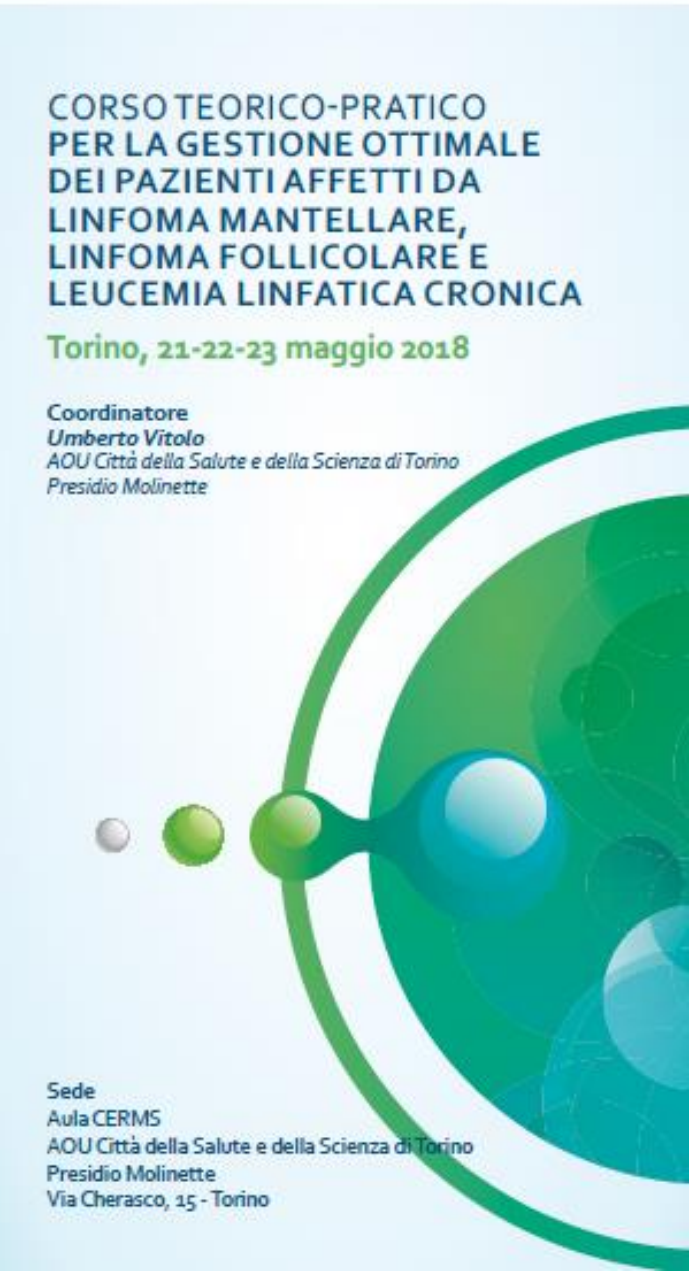



# La terapia delle recidive e nuovi farmaci nel linfoma follicolare

Luca Arcaini

**Dipartimento di Ematologia Oncologia, Fondazione IRCCS Policlinico San Matteo &**
**Dipartimento di Medicina Molecolare, Università di Pavia**

# DICHIARAZIONE

## Relatore: **Luca Arcaini**

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario **CELGENE, ROCHE. BAYER**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **GILEAD**
- Partecipazione ad Advisory Board **ROCHE, PFIZER, CELGENE, GILEAD**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario

**NIENTE DA DICHIARARE**

- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Altro

Alcuni farmaci discussi nella presentazione sono fuori indicazione nei linfomi non Hodgkin follicolari

