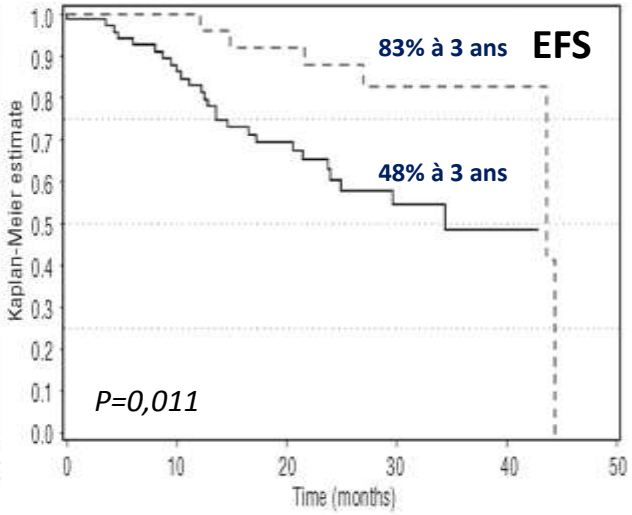
## Étude FL 2000




**Pts réfractaire**

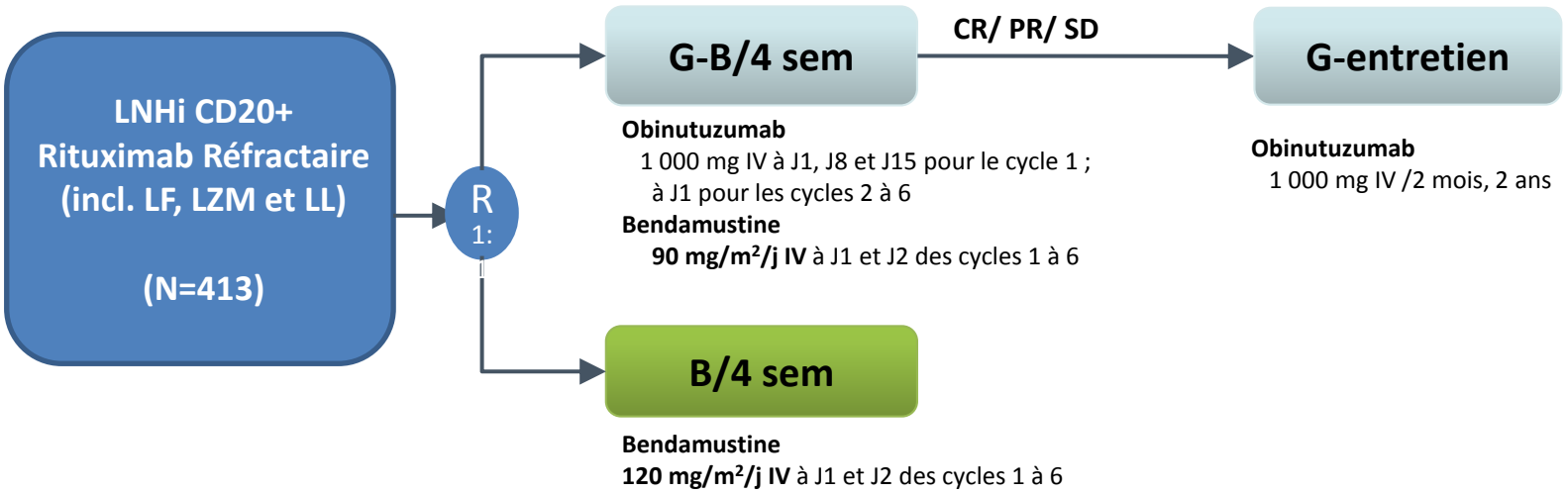



**Pts en rechute**

*Le Gouill S, et al. Haematologica 2011*

# Place de l'OBINITUZUMAB dans la rechute précoce: GADOLIN

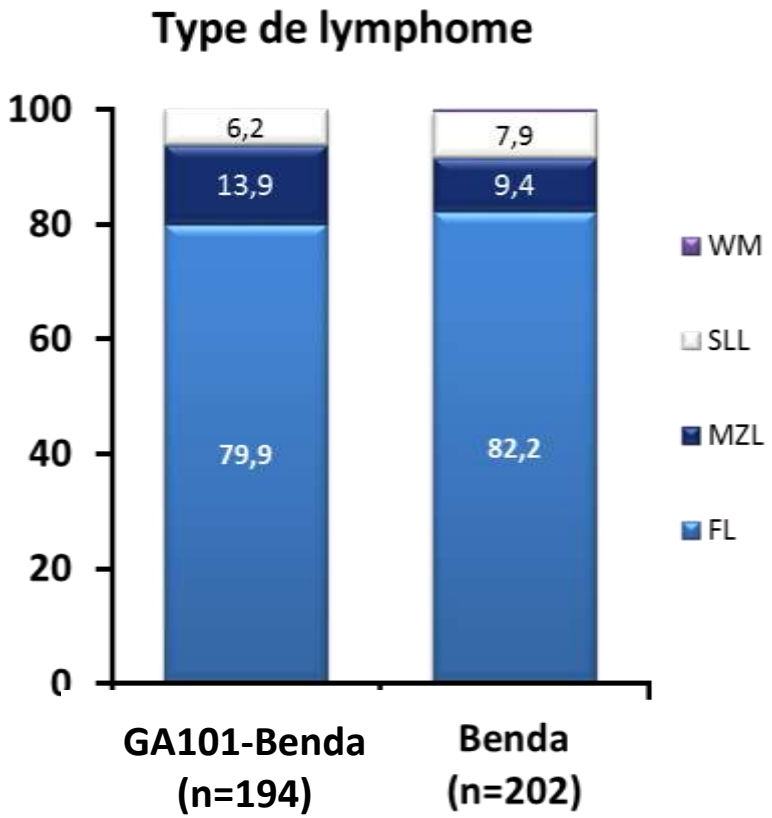
## Etude de phase III, multicentrique, internationale, randomisée, en ouvert




**Critère principal: PFS revue par comité indépendant**

*Sehn et al. Lancet Oncol 2016*

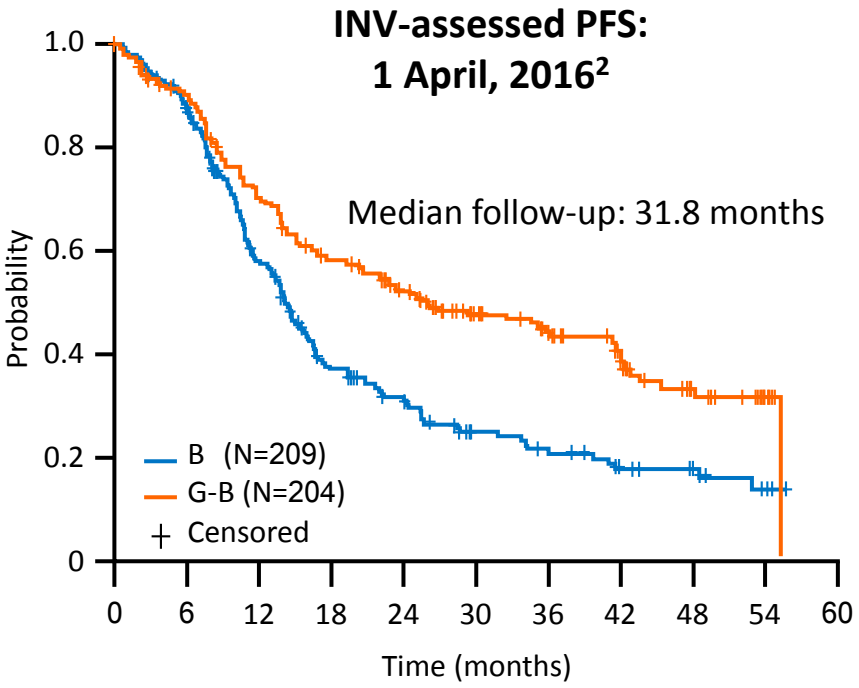
# Place de l'OBINITUZUMAB dans la rechute précoce: GADOLIN

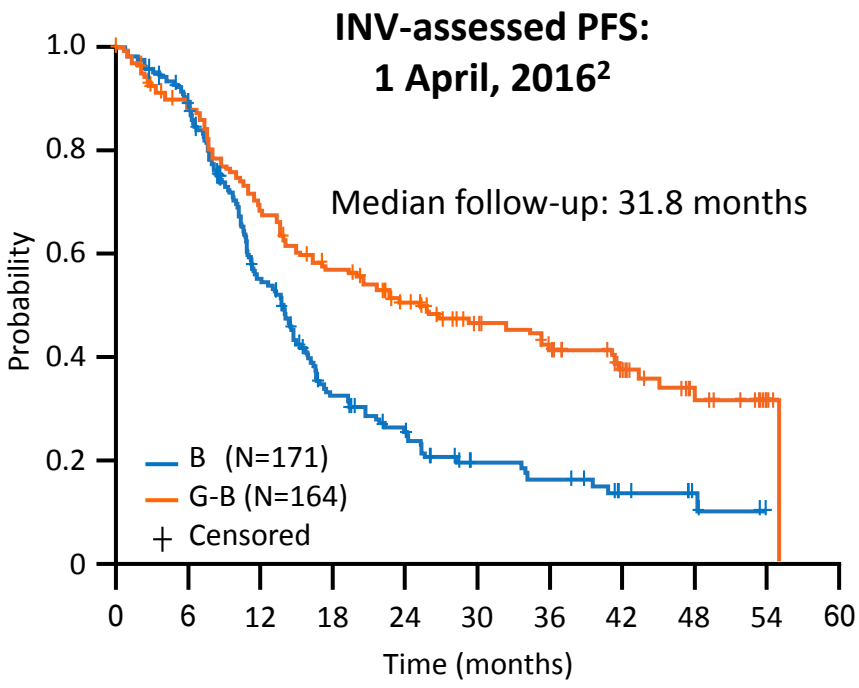



| | B, N=166 | G-B N=155 |
|---|---|---|
| **AGE** | 62.5 (35–87) | 61.8 (34–87) |
| **Médiane Dg-Rando, années** | 4.2 (0.3–29.9) | 4.4 (0.3–32.1) |
| **Traitements antérieurs** | 2 (1–7) | 2 (1–10) |
| **Durée médiane dernière réponse** | 3,7 mois | 3,9 mois |
| **Patients doubles réfractaires** | 80% | 77% |

*Sehn et al. Lancet Oncol 2016*

# Place de l'OBINITUZUMAB dans la rechute précoce: GADOLIN




## ALL PATIENTS

| | B (n=209) | G-B (n=204) |
|---|---|---|
| Events, n (%) | 146 (69.9) | 115 (56.4) |
| Median PFS, months (95% CI) | 14.1 (12.6, 16.0) | 25.8 (19.5, 41.1) |
| Stratified* HR (95% CI), p-value | 0.57 (0.44, 0.73), p<0.0001 | |

## FL PATIENTS

| | B (n=171) | G-B (n=164) |
|---|---|---|
| Events, n (%) | 125 (73.1) | 93 (56.7) |
| Median PFS, months (95% CI) | 14.0 (11.3, 15.3) | 25.3 (17.4, 36.0) |
| Stratified† HR (95% CI), p-value | 0.52 (0.39, 0.69), p<0.0001 | |

*Cheson B et al, ASH 2016*

# THERAPIES CIBLEES EN 2017

- Naked Monoclonal Antibodies
- Antibody Drug Conjugated (ADC)
- Lenalidomide
- BCR inhibitors
- Pi3K inhibitors
- Anti-Bcl2
- Allogreffe
- CAR-T cells

# Leucémie Lymphoïde Chronique

## Etat des lieux en 2017

*Société Algérienne d'Hématologie*

*Le 26 Octobre 2017*

*Réda Bouabdallah*

*Institut Paoli-Calmettes, Marseille, France*

# LLC: Le paradoxe

Malgré un définition « cyto-phénotypique » précise:

- Extrême hétérogénéité clinique
  - De l'abstention thérapeutique pendant 20 ans à une espérance de vie de moins de 3 ans en rechute réfractaire…
- Problématique « triple »
  - Caractérisation pronostique
  - Décision d'initiation de traitement
  - Choix thérapeutique

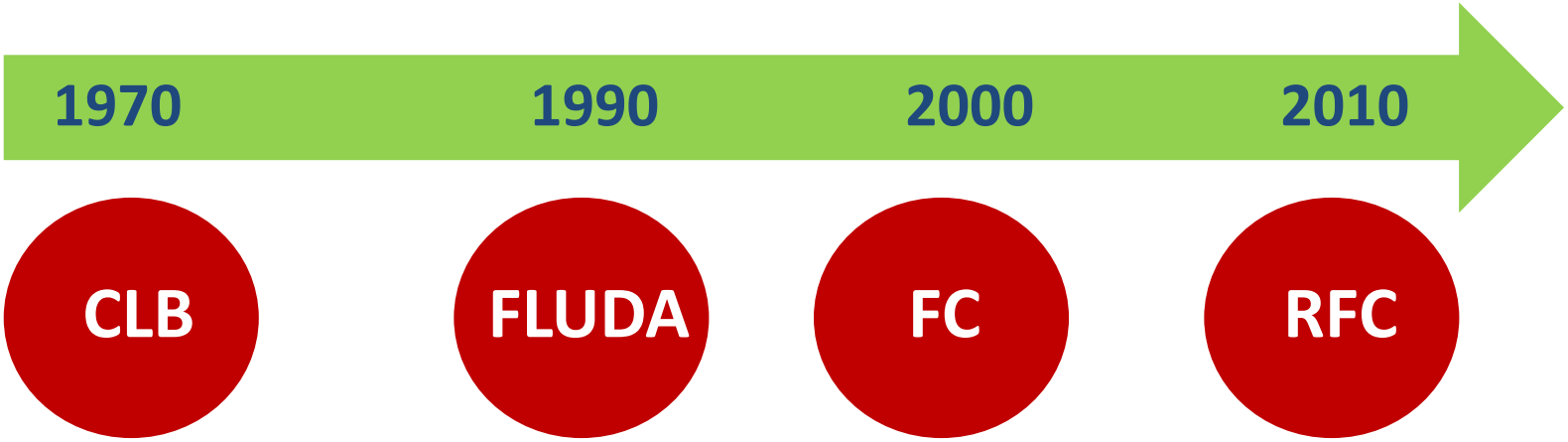
# Facteurs décisionnels du traitement

- AGE (65)
- COMORBIDITES (CIRS 6)
- FISH
  - Del(17p)/TP53
  - Del(11q)
- Futurs:
  - IGVH Muté/IGVH Non Muté
  - NOTCHE
  - Nouveaux traitements

# Objectifs du traitement de 1ière ligne

- Rémission complète?
- Rémission moléculaire?
- Allongement PFS?
- Allongement OS?
- Réduire la toxicité?