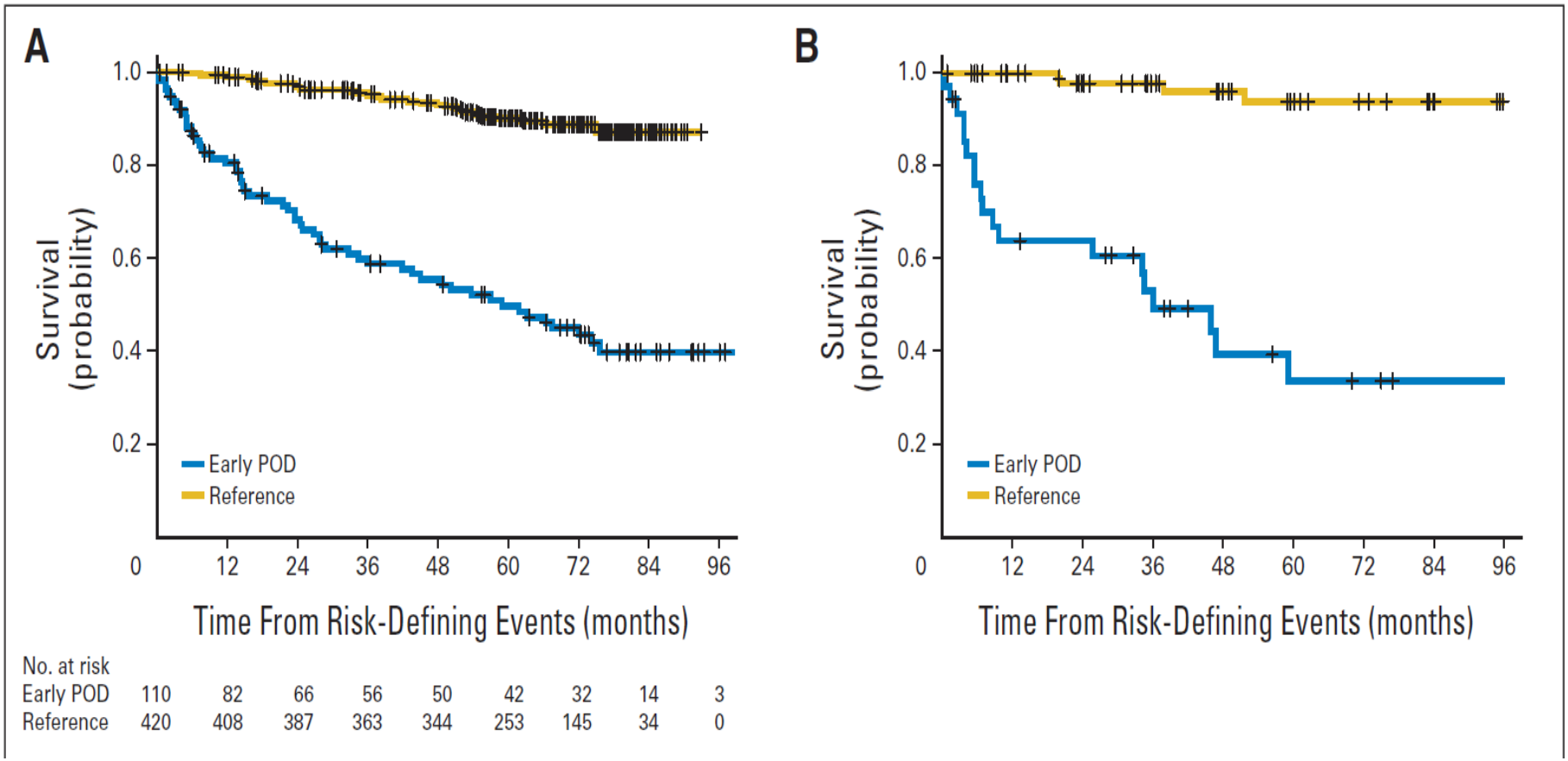
# Therapy of relapsed/refractory follicular lymphoma

- Histology
- Prior treatment
- Duration of prior response
- Patient's age
- Comorbidity
- Goals of therapy
- Clinical trial availability
- Logistics

# Relapsed vs. Refractory FL

- **Relapsed**
  - Initial response (CR or PR)
  - Progress >6 months following completion of standard induction therapy
- **Poor risk relapse**
  - PET/CT scan positive postinduction
  - <12 months following treatment
- **Refractory**
  - <PR to standard induction
  - CR or PR that lasts <6 months

# Early progressors




*Casulo et al JCO 2015*

# 20% of patients experience PD within 24 mo from chemoimmunotherapy

- Early relapse after chemoimmunotherapy defines patients at high risk for death

**Stage II, III and IV FL treated with R-CHOP in the first-line setting**

| | N | 2-year OS (95% CI) | 5-year OS (95% CI) |
|---|---|---|---|
| Early PD following R-CHOP (<2 years) | 122 | 71% (61.5–78.0) | 50% (40.3–58.8) |
| Reference (late/no progression) | 420 (102/318) | 100% | 95% (92.7–97.0) |

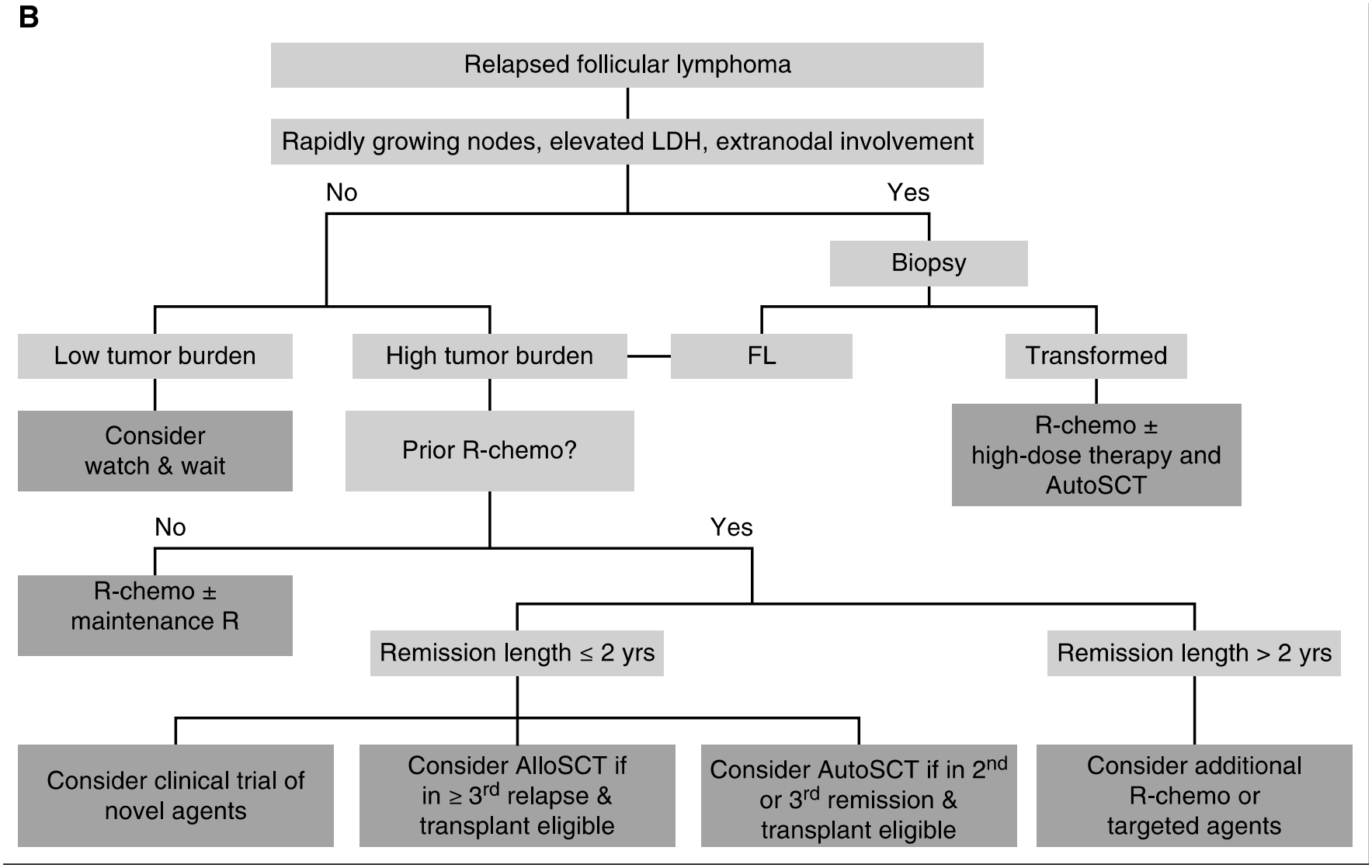
PD: progression of disease

*Casulo et al JCO 2015*

# FOLL05 Salvage treatment

| Treatment | N | % |
|---|---|---|
| **Chemotherapy** | 98 | **55** |
| **PBSCT** | 33 | **19** |
| **RT** | 9 | **5** |
| W&W | 12 | 7 |
| Palliative | 3 | 2 |
| Death before therapy | 2 | 1 |
| Loss to FU | 1 | 1 |
| NA | 19 | 11 |

# Therapy of relapsed/refractory follicular lymphoma: an algorithm




*Kahl et al Blood 2016*

# BENDAMUSTINE

# US Bendamustine Trials

- Two phase II, multicenter, single-agent studies
- Relapsed, follicular and low-grade
- *Refractory to rituximab:* progression <6 months
  - First dose of rituximab
  - Completion of rituximab maintenance
  - Completion of chemotherapy + rituximab
- Dosage: bendamustine 120 mg/m$^2$ IV over 30-60 minutes, Days 1 and 2 every 21 days x 6 cycles