# LLC: Historique des traitements



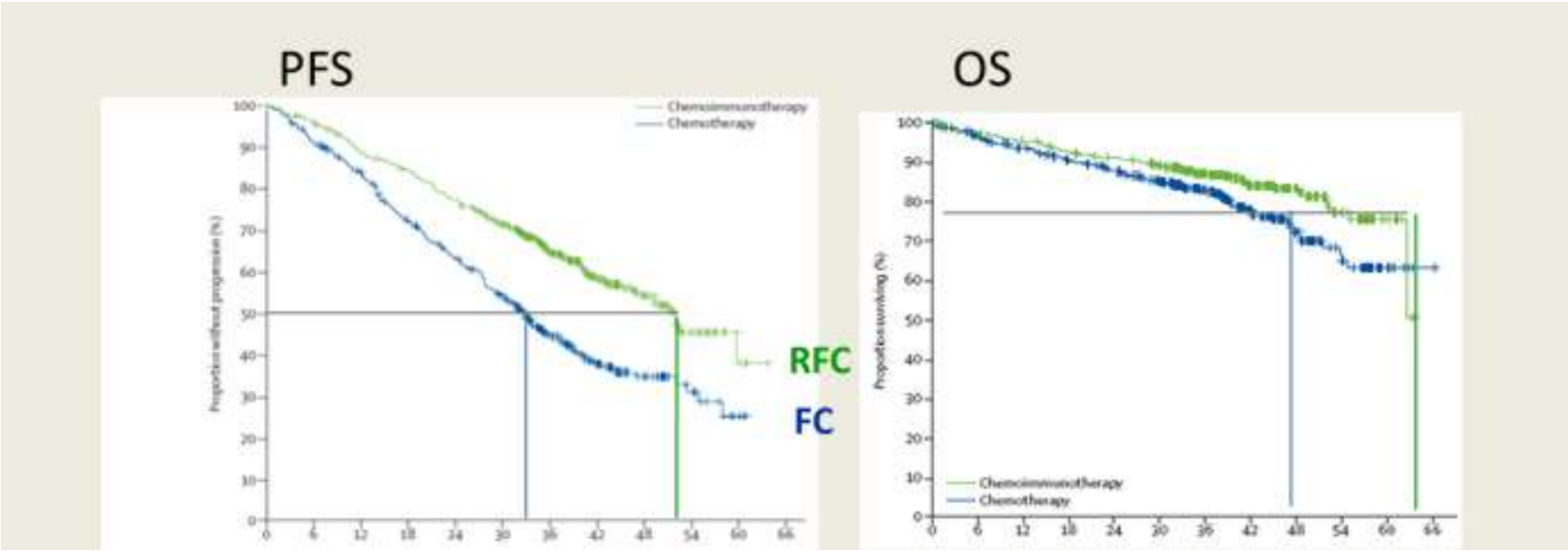

| | | | | |
|---|---|---|---|---|
| **OR** | 50% | 60-80% | 80-90% | > **90%** |
| **CR** | < 5% | < 20% | 25-35% | **50-70%** |
| **MRD-** | 0 | < 10% | 15-25% | > **50%** |
| **DDR** | < 2 y | 2-3 y | 3-4 y | > **4 y** |

**AGE ≤ 65 ANS OU CIRS ≤ 6**
**« Young/Fit »**
**No del17 and/or TP53 mutation**

# RFC: Gold Standard (CLL8)

| | |
|---|---|
| **RITUXIMAB:** | 375 mg/m² C1 |
| | 500 mg/m² C2-C6 |
| **FLUDARABINE:** | 25 mg/m² d1-d3 (40) |
| **CYCLOPHOSPHAMIDE:** | 250 mg/m² d1-d3 |

6 cycles; d1-d28




*Hallek, Lancet 2010*

# CLL10: FCR vs BR en 1ière ligne

## CLL10 STUDY: FCR VS BR IN FRONT-LINE

Design

Patients with untreated, active CLL without del(17p) and good physical fitness
(CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

Randomization

**FCR**

Fludarabine 25 mg/m² i.v., days 1-3
Cyclophosphamide 250 mg/m², days 1-3,
Rituximab 375 mg/ m² i.v day 0, cycle 1
Rituximab 500 mg/m² i.v. day 1, cycle 2-6

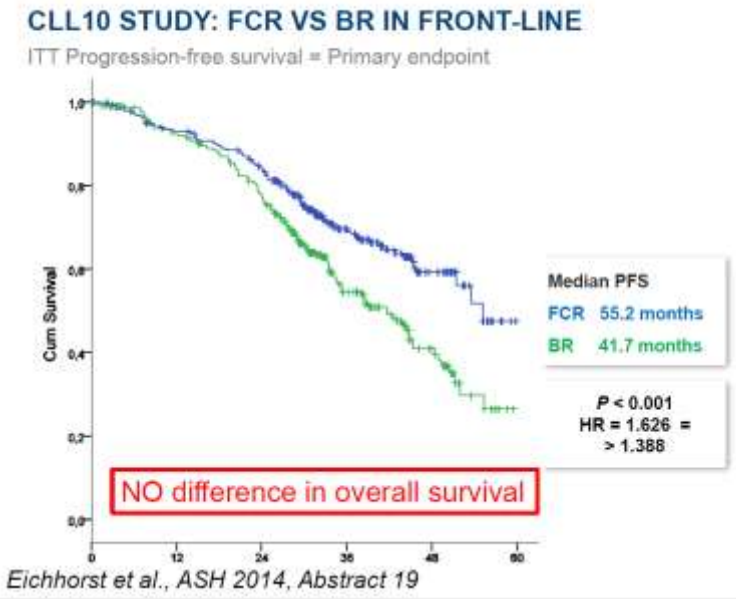
**BR**

Bendamustine 90mg/m² day 1-2
Rituximab 375 mg/m² day 0, cycle 1
Rituximab 500 mg/m² day 1, cycle 2-6

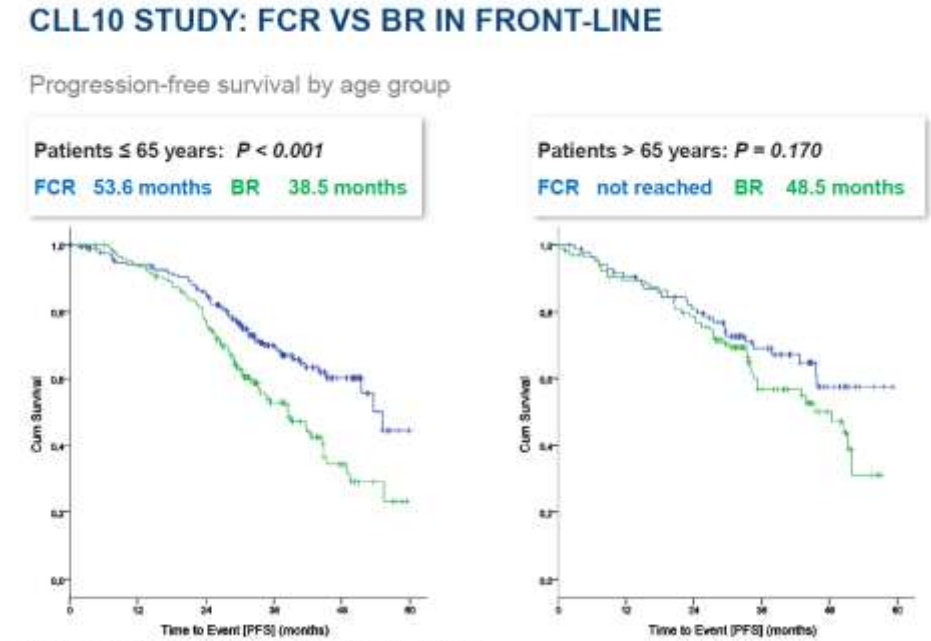
Non-Inferiority of BR in comparison to FCR for PFS:
HR (λ BR/FCR) less than 1.388

*Eichhorst et al., ASH 2014, Abstract 19*

# CLL10: FCR vs BR en 1ière ligne

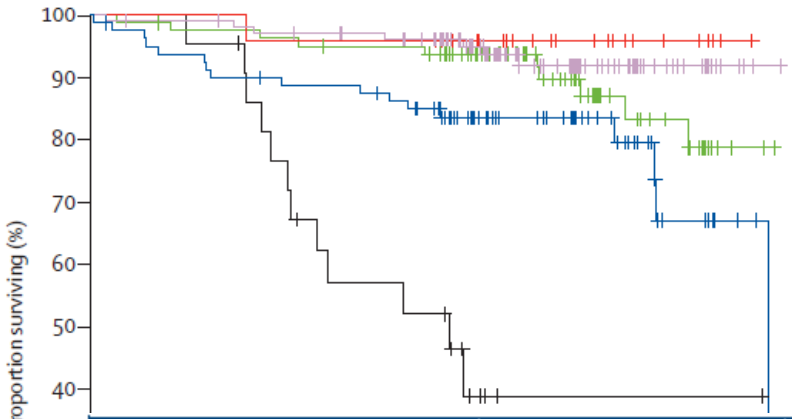


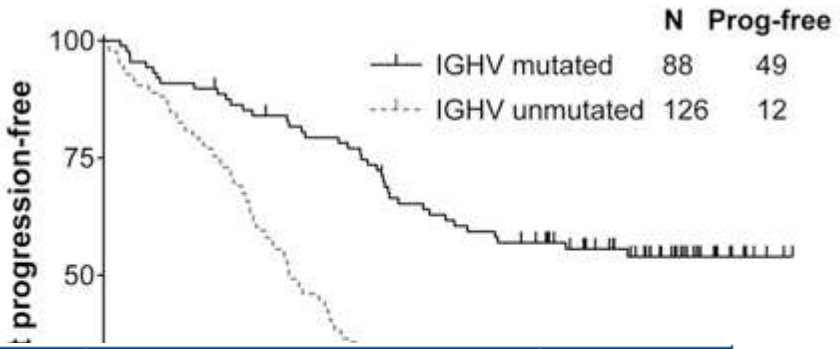

*Eichhorst et al., ASH 2014, Abstract 19*




*Eichhorst et al., ASH 2014, Abstract 19*

# FCR pour tous les patients?



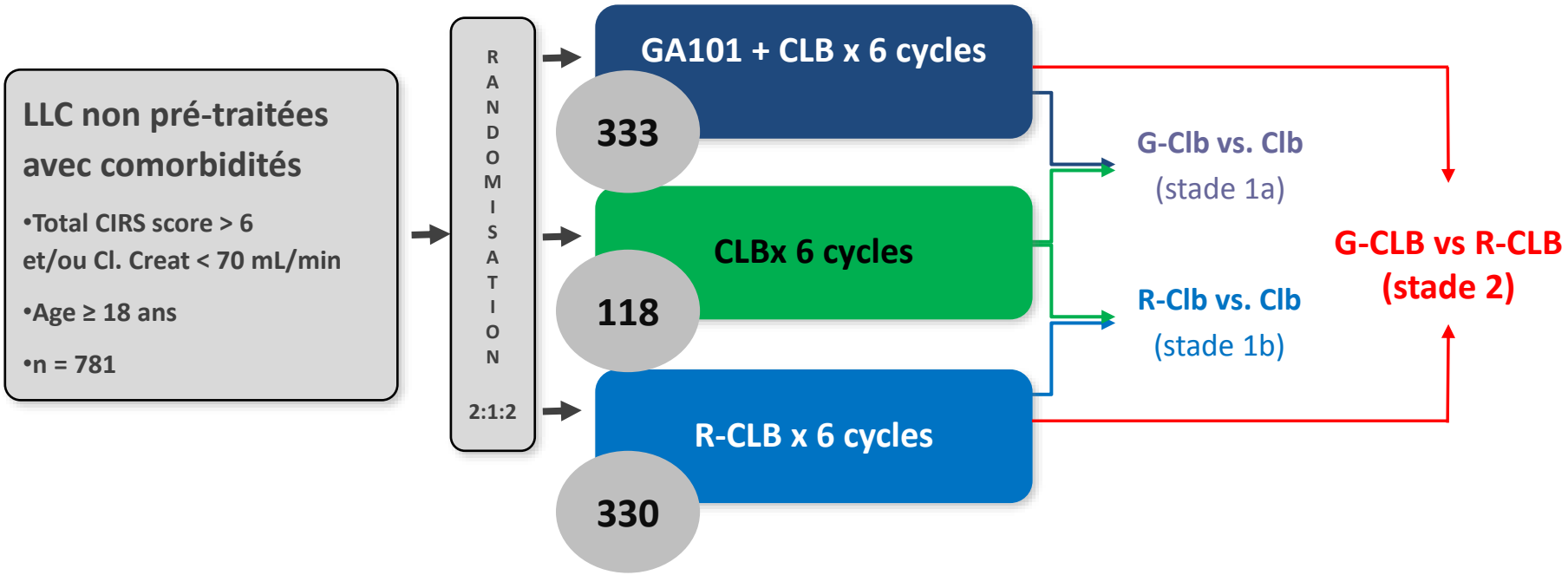




| COX regression PFS | Univariate comparison | HR | 95 % CI | | p value |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| **MRD status** | | | | | |
| Positive | *vs.* negative | **3.487** | 2.678 | 4.541 | **< 0.001** |
| **Clinical response** | | | | | |
| PR | *vs.* CR | **1.420** | 1.075 | 1.876 | **= 0.014** |
| **Deletion 17p** | | | | | |
| Yes | *vs.* no | **9.082** | 4.325 | 19.072 | **< 0.001** |
| ***IGHV* analysis** | | | | | |
| Unmutated | *vs.* mutated | **2.582** | 1.930 | 3.455 | **< 0.001** |

*Hallek Lancet 2010; Thompson Blood 2016; Fischer Blood 2016; Kovacs ASH 2014*

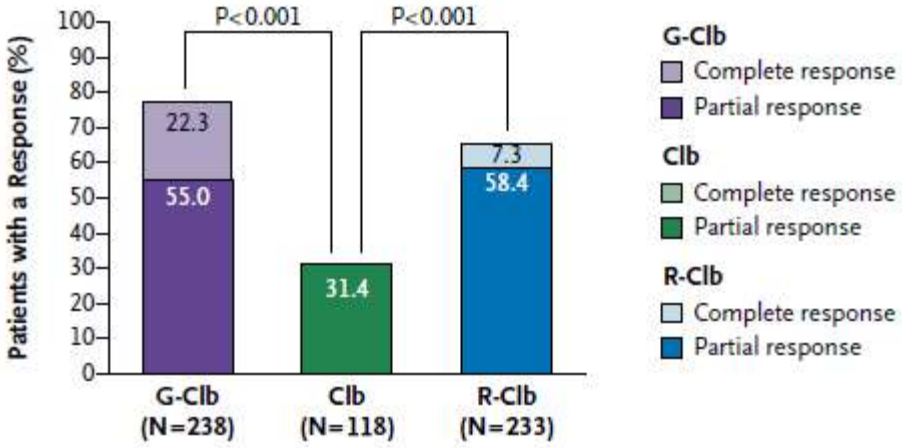
**AGE > 65 ANS OU CIRS > 6**
**« Elderly/Non-fit »**
**No del 17 and/or TP53 mutation**

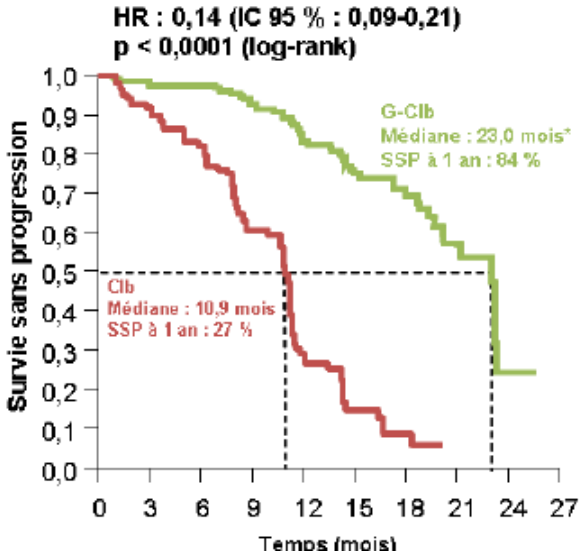
# CLL11: Design de l'étude

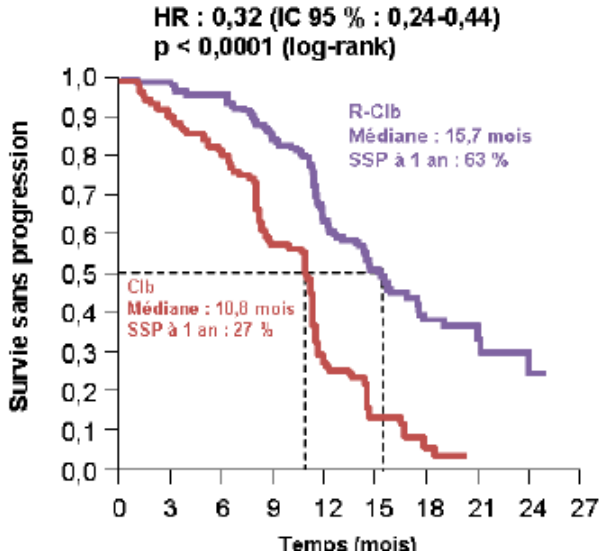



- GA101 : 1 000 mg jours 1, 8 et 15 cycle 1 ; jour 1 cycles 2–6, tous les 28 jours
- Rituximab : 375 mg/m$^2$ jour 1 cycle 1, 500 mg/m$^2$ jour 1 cycles 2–6, tous les 28 jours
- Chlorambucil : 0,5 mg/kg jour 1 et jour 15 cycle 1–6, tous les 28 jours
- Patients avec progression dans le bras Clb autorisés au cross over G-Clb

# CLL11: Réponse et PFS stade 1

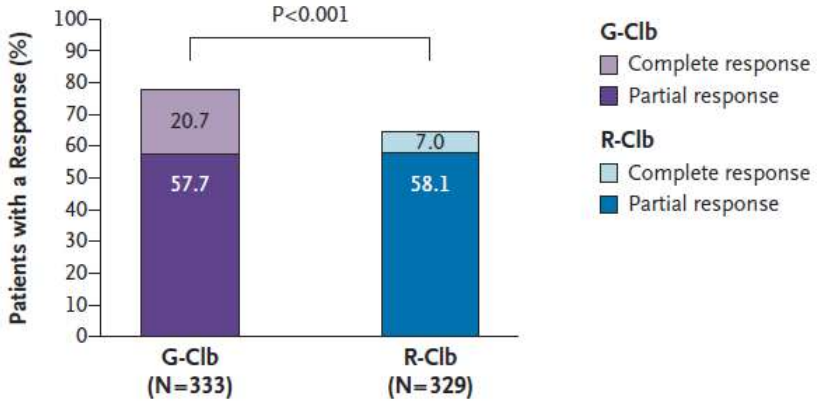


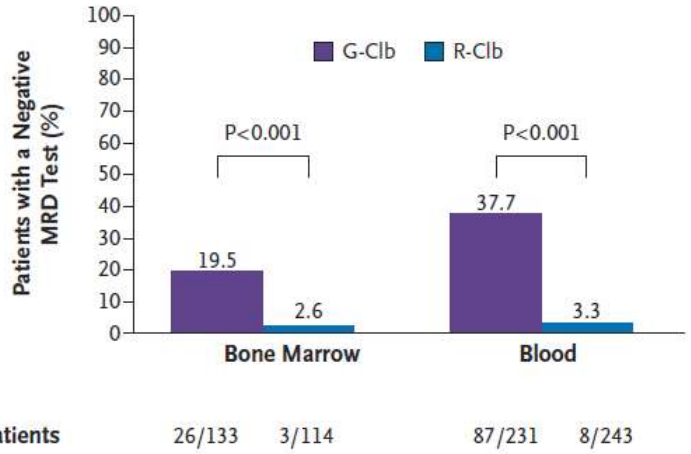



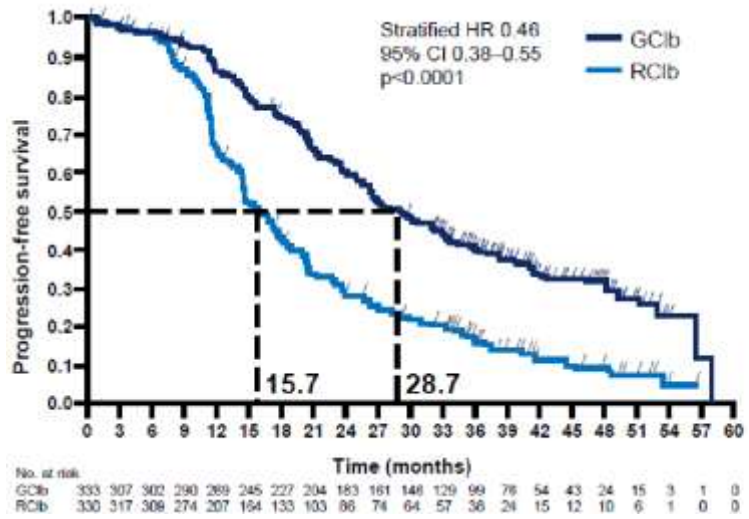



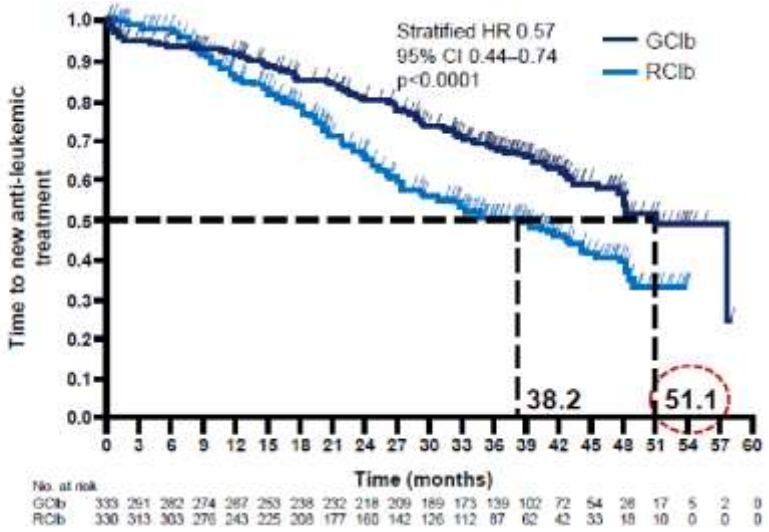

*Goede, NEJM 2014*

# CLL11: Réponse et PFS stade 2




*Goede, NEJM 2014*

# Traitement de 1ière ligne > 65 ans/Non Fit, DEL(17p)- TP53-

## ANTI CD20 - CHIMIOTHERAPIE +++

**BÉNÉFICE EN TERME DE SURVIE GLOBALE**

- R-CLB / CLB : HR 0,6 (p=0,024)
- G-CLB/CLB : HR 0,47 (p=0,0014)
- G-CLB = R-CLB en termes de survie globale…

**BÉNÉFICE EN TERME DE PFS**

- GA101-CLB/R-CLB: HR 0,39 (p<0,0001)
- R-Benda/R-CLB: HR 0,52 (p=0,003)
- OFA-CLB/CLB: HR 0,57 (p<0,001)

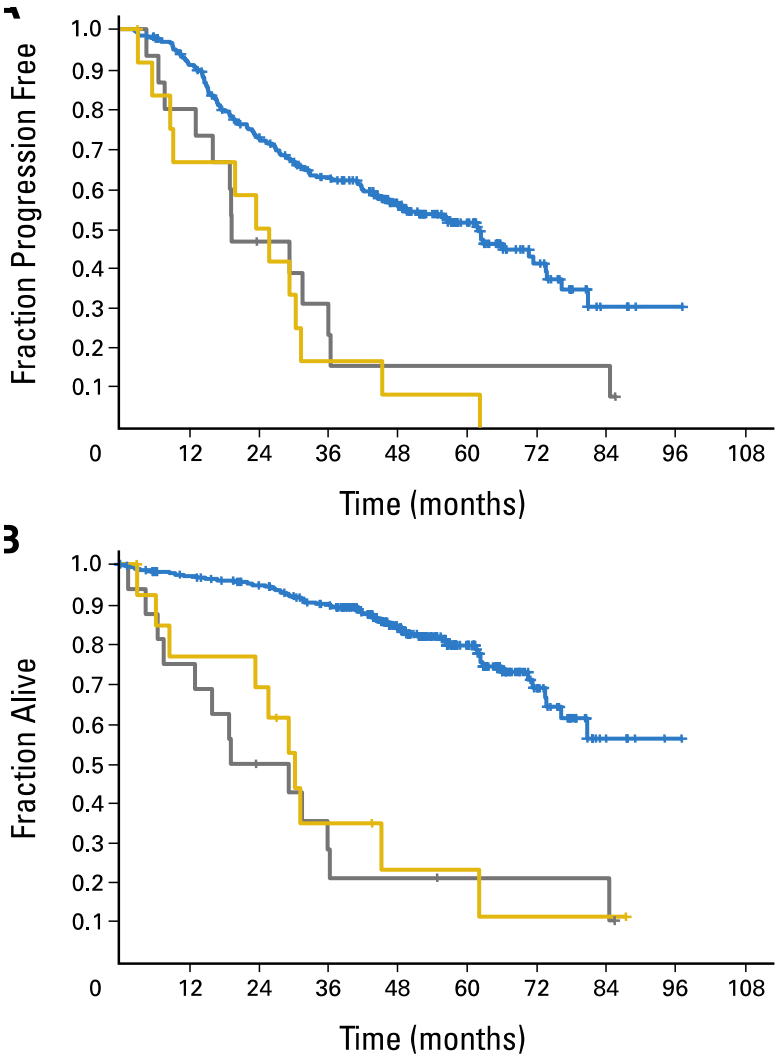
R-BENDA: Option en 1ière ligne chez les patients inéligibles à la fluda

# Del(17p) et/ou Mutation TP53

# Del(17p) et/ou Mutation TP53

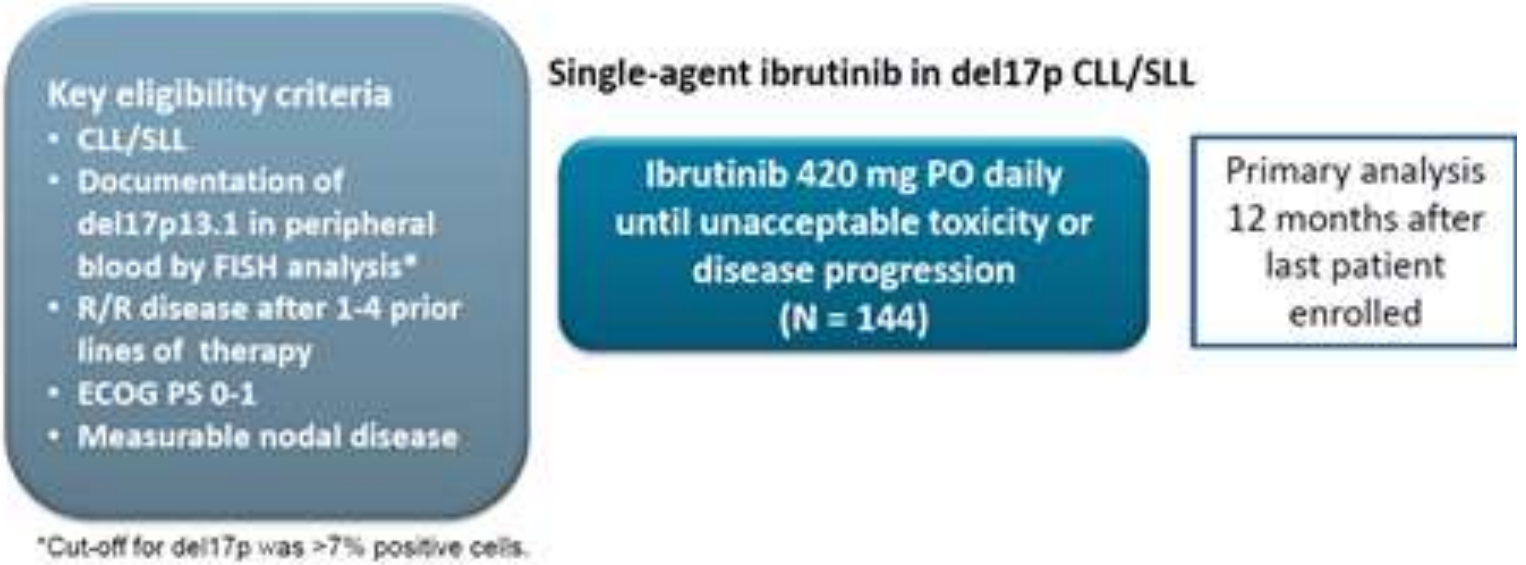
Réfractaires à la Fludarabine

- Absence de réponse ou Progression < 2-3 ans post FCR
- Survie médiane:
  - Progression < 6 m: 14 m
  - Progression 6-12 m: 29 m
  - Progression 12-24 m: 52 m




*Zenz 2010; Stilgenbauer 2014*

# Ibrutinib: RESONATE™

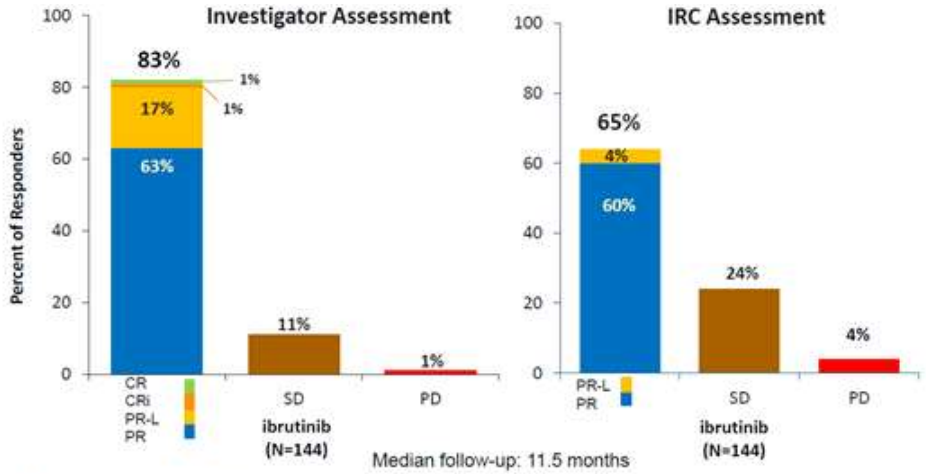



- Phase 2, open-label, single-arm, multicenter, international study
- **Primary endpoint**: ORR as evaluated by IRC (2008 IWCLL criteria)[1,2]
- **Secondary endpoints**: DOR, safety, tolerability
- **Exploratory endpoints**: PFS, OS