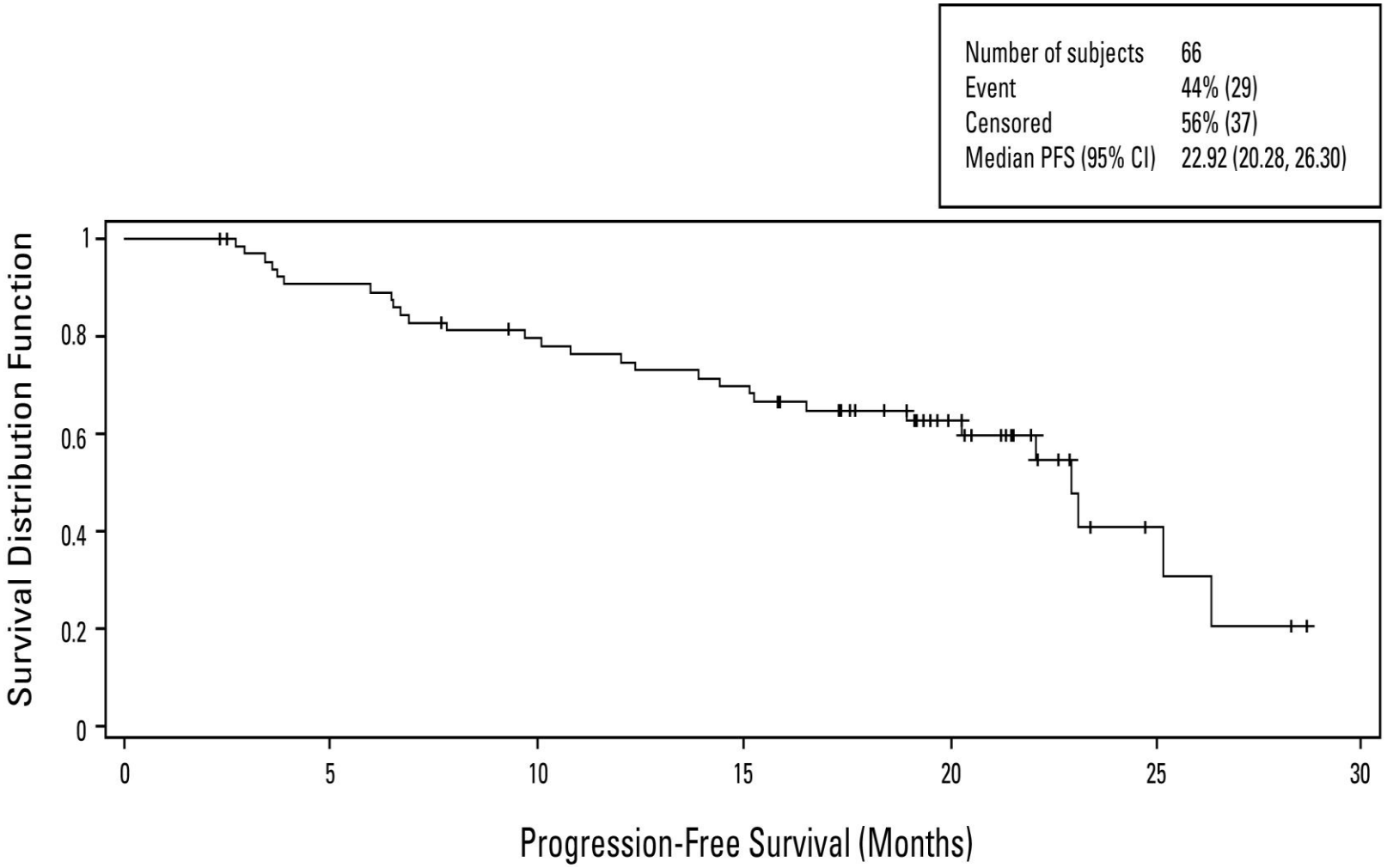
*Cheson et al. JCO 2009*

# US Bendamustine Trials

- N=176
- Median age 61 years (range, 31-84)
- Histologies: FL ( 68%), SLL (20%), MZL (11%), and LPL (1%)
- Stage III-IV in 81%
- Median three prior chemotherapy regimens
- 34% refractory to last chemotherapy

*Cheson et al. JCO 2009*

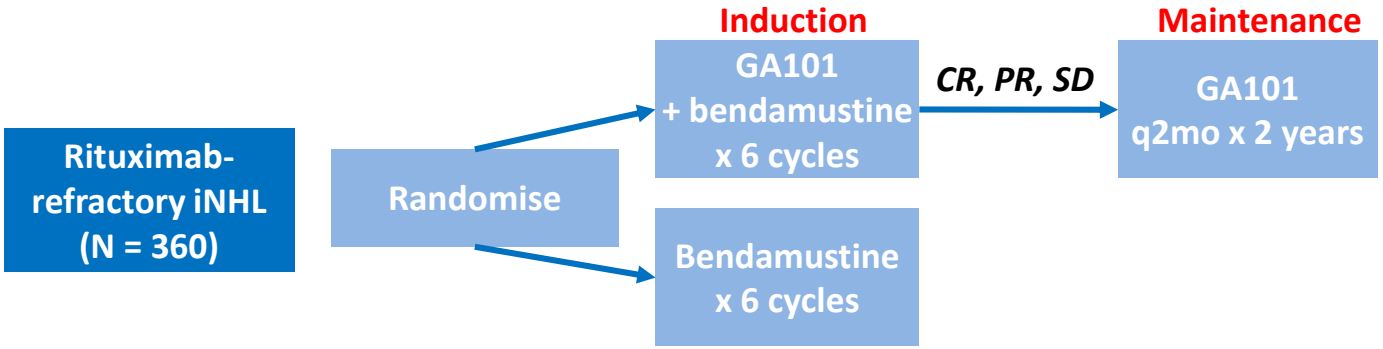
# PROGRESSION-FREE SURVIVAL




*Cheson et al. JCO 2009*

# Obinotuzumab (GA101)

# GADOLIN (GAO4753g) Phase III: Study design




GA101: 1,000 mg d1, d8, d15, cycle 1; d1, cycles 2–6, every 28 days
Bendamustine: 90 mg/m$^2$ (+ GA101), 120 mg/m$^2$ (monotherapy) d1, d2, cycles 1–6, every 28 days