1. Hallek et al. *Blood*. 2008;111:5446-5456; 2. Hallek et al, *Blood*. 2012; e-letter, June 04, 2012

*O'Brien et al., ASH 2014, Abstract 327*

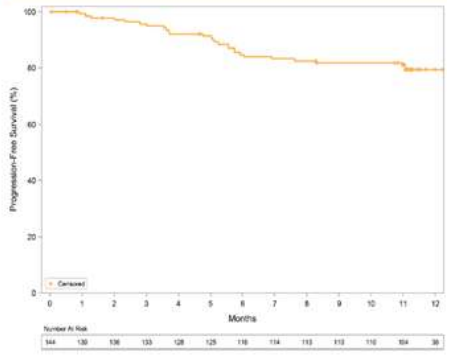
# RESONATE™: ORR and Survivals



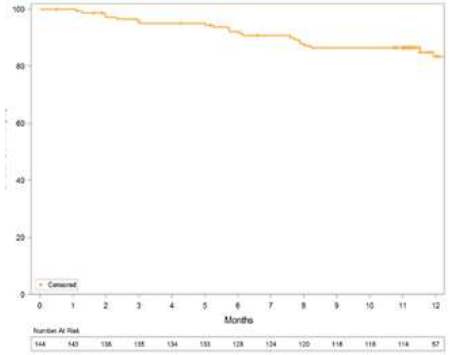

- Best response (ORR+PR-L) by IRC without second confirmatory CT scan: 74% (95% CI: 66-80)
- Median DOR was not reached; 12-month DOR rate: 88.3%

*O'Brien et al., ASH 2014, Abstract 327*

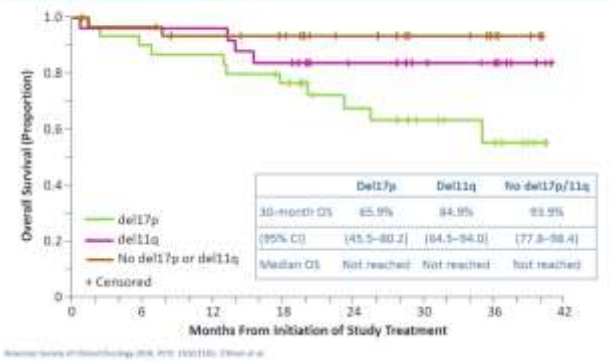
## Progression-Free Survival



## Overall Survival



## Overall Survival by Cytogenetics (FISH) in Relapsed/Refractory Population

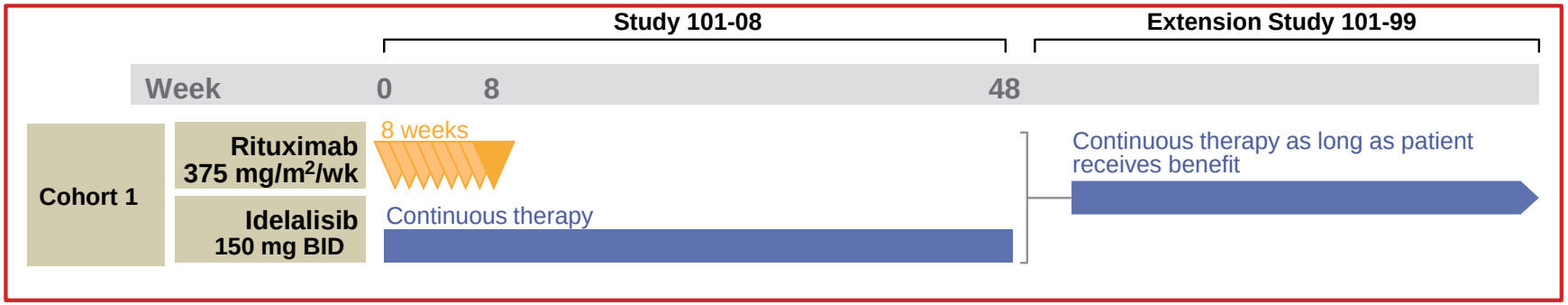



**Median Follow-up: 11,5 months**

# Idélalisib + R: étude pivotale 101-08

- phase II ouverte multicentrique non comparative, évaluant l'association idelalisib + rituximab chez 64 patients atteints de LLC (ou lymphome lymphocytique) **non précédemment traitée**

- Median age: 71 (65-90)
- Del(17p) or TP53 mutation: 9 (14%)
- IGVH unmutated: 37 (58%)

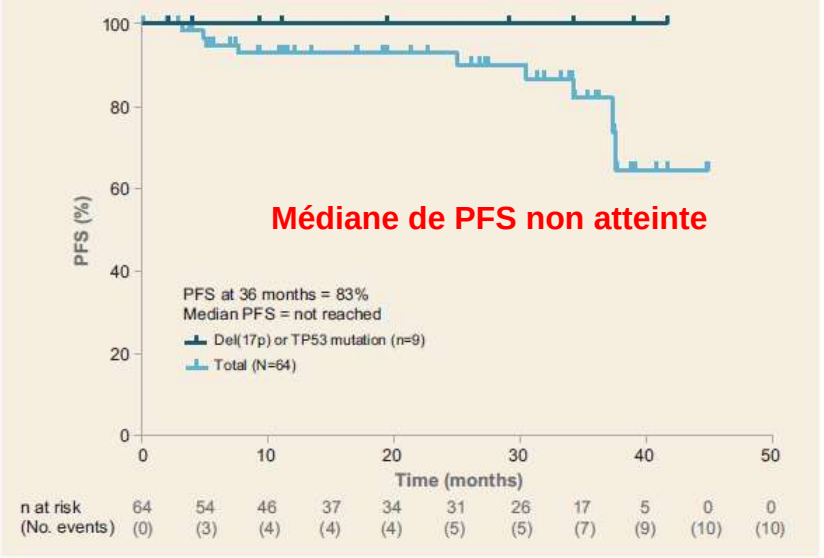


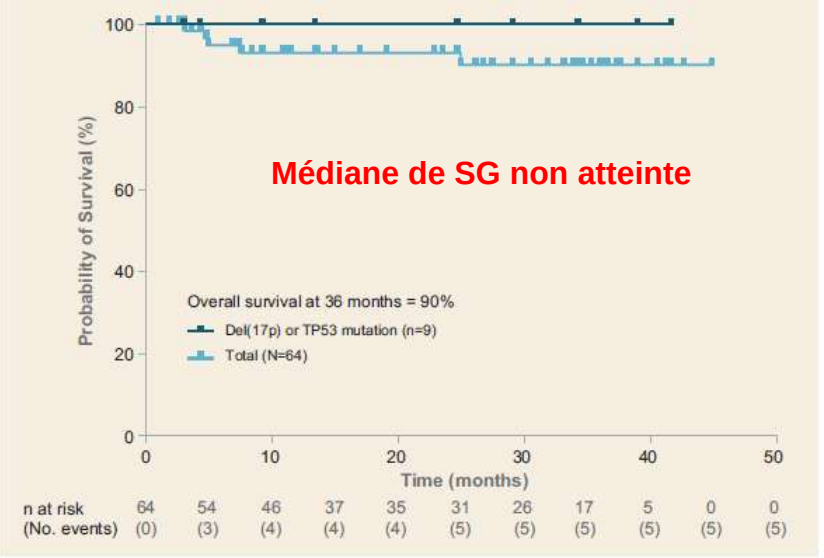
# Idélalisib + R: étude pivotale 101-08

Primary Endpoint: ORR

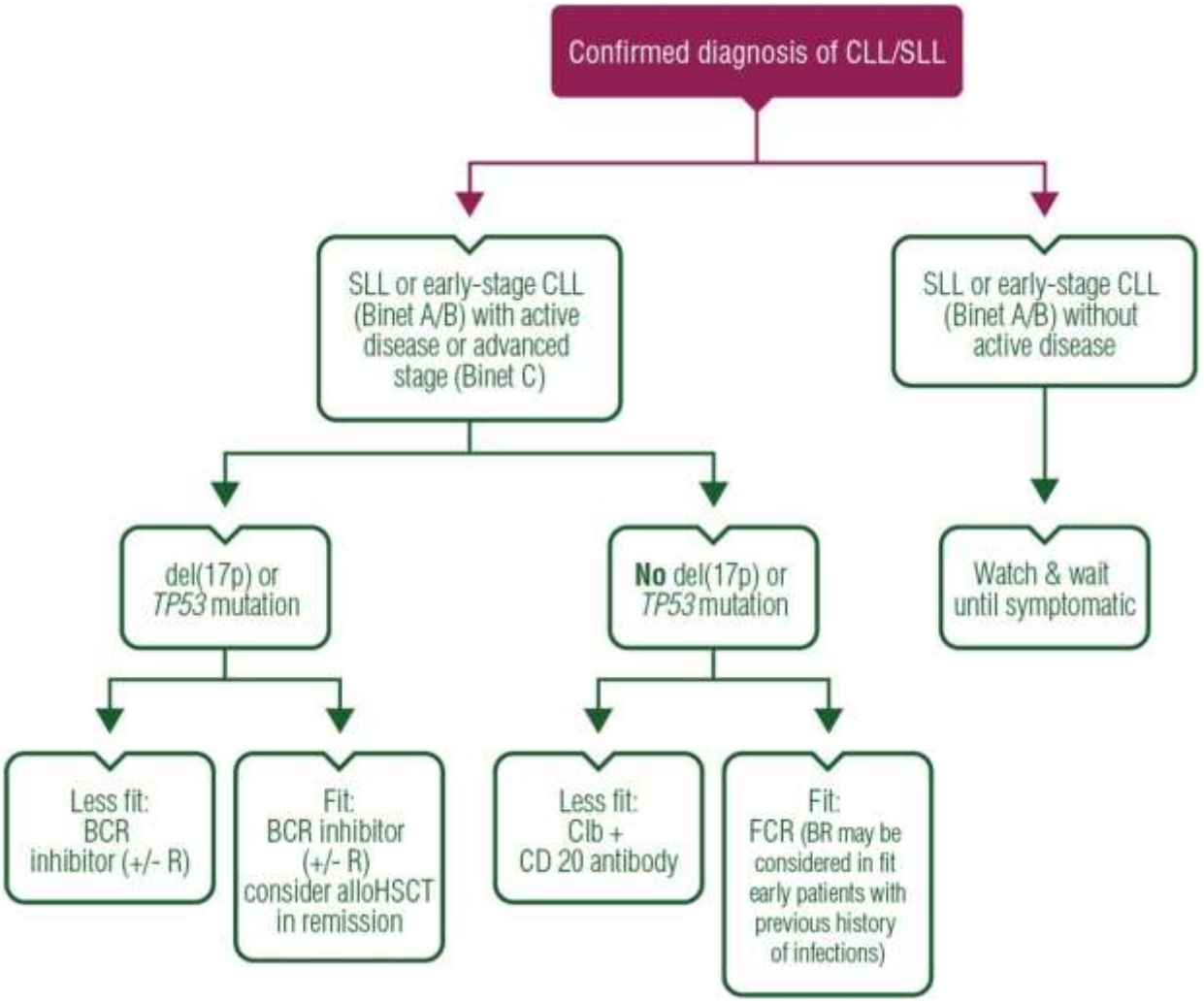
| Patients, n (%) | All Patients N=64 | Del(17p) and/or TP53 mutation n=9 |
|---|---|---|
| Complete response | 12 (19) | 3 (33) |
| Partial response | 50 (78) | 6 (67) |
| Stable disease | 0 | 0 |
| Progressive disease | 0 | 0 |
| Not evaluable | 2 (3) | 0 |
| **Overall response** | **62 (97)** | **9 (100)** |

Median time to response: 1.9 months (range, 1.6–5.7)



# LLC: Prise en charge primaire




Annals of Oncology

*B. Eichhorst et al. Ann Oncol 2015;26:v78-v84*

# Leucémie Lymphoïde Chronique

## Avancées compréhensives

*Société Algérienne d'Hématologie*

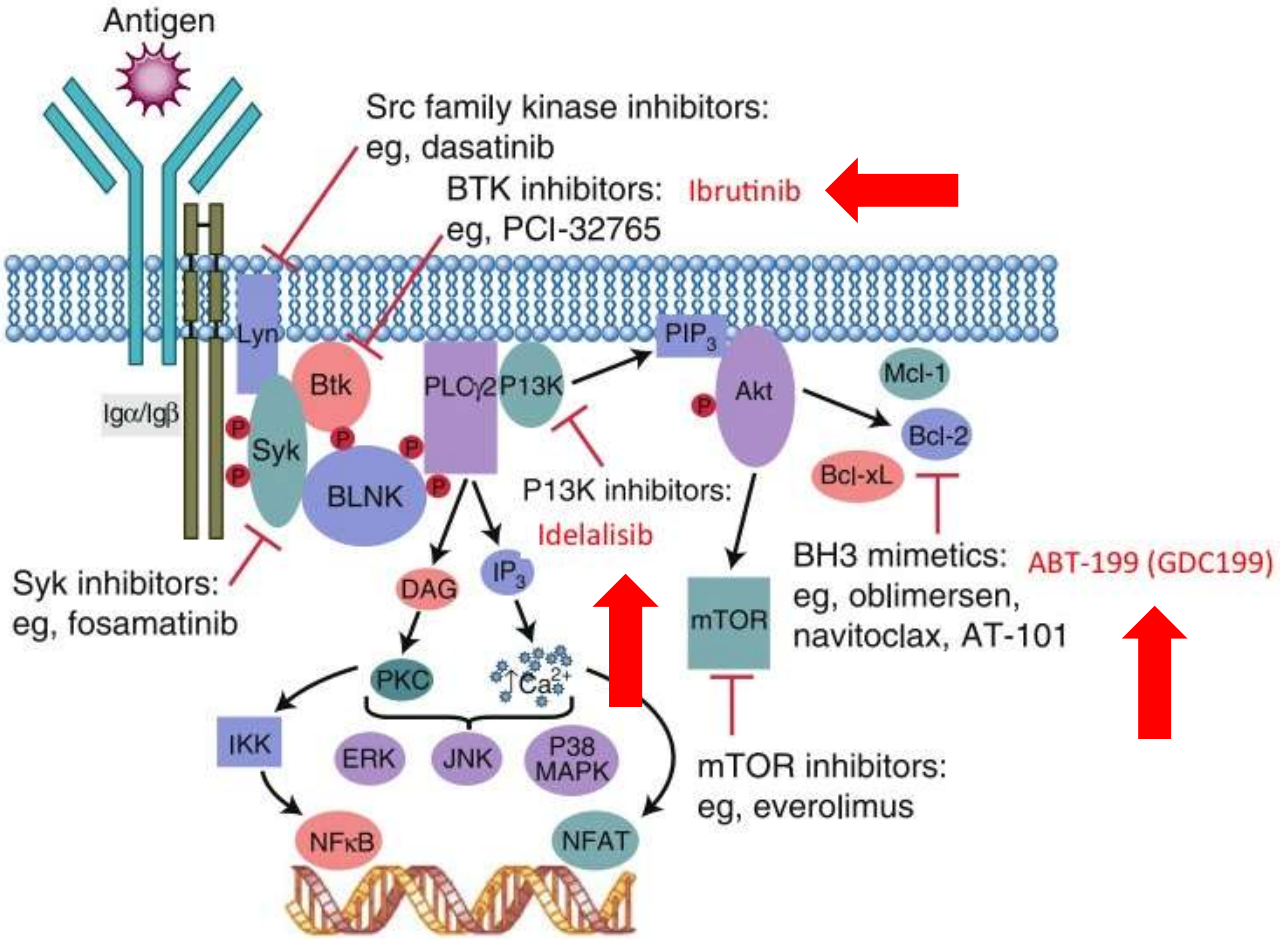
*Le 26 Octobre 2017*

*Réda Bouabdallah*

*Institut Paoli-Calmettes, Marseille, France*

1. **Avènement des Thérapies ciblées**
2. **Intérêt d'un Traitement de Maintenance**
3. **Impact de la MRD sur la Survie**

# Cibles thérapeutiques d'intérêt




*John C. Riches, Alan G. Ramsay, John G. Gribben*
*Current Oncology Reports*
*October 2011, Volume 13, Issue 5, pp 379-385*
*Chronic Lymphocytic Leukemia: An Update on Biology and Treatment*

# THERAPIES CIBLEES

## IBRUTINIB

# HELIOS Ph 3

**Patients with previously treated CLL/SLL**

RANDOMIZE 1:1*

**Ibrutinib + BR (n=289)**
BR† (maximum of 6 cycles)

Oral ibrutinib 420 mg once daily starting on cycle 1, day 2

→ Ibrutinib (treat to PD or unacceptable toxicity)

**Placebo + BR (n=289)**
BR† (maximum of 6 cycles)

Oral placebo once daily starting on cycle 1, day 2

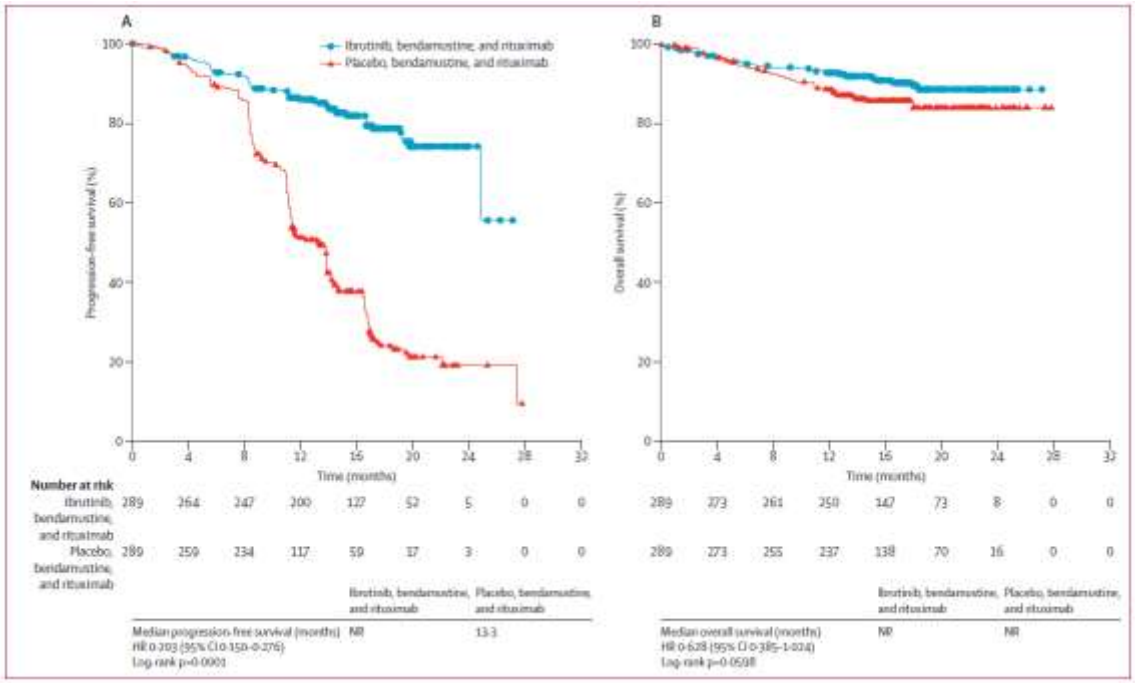
→ Placebo (treat to PD or unacceptable toxicity)

→ **Crossover to Ibrutinib 420 mg PO QD after IRC-confirmed PD (n=90) First patient crossed over in May 2014**

**Enrolment dates**
Sept 2012 – Jan 2014

***Eligibility Criteria***
- Active CLL/SLL requiring treatment according to ≥1 iwCLL criteria
- R/R CLL/SLL following ≥1 prior line of therapy
- ECOG PS of 0 - 1
- No del17p

***Study Endpoints***
- Primary: PFS
- Secondary: ORR, OS, MRD, Safety




*A. Chanan-Khan et al, Lancet Oncol 2015 S1470-2045(15)00465-9*

# IBRUTINIB en 1ière Ligne?

The NEW ENGLAND JOURNAL of MEDICINE

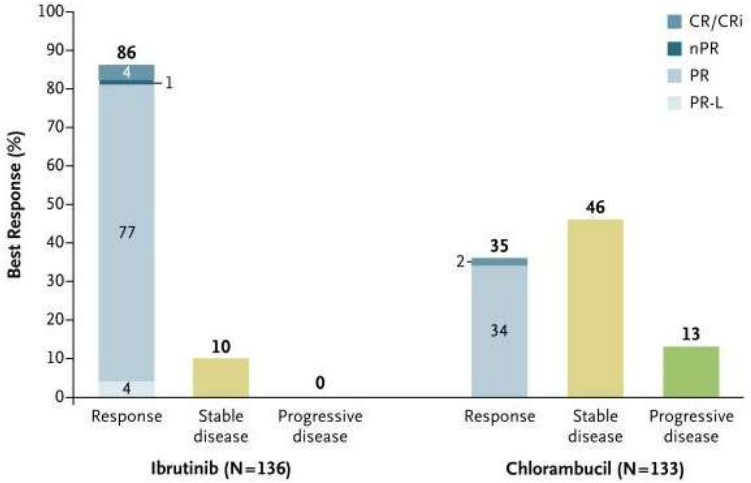
ORIGINAL ARTICLE

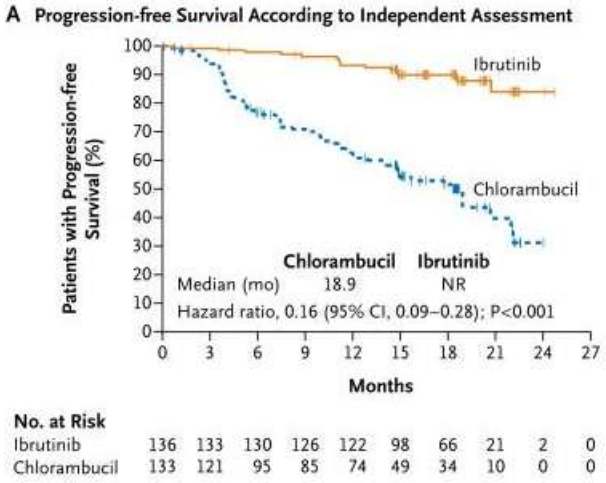
## Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

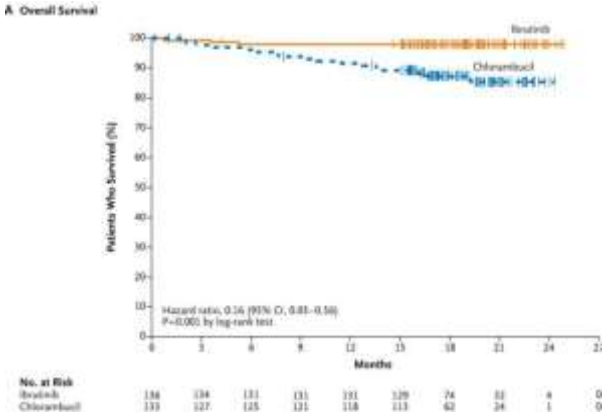
J.A. Burger, A. Tedeschi, P.M. Barr, T. Robak, C. Owen, P. Ghia, O. Bairey, P. Hillmen, N.L. Bartlett, J. Li, D. Simpson, S. Grosicki, S. Devereux, H. McCarthy, S. Coutre, H. Quach, G. Gaidano, Z. Maslyak, D.A. Stevens, A. Janssens, F. Offner, J. Mayer, M. O'Dwyer, A. Hellmann, A. Schuh, T. Siddiqi, A. Polliack, C.S. Tam, D. Suri, M. Cheng, F. Clow, L. Styles, D.F. James, and T.J. Kipps, for the RESONATE-2 Investigators*

- N= 269
  - IBRUTINIB: 136
  - CLB: 133
- AGE
  - Médiane: 73
  - ≥ 70: 189 (70%)
- RAI III-IV: 122 (45%)
- DEL11q: 54 (20%)
- IGVH NON MUTE: 118 (44%)

| Overall Response Rate | Ibrutinib | Chlorambucil | Rate Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *% of patients* | | | |
| With PR-L | 86 | 35 | 2.42 (1.91–3.07) | <0.001 |
| Without PR-L | 82 | 35 | 2.32 (1.82–2.95) | <0.001 |



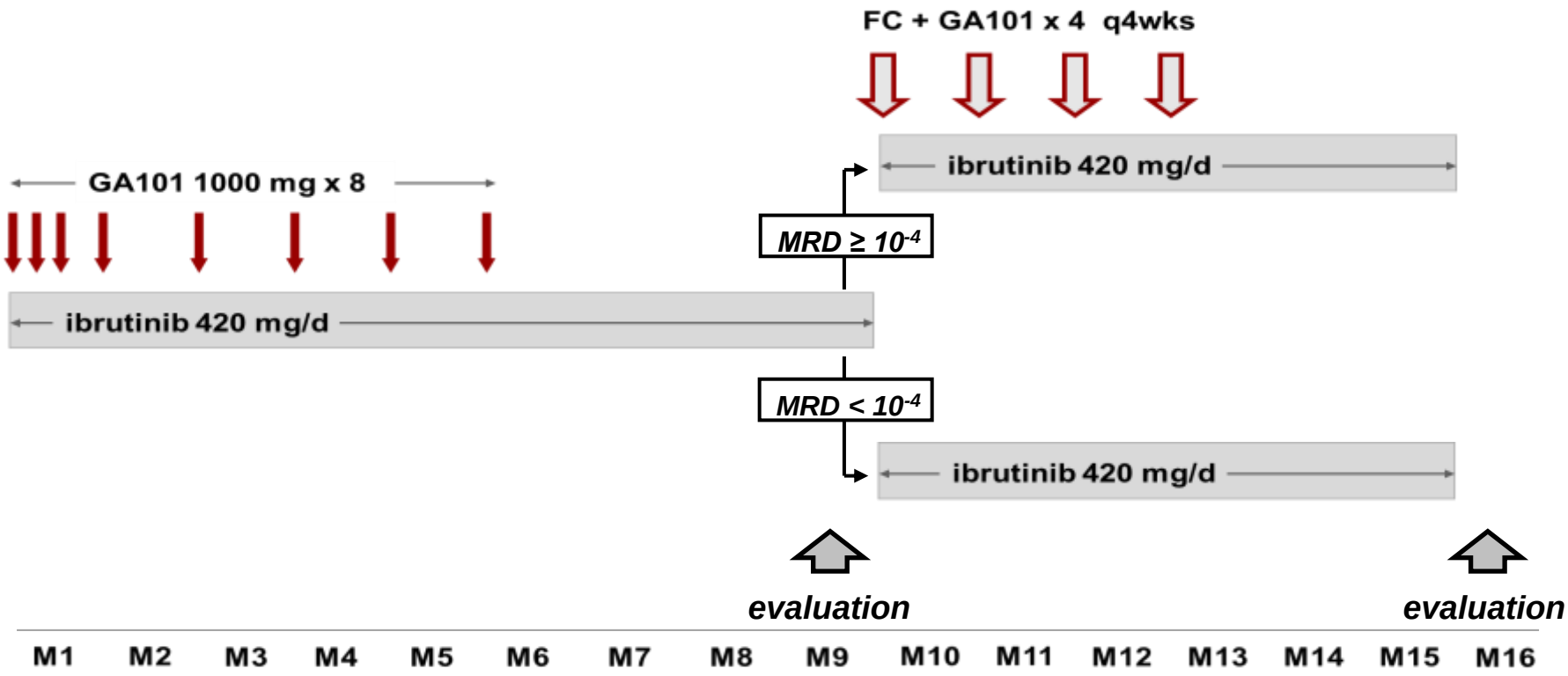
# IBRUTINIB en 2017

- **AMM** :
  - Première ligne del17/p53
  - En rechute……**réflexion collective à avoir**
- **Nombreuses études en cours**
  - Phase 3 (R/R) Rituximab+Benda ± Ibrutinib
  - Première ligne unfit : GA+CLB vs GA+Ibru
- **intergroupe français de la LLC (FILO) :**
  - essai première ligne actuel ICLL07

# ICLL-07 GAI

## "PHASE II, MULTICENTER, TRIAL, EXPLORING "CHEMO-FREE" TREATMENT (GA101+IBRUTINIB) AND MRD-DRIVEN STRATEGY IN PREVIOUSLY UNTREATED SYMPTOMATIC B-CHRONIC LYMPHOCYTIC MEDICALLY FIT LEUKEMIA PATIENTS (CLL)."

## A STUDY FROM THE GOELAMS/GCFLLC/MW INTERGROUP



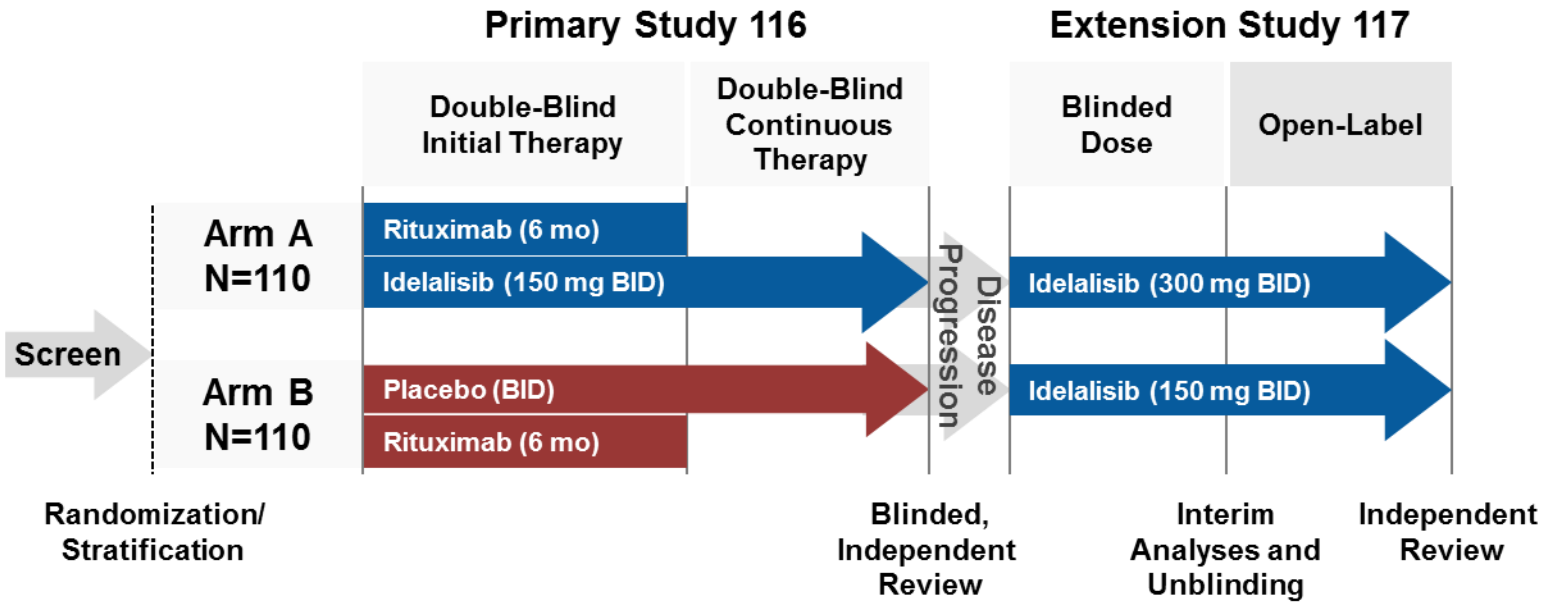
# THERAPIES CIBLEES

## IDELALISIB

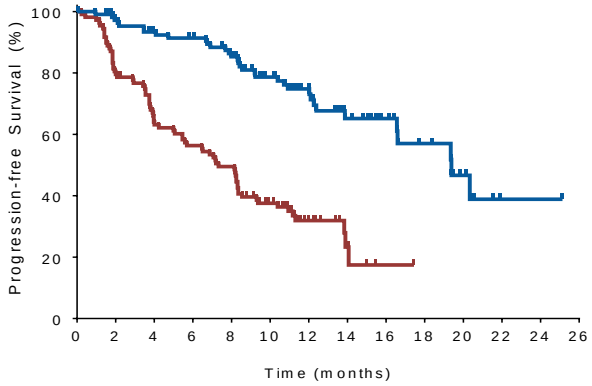
# GS-US-312-0116 Ph 3

Median age:71 (47-92)
Median prior therapies: 3 (1-12)