## Primary endpoint

- PFS

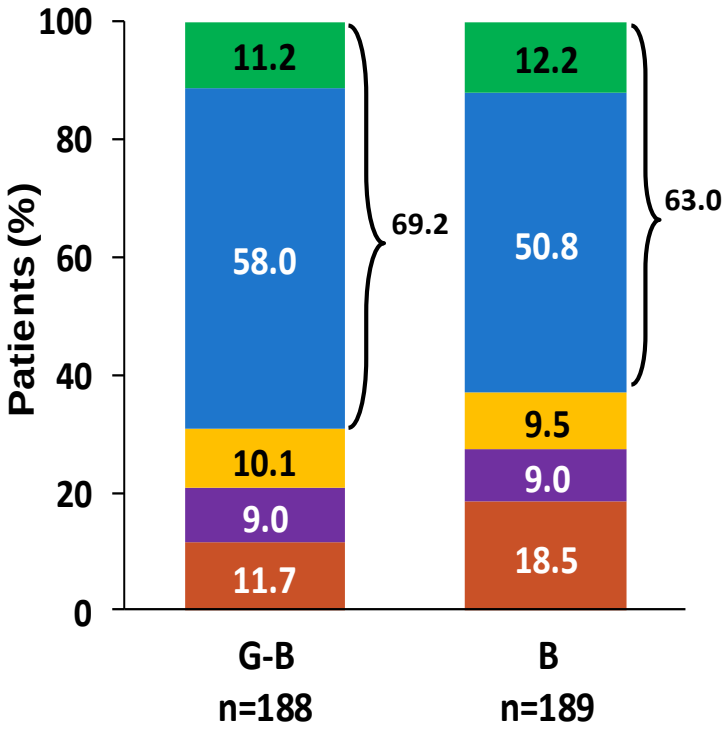
## Secondary endpoints

- ORR and CR rate
- Overall survival
- Best response

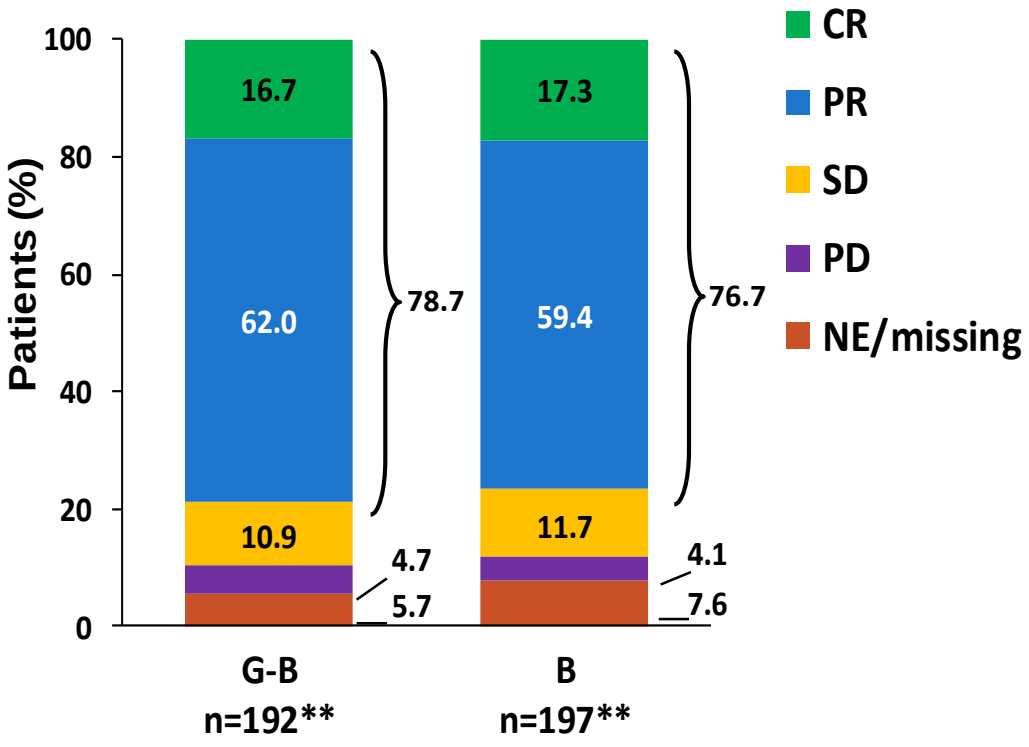
*Sehn et al ASCO 2015*

# Response to therapy

## End-of-induction response (IRF)




## Best overall response to 12 months (IRF)




- 19 patients still in induction (G-B, n=6; B, n=13)*

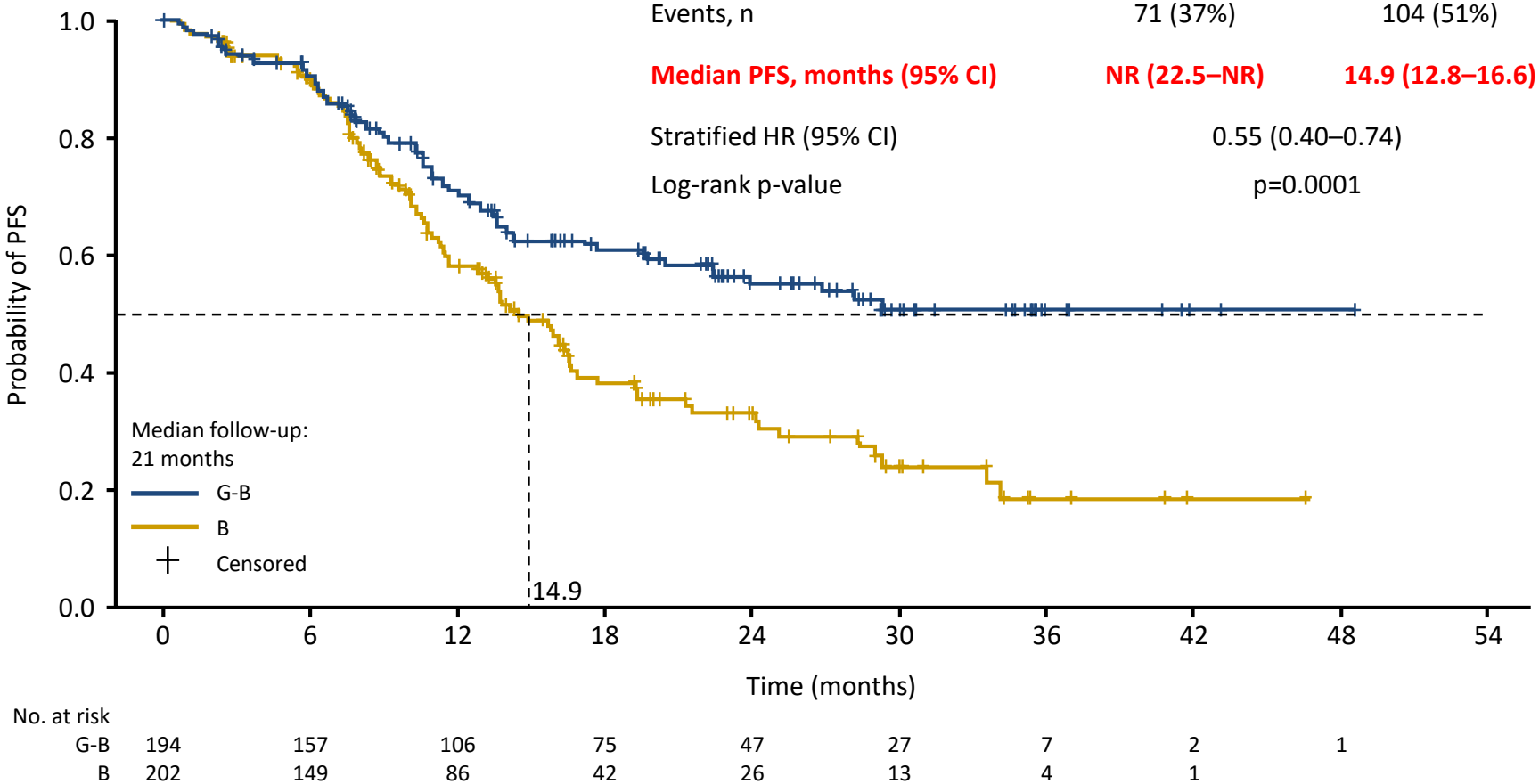
* Patients ongoing in induction therapy are excluded from analysis. Patients with end of induction response assessment performed >60 days after last induction dose shown as missing.

** Best overall response excludes ongoing patients who have not yet reached the first response assessment.

IRF, independent radiology facility

# IRF-assessed PFS

| IRF-assessed PFS | G-B (n=194) | B (n=202) |
|---|---|---|
| Events, n | 71 (37%) | 104 (51%) |
| **Median PFS, months (95% CI)** | **NR (22.5–NR)** | **14.9 (12.8–16.6)** |
| Stratified HR (95% CI) | 0.55 (0.40–0.74) | |
| Log-rank p-value | p=0.0001 | |