**Total CIRS score > 6: 88% (IR); 82% (PR)**
**Del(17p) and/or TP53 mutation: 42 §  (IR); 45% (PR)**
**IGVH unmutated: 83% (IR); 85% (PR)**

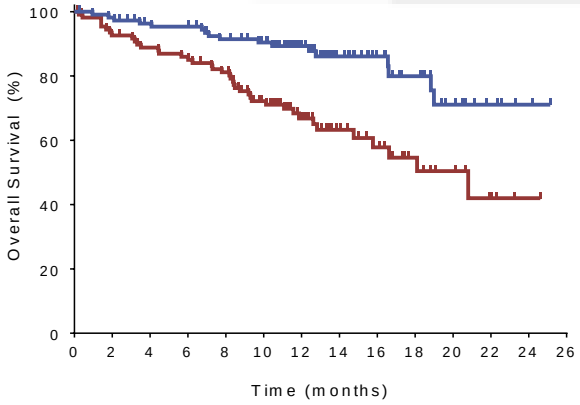


| | Median PFS (95% CI) | HR (95% CI) | p-value |
|---|---|---|---|
| IDELA + R | 19.4 mo (16.6, – ) | 0.25 (0.16, 0.39) | <0.0001 |
| PBO + R | 7.3 mo (5.5, 8.5) | | |



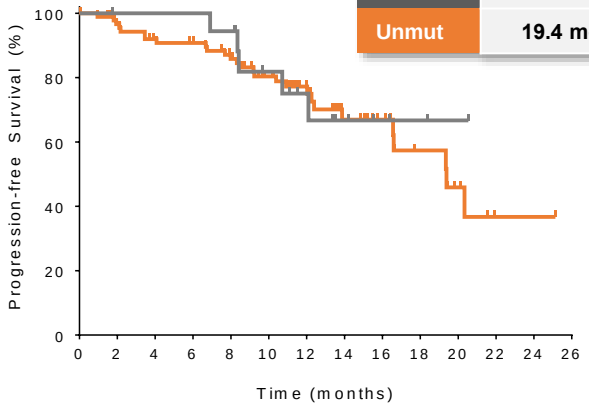

## PFS - All Patients

| | Median OS (95% CI) | HR (95% CI) | p-value |
|---|---|---|---|
| IDELA + R | NR ( –, – ) | 0.34 (0.19, 0.6) | 0.0001 |
| PBO + R | 20.8 mo (14.8, – ) | | |



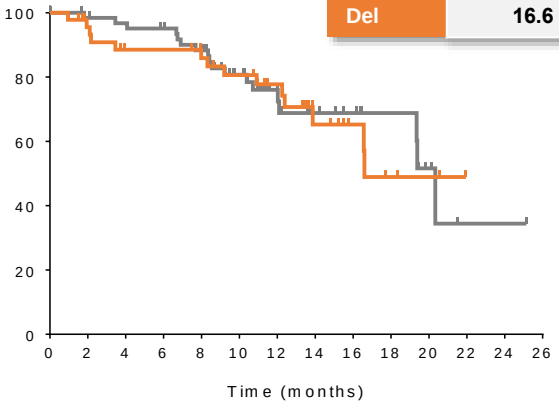

## OS - All Patients

| | Median PFS (95% CI) | p-value |
|---|---|---|
| Mut | NR (10.7, – ) | 0.75 |
| Unmut | 19.4 mo (16.6, – ) | |




## *IGHV*: Unmutated vs Mutated

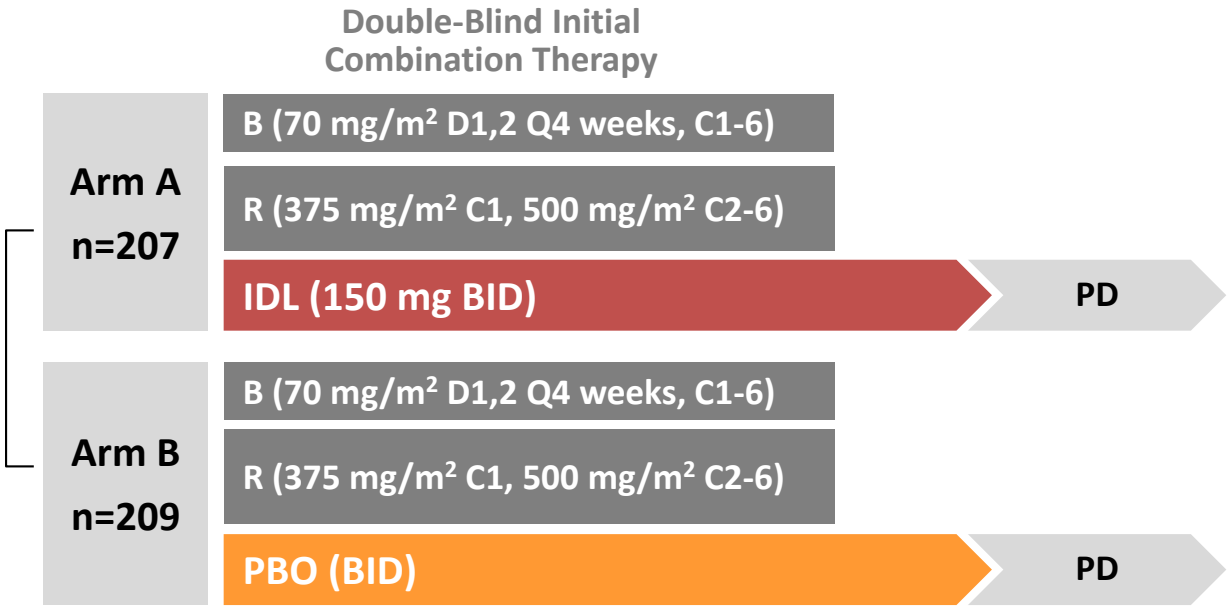
| | Median PFS (95% CI) | p-value |
|---|---|---|
| No del | 20.3 mo (19.4, – ) | 0.94 |
| Del | 16.6 mo (13.9, – ) | |




## Del17p/TP53mut: Present vs Not Present

*Sharman, ASH, 2014, Abstract 330*

# GS-US-312-011 Ph 3




## Key Eligibility Criteria

- **CLL progression <36 mo from last therapy, requiring treatment**
- No history of CLL transformation
- **Not refractory to bendamustine**
- No prior inhibitors of BTK, PI3Kδ, SYK

## Stratification

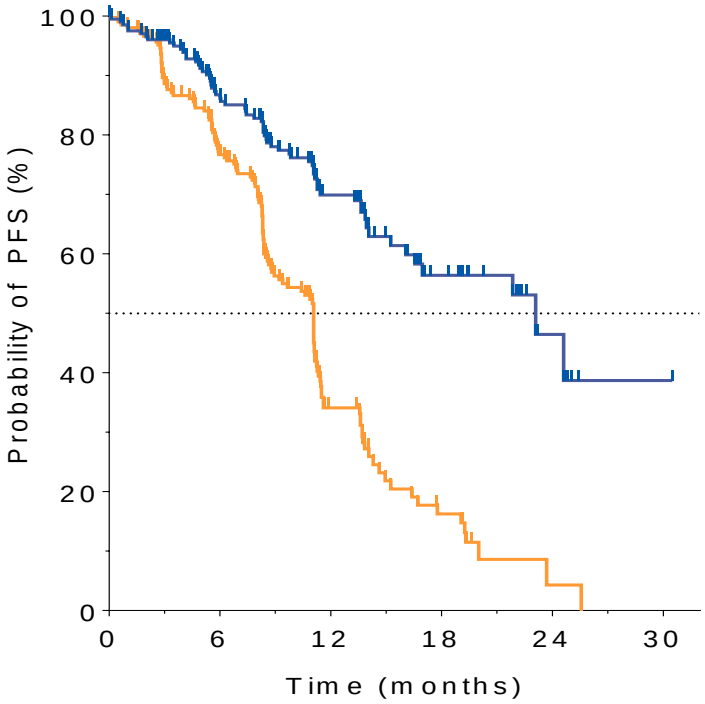
- 17p deletion and/or *TP53* mutation
- IGHV gene mutation status
- Refractory vs relapsed disease

## Endpoints

- Primary: PFS
- Secondary: ORR, nodal response, OS, CR

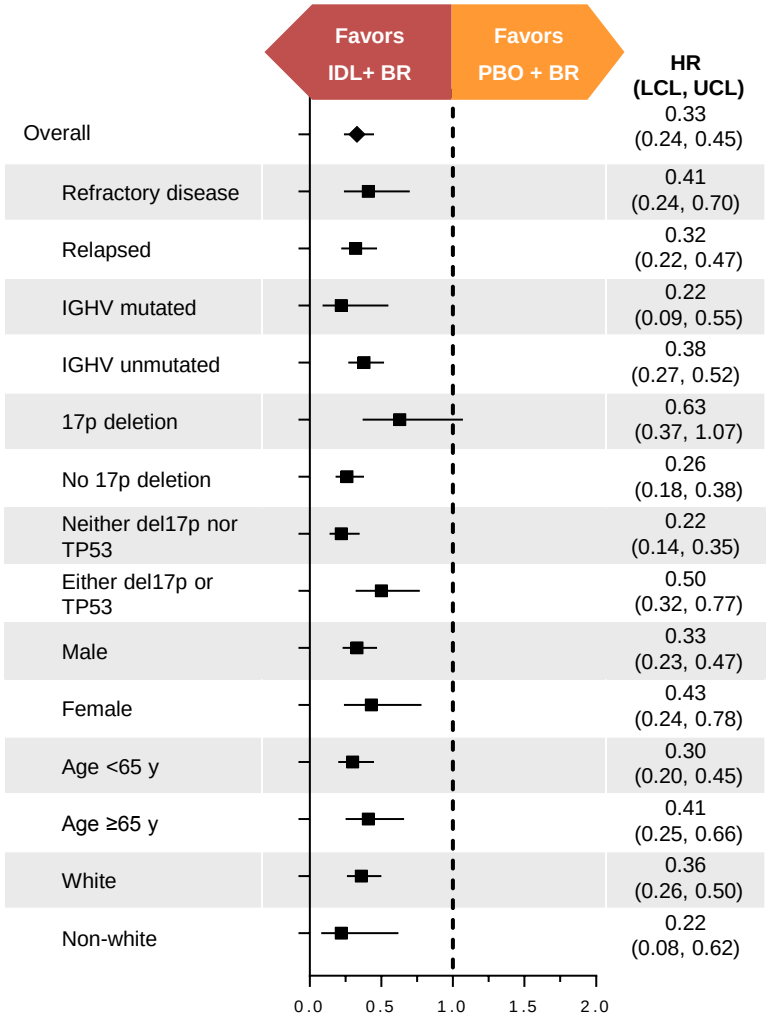
*Zelenetz A, et al. ASH 2015 LBA-5*

# GS-US-312-011 Ph 3




**Median follow-up time = 12 months**

| | IDL + BR | PBO +BR |
|---|---|---|
| Median PFS (mo) | 23.1 | 11.1 |
| HR (95% CI) | 0.33 (0.24, 0.45) | |
| p-value | <0.0001 | |




*Zelenetz A, ASH 2015 LBA-5*

# IBRUTINIB ET IDELALISIB EN 2017

- **Apport majeur notamment dans les formes les plus agressives**
  - p53, rechutes précoces post FCR
- **Faible taux de RC en monothérapie mais PFS prolongée**
- **Toxicité et maniement à apprendre++++ (thérapies orales)**
- **Privilégier les essais cliniques**
- **Nombreuses questions restantes**
  - Doses et Durée (peut on s'arrêter ?)
  - Santé publique (coût)
  - Place en rechute (AMM très large!!!)
  - Mécanismes de résistances qui apparaissent
- **Place dans l'arsenal thérapeutique**
  - Thérapie ciblant bcl2 (ABT199)
  - Nouveaux anti BTK
  - Nouveaux anti PI3K (γδ αδ)
  - Place de l'Allogreffe

# THERAPIES CIBLEES

## VENETOCLAX

# VENETOCLAX dans les LLC R/R

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 28, 2016 VOL. 374 NO. 4

## Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia

Andrew W. Roberts, M.B., B.S., Ph.D., Matthew S. Davids, M.D., John M. Pagel, M.D., Ph.D., Brad S. Kahl, M.D., Soham D. Puvvada, M.D., John F. Gerecitano, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Mary Ann Anderson, M.B., B.S., Jennifer R. Brown, M.D., Ph.D., Lori Gressick, B.S., Shekman Wong, Ph.D., Martin Dunbar, Dr.P.H., Ming Zhu, Ph.D., Monali B. Desai, M.D., M.P.H., Elisa Cerri, M.D., Sari Heitner Enschede, M.D., Rod A. Humerickhouse, M.D., Ph.D., William G. Wierda, M.D., Ph.D., and John F. Seymour, M.B., B.S., Ph.D.

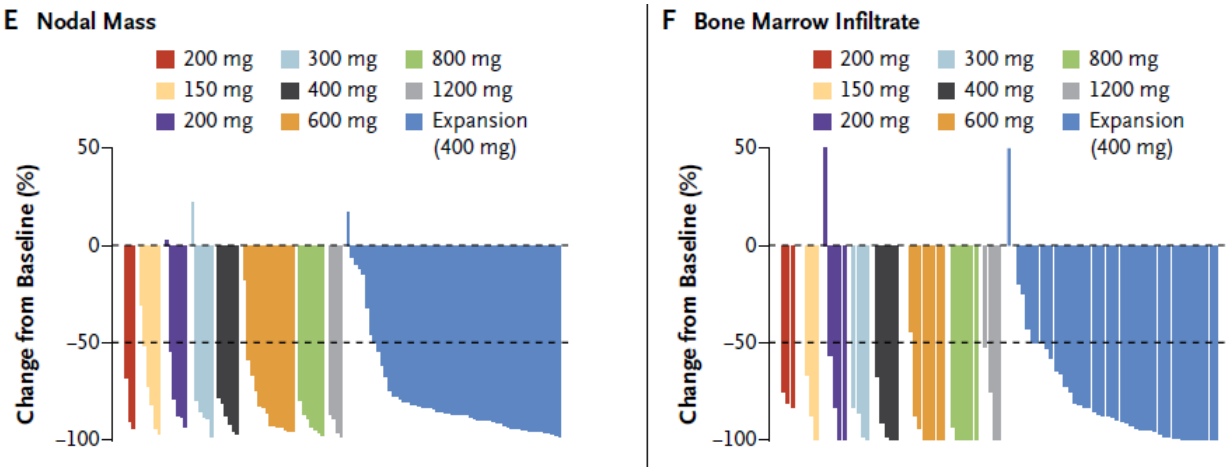
| N PATIENTS | 116 |
|---|---|
| AGE | 66 (36-86) |
| DISEASE<br>CLL<br>SLL | <br>102 (88%)<br>14 (12%) |
| RAI III-IV | 67 (58%) |
| PRIOR THERAPY<br>FLUDA<br>FLUDA Resistant | 3 (1-11)<br>100 (86%)<br>70 (60%) |
| CYTOGENETIC<br>DEL17p<br>DEL11q | <br>31/102 (30%)<br>28/102 (27%) |
| IGVH Unmutated | 46/102 (45%) |

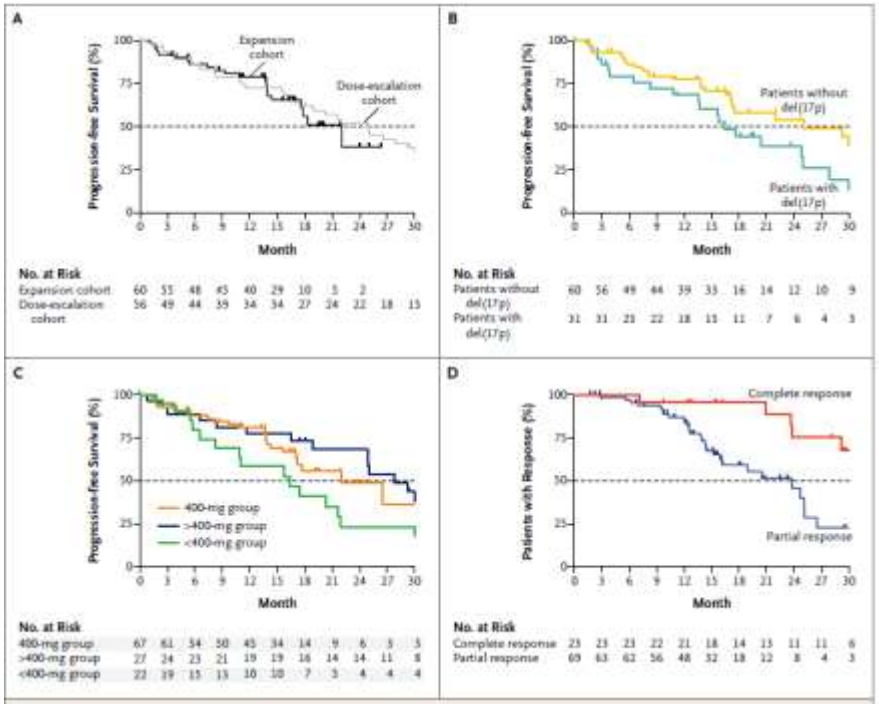
**Phase I Escalade de dose**
**(150 mg-1200 mg/j)**
**N= 56**

**Phase I d' Extension**
**(400 mg/j)**
**N= 60**

| | ORR | CR |
|---|---|---|
| **ALL (N= 116)** | **79%** | **20%** |
| **DEL17p+**<br>DEL 17p- | **71%**<br>80% | **16%**<br>18% |
| **DEL11q+**<br>DEL11q- | **82%**<br>76% | **11%**<br>21% |
| **IGVH Unmutated**<br>IGVH Mutated | **76%**<br>94% | **17%**<br>29% |

# VENETOCLAX dans les LLC R/R



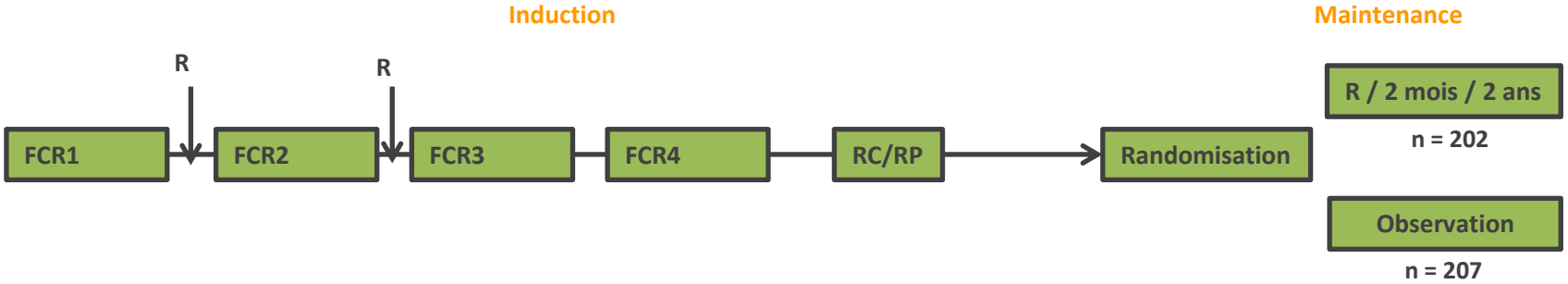
# VENETOCLAX dans les LLC R/R post BCRi ou Pi3k

- **Evaluation de l'efficacité du Venetoclax chez des patients en rechute ou réfractaires à l'Ibrutinib ou à l'Idelalisib à la dose cible de 400 mg**
- **ORR (médiane de réponse < 2 mois)**
  - **Post Ibrutinib: 70%**
  - **Post Idelalisib: 48%**

*J. Jones, ASCO 2016, Abs 7519*

1. Avènement des Thérapies ciblées
2. **Intérêt d'un Traitement de Maintenance**
3. Impact de la MRD sur la Survie

# CLL07




**Objectif principal = PFS à 3 ans**

**Augmentation de 50 % (bras OBS) à 66 % (bras RTX)**

**Stratification : *IGHV* status, del11q et réponse**

**N= 409 patients**

**Suivi médian = 43,6 mois**

**Age médian = 71,3 ans**

**11,0 % en RC/Cri et 62,8 % en RP post-FCR**

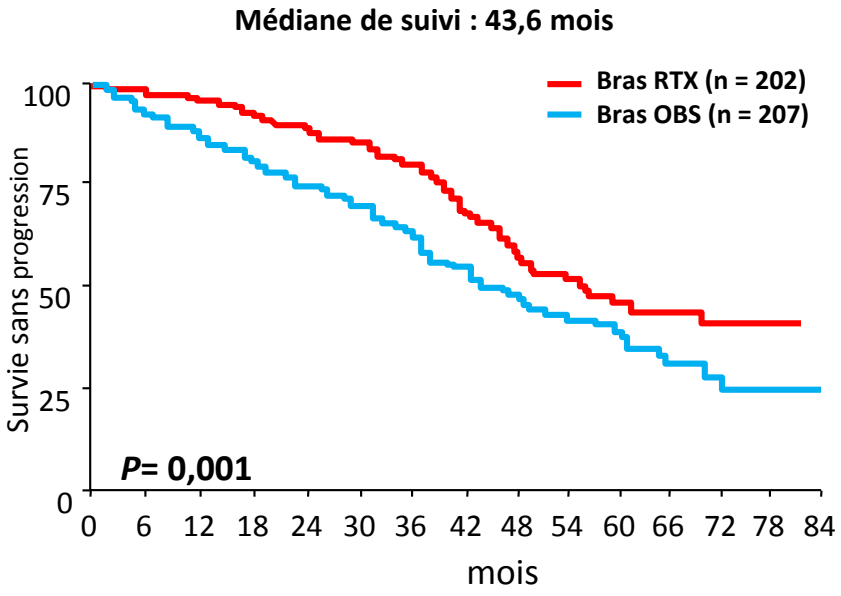
**21,3 % avec del11q**

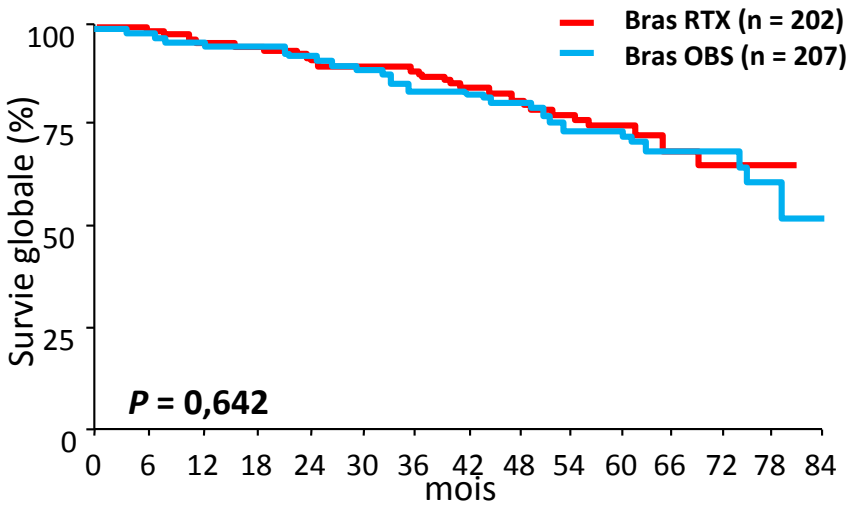
**54,8 % statut *IGHV non muté***

| Caractéristiques | Tous patients (n = 409) | Maintenance (n = 202) | Observation (n = 207) |
|---|---|---|---|
| **Age médian** | **71,3 (65-85)** | **71,7 (65-85)** | **71,1 (65-85)** |
| 65-69 | 39,9 % | 36,6 % | 43,0 % |
| 70-74 | 33,7 % | 33,7 % | 33,8 % |
| 75-79 | 20,5 % | 22,8 % | 18,4 % |
| ≥ 80 | 5,9 % | 6,9 % | 4,8 % |
| **Homme** | **66,3 %** | **62,4 %** | **70,0 %** |
| **Stade de Binet** | | | |
| B | **66,3 %** | **64,9 %** | **67,6 %** |
| C | **33,7 %** | **35,1 %** | **32,4 %** |
| **Score CIRS médian** | **2 (0-6)** | **1 (0-6)** | **2 (0-6)** |

*C Dartigeas et al., abstract 7505, ASCO 2016*

# CLL07: SSP




| | RTX | OBS | HR | *P* |
|---|---|---|---|---|
| Médiane SSP (mois) | 59,3 | 49,0 | 0,59<br>IC95%: 0,43-0,81 | 0,0011 |
| Estimated 3-y PFS | 83% | 64% | | |

| | RTX | OBS |
|---|---|---|
| Médiane de SSP (mois) | NR | NR |
| HR 0,894 (IC 95 % 0,556 ; 1,437) | | |

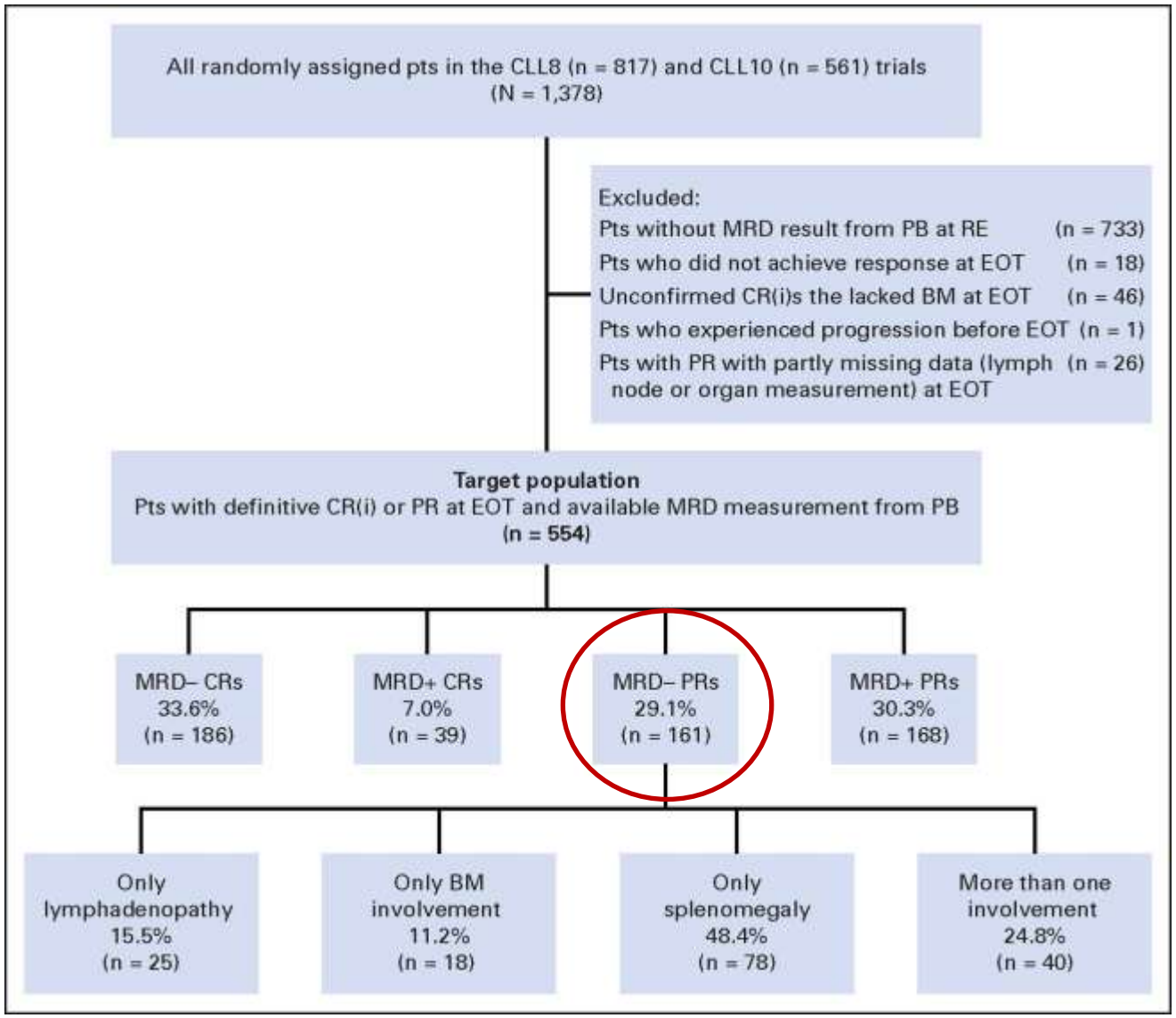
**OS estimée à 3 ans =**
**92,6 % (RTX) et (OBS) (NS)**

# CLL07: conclusions

- FCR x 4 plus maintenance R 2 mois / 2 ans = Amélioration de la PFS comparativement au bras observation
- Bénéfice plus marqué pour les patients IGVH non mutés
- Mais stratégie plus toxique (infections)
- Pas de données sur l'impact en termes de qualité de vie
- **Pour quels patients ?**