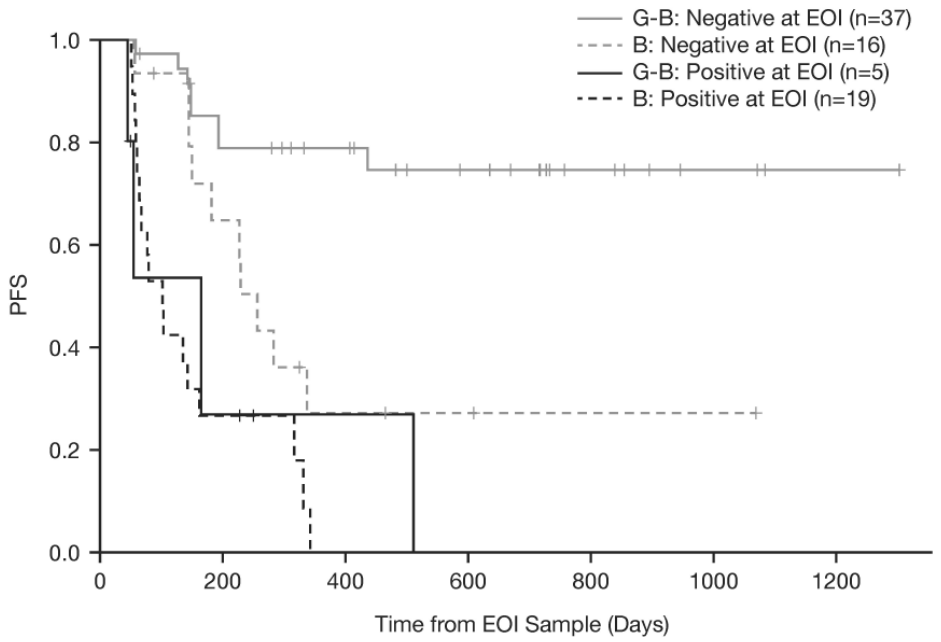



| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| G-B | 194 | 157 | 106 | 75 | 47 | 27 | 7 | 2 | 1 |
| B | 202 | 149 | 86 | 42 | 26 | 13 | 4 | 1 | |

IRF, independent radiology facility; HR, hazard ratio; CI, confidence interval; NR, not reached