# AVANCEES COMPREHENSIVES DANS LA LLC

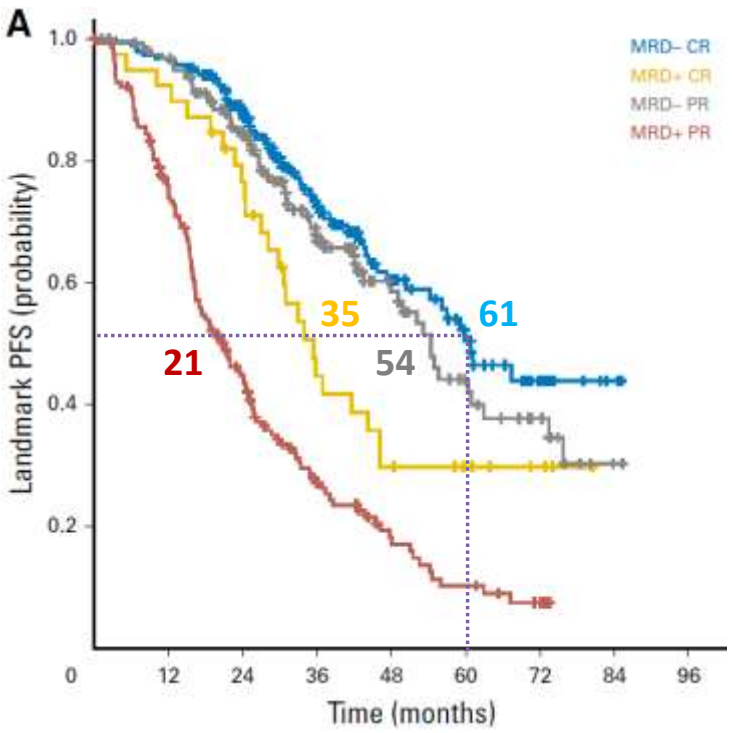
1. Avènement des Thérapies ciblées
2. Intérêt d'un Traitement de Maintenance
3. **Impact de la MRD sur la Survie**

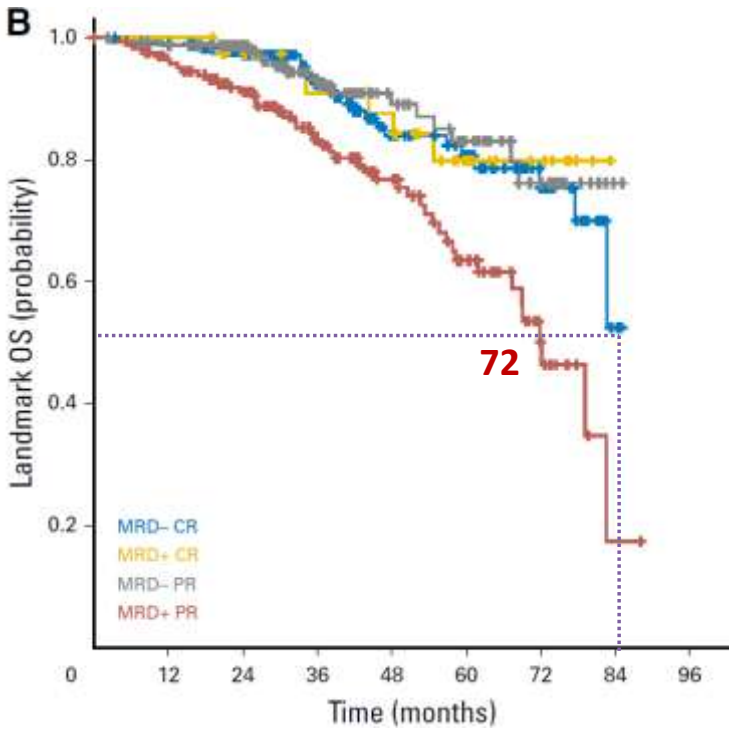





*Gabor Kovacs et al. JCO doi:10.1200/JCO.2016.67.1305*

# PFS et OS/Réponse et MRD




JOURNAL OF CLINICAL ONCOLOGY ASCO

*Gabor Kovacs et al. JCO doi:10.1200/JCO.2016.67.1305*

# PFS et OS: Analyse multivariée

**Table 2.** Multivariable Analyses of the Effects of Prognostic Factors on PFS and OS as Assessed by End of Treatment Landmark

| Variable | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Total CIRS score | | | | 1.21 | 1.05 to 1.39 | .010 |
| Age > 65 years | | | | 1.65 | 1.03 to 2.64 | .038 |
| Del(17p) | 9.67 | 4.61 to 20.25 | < .001 | 5.02 | 2.24 to 11.26 | < .001 |
| Del(11q) | 1.32 | 1.00 to 1.75 | .049 | | | |
| *IGHV* unmutated | 2.40 | 1.76 to 3.27 | < .001 | 3.35 | 1.84 to 6.12 | < .001 |
| Treatment arm | | | .001 | | | |
| FC *v* FCR | 0.87 | 0.64 to 1.19 | .387 | | | |
| BR *v* FCR | 1.63 | 1.18 to 2.24 | .003 | | | |
| Partial response | 1.48 | 1.11 to 1.96 | .007 | | | |
| MRD positivity in PB | 3.55 | 2.69 to 4.69 | < .001 | 2.34 | 1.50 to 3.66 | < .001 |

NOTE. Blank cells denote the lack of a significant association in multivariable analysis. Multivariable analyses for PFS and OS were performed on 515 and 516 patients, respectively, with all data available.

Abbreviations: BR, bendamustine plus rituximab; CIRS, cumulative illness rating scale; FC, fludarabine and cyclophosphamide; FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio; MRD, minimal residual disease; OS, overall survival; PB, peripheral blood; PFS, progression-free survival.

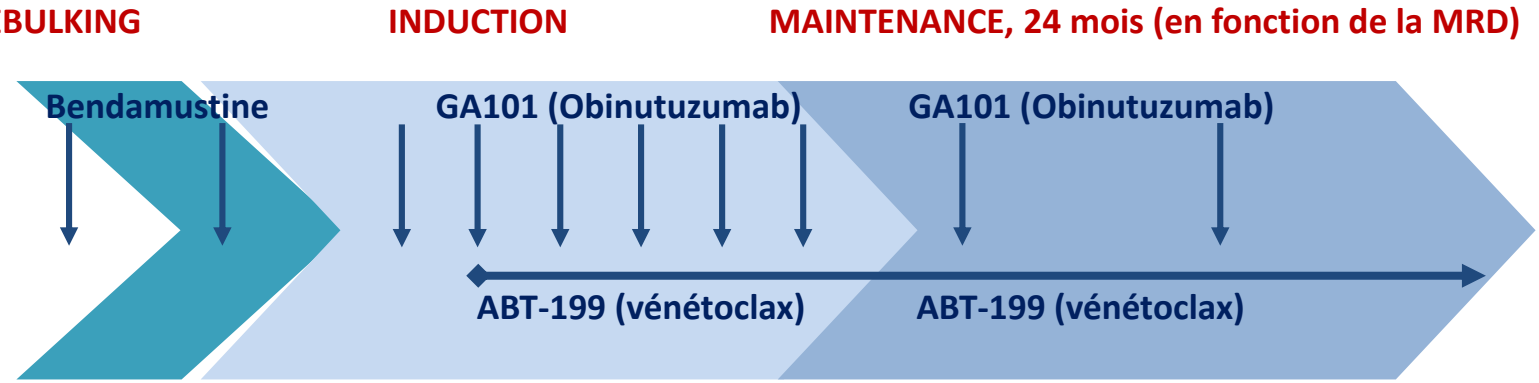
JOURNAL OF CLINICAL ONCOLOGY ASCO

*Gabor Kovacs et al. JCO doi:10.1200/JCO.2016.67.1305*

# Conclusions: Futur (déjà là…) & Interrogations

- **ASSOCIATIONS?**
  - AVEC CHIMIOTHERAPIE (CT): GA-FC; GA-Benda; GA-Ibru-CT; GA-Idéla-CT; ABT-CT…
  - SANS CHIMIOTHERAPIE: GA-Ibru; GA-Idéla; GA-Ibru-Idéla; GA-ABT…
- **POUR QUELS OBJECTIFS?** PFS, OS, MRD, Bénéfice Clinique
- **POUR QUELS PATIENTS?**
- **IMPACT EN TERME DE QUALITE DE VIE?**
- **COUT EXHORBITANT!!!**

# ETUDE Ph2 CLL2-BAG (GERMAN CLL STUDY GROUP)




**Objectif principal : évaluation de l'efficacité et de la tolérance**

| | 1ère Ligne (n = 34) | R/R (n = 29) | TOTAL (n = 63) |
|---|---|---|---|
| Age | 58 (43-76) | 61 (28-77) | **59 (28-77)** |
| Stade de Binet B-C | 27 (79 %) | 19 (65 %) | **46 pts (73 %)** |
| Score CIRS > 6 | 6 % | 17 % | **11 %** |
| Cytogénétique<br>del(17p)<br>del(11q) | <br>3 (9 %)<br>7 (21 %) | <br>8 (30 %)<br>8 (30 %) | <br>**11 pts (18 %)**<br>**15 pts (25 %)** |
| Mutations<br>TP53<br>NOTCH51<br>SF3B1 | <br>6 (18 %)<br>1 (3 %)<br>7 (21 %) | <br>11 (39 %)<br>6 (21 %)<br>9 (32 %) | <br>**17 pts (27 %)**<br>**7 pts (11 %)**<br>**16 pts (26 %)** |
| Statut IGHV non muté | 20 (59 %) | 26 (93 %) | **46 pts (74%)** |

***Debulking par bendamustine: N= 45 (71%)***

***60 patients ont reçu les 6 cycles d'induction***

| REPONSE en FIN D' INDUCTION | 1ère Ligne (n=34) | R/R (n=29) | TOTAL (n=63) |
|---|---|---|---|
| ORR | 34 (100 %) | 26 (90 %) | **60 (95 %)** |
| RC | 3 (9 %) | 2 (7 %) | **5 (8 %)** |
| RC/RCu | 14 (41 %) | 6 (21 %) | **20 (32 %)** |
| RP | 17 (50 %) | 18 (62 %) | **35 (56 %)** |
| MRD < $10^{-4}$ (sang) | 31 (91 %) | 24 (83 %) | **55 (87 %)** |
| MRD < $10^{-4}$ (MO) | 4 (12 %) | 4 (14 %) | **8 (13 %)** |

*P. Cramer, et al., abstract #6, ICML 2017*

# IBRUTINIB, FLUDARABINE, CYCLOPHOSPHAMIDE ET OBINUTUZUMAB (IFCG)
# En 1ière Ligne LLC MUTÉE et DEL(17P)-

**Les patients atteints de LLC avec statut TP53 non muté ont une PFS à 10 ans > 60 % après traitement FCR en 1L**

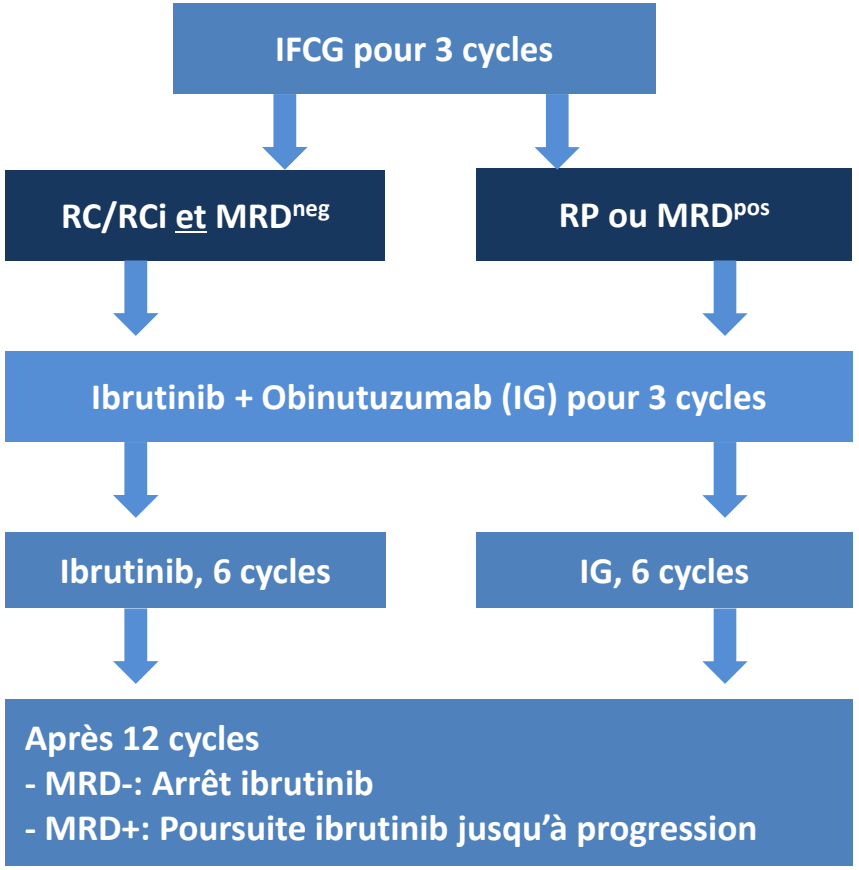
**Dans la LLC du sujet jeune, après 6 FCR, on obtient 44 à 72 % de rémissions complètes**

**La MRD négative dans la moelle est obtenue dans 43 à 58 % des cas après 6 cycles**

**5 % de SMD et LAM**

**L'objectif de cet essai est de réduire le nombre de cycles de FC à 3 en introduisant l'ibrutinib et l'obinutuzumab pour augmenter le taux de MRD négative**

| | Cycle 1 | | | | | | Cycles 2-3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | J1 | J2 | J3 | J4 | J8 | J15 | J1 | J2 | J3 |
| GA101 (mg) | 100 | 900 | - | - | 1000 | 1000 | 1000 | - | - |
| Fluda ($mg/m^2$) | - | 25 | 25 | 25 | - | - | 25 | 25 | 25 |
| Endoxan ($mg/m^2$) | - | 250 | 250 | 250 | - | - | 250 | 250 | 250 |
| Ibrutinib | 420 mg / J en continu | | | | | | | | |




*N. Jain et al., abstract S463, EHA 2017*

# IBRUTINIB, FLUDARABINE, CYCLOPHOSPHAMIDE ET OBINUTUZUMAB (IFCG)
# En 1ière Ligne LLC MUTÉE et DEL(17P)-

| | N=31 |
|---|---|
| Age | 60 (25-71) |
| Del(13q)<br>Trisomie 12 | 22 (71)<br>6 (19) |
| Mutations MYD 88<br>Mutations SF3B1<br>Mutations NOTCH1 | 3 (10)<br>2 (7)<br>1 (3) |

| | N (%) | |
|---|---|---|
| | G3 | G4 |
| Neutropénie | 9 (29) | 12 (39) |
| Thrombopénie | 14 (45) | 1 (3) |
| ALAT/ASAT | 3 (10) | 1 (3) |
| Fibrillation atriale | 2 (6) | |
| Arthralgie | 1 (3) | |
| IRR | 1 (3) | |

**IFCG induit un fort taux de réponse MRD négative dans la moelle après 3 cycles**

**Les 10 patients ayant terminé leur traitement de 1 an sont tous en MRD négative dans la moelle**

**Infections**

- **Neutropénie fébrile, 4**
- **Pneumonie à *Pneumocystis* (PCP), 1**
- **Infection pulmonaire à MAC, 1**
- **Cholécystite aiguë, 1**
- **Zona, 1**

**Réduction de dose**

- **FC, 57 %**
- **Ibrutinib, 20 %**
- **Retard de traitement > 2 semaines 35 %**
  **(thrombopénie, ASAT/ALAT, infection)**

*N. Jain et al., abstract S463, EHA 2017*

# Conclusions: Etat des lieux en 2017