# PFS and MRD

**Figure. PFS from the Date of the EOI Sample, by Treatment Arm and MRD Status**

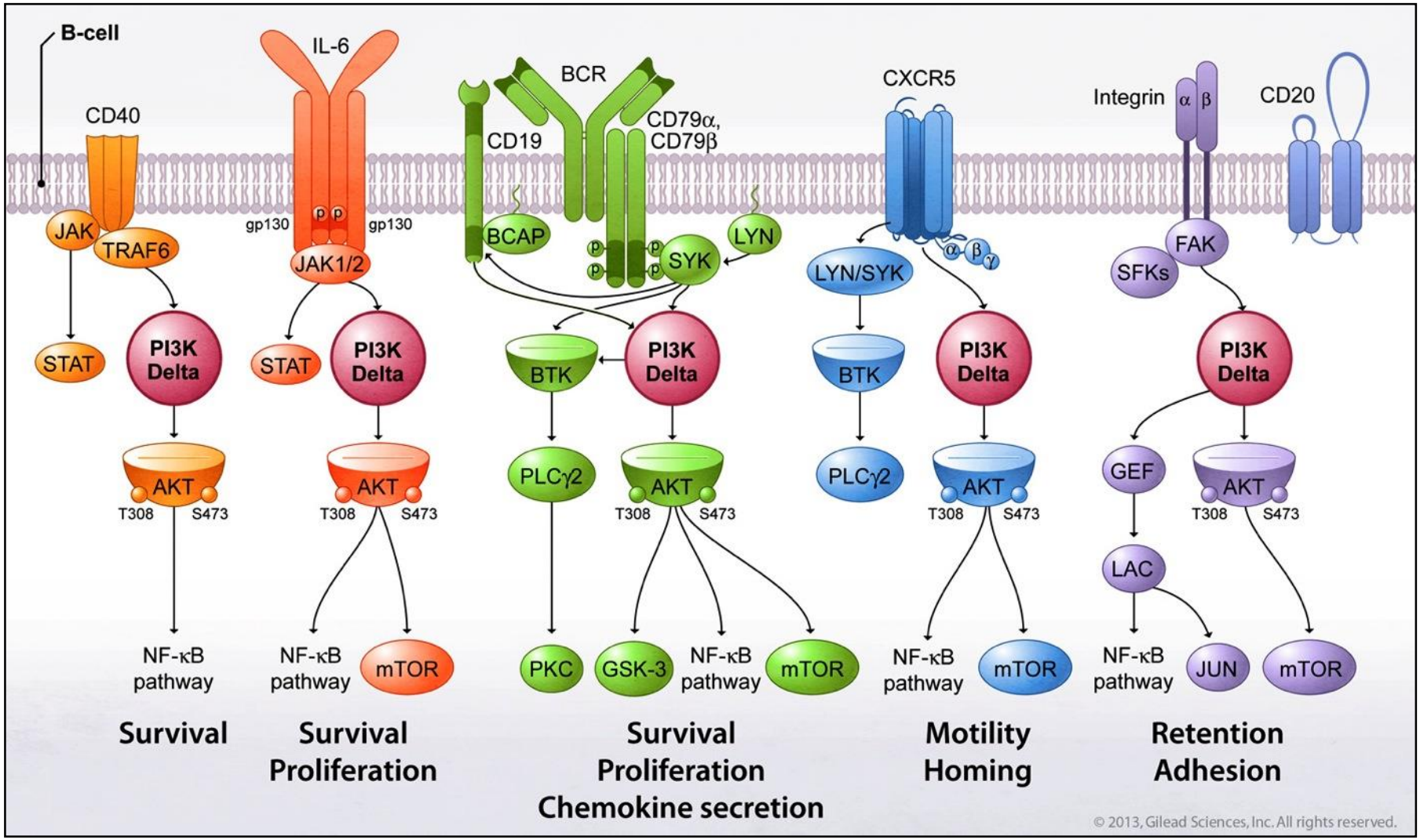



PFS measured from the date of the EOI sample. The differences in pt numbers from the table reflect subjects whose last tumor assessment before the clinical cut-off was before the EOI sample date or who progressed at or before the EOI sample date.

*Pott et al, ASH 2015*

# PI3K inhibitors

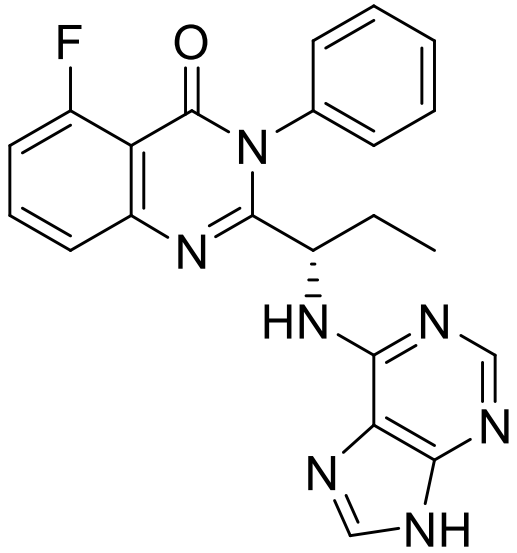
# PI3Kδ inhibition impacts multiple critical pathways in indolent lymphomas



# Idelalisib oral, selective PI3Kδ inhibitor

Direct and indirect attack on malignant B cells to:

- Reduce proliferation
- Induce apoptosis
- Inhibit homing and retention of B cells in the protective microenvironments (lymph nodes and bone marrow)




*Lannutti et al Blood 2011*
*Hoellenriegel et al Blood 2011*
*4.Figure adapted from Somoza et al J Biol Chem 2015*

# Potent inhibitor of PI3Kδ, which is selectively expressed in leukocytes

| PI3K isoform | Expression[1] | $IC_{50}$ (nM)[2] | $EC_{50}$ (nM)[3] |
|---|---|---|---|
| δ | Leukocytes | 19 | 8 |
| α | Ubiquitous | 8,600 | >10,000 |
| β | Ubiquitous | 4,000 | 1,900 |
| γ | Leukocytes | 2,100 | 3,000 |

*Vanhaesebroeck et al Nature Rev Mol Cell Biol 2010*
*Somoza et al. J Biol Chem 2015*
*Lannutti et al Blood 2011*

$EC_{50}$: half maximal effective concentration;
$IC_{50}$: half maximal inhibitory concentration

# Class I PI3K isoforms

| Class I PI3K isoform | Cellular expression | Primary physiological role |
|---|---|---|
| Alpha (α) | Broad | • Insulin signaling and angiogenesis<br>• Resistance mechanism in lymphoma |
| Beta (β) | Broad | • Platelet function |
| Gamma (γ) | Leukocytes | • Neutrophil and T-cell function |
| Delta (δ) | Leukocytes | • B-cell signaling, development, and survival |


•1. Okkenhaug, Vanhaesebroeck. *Nat Rev Immunol* 2003; 3: 317-330;
•2. Seiler et al. *Drugs* 2016; 76: 639-646;
•3. Iyengar et al. *Blood* 2013; 121: 2274-2284

# Study 101-09: single-group, open-label Phase II study


**Key endpoints**

Primary: ORR

Secondary: DoR, PFS, OS and safety

Refractory was defined as less than partial response or progression of disease within 6 months after completion of a prior therapy

*Gopal et al NEJM 2014*

# Clinical features

| Baseline characteristics | Patients (N=125) |
|---|---|
| Median age (range), y | 64 (33–87) |
| Subtype of iNHL, n (%) | |
| **Follicular lymphoma** | **72 (58)** |
| Small lymphocytic lymphoma | 28 (22) |
| Marginal zone lymphoma | 15 (12) |
| Lymphoplasmacytic lymphoma with/without Waldenström's macroglobulinaemia | 10 (8) |
| Disease status, n (%) | |
| Stage III or IV | 111 (89) |
| Elevated LDH | 38 (30) |
| Bulky disease (≥7 cm in one dimension) | 33 (26) |

LDH: lactate dehydrogenase

*Gopal et al NEJM 2014*

# Clinical features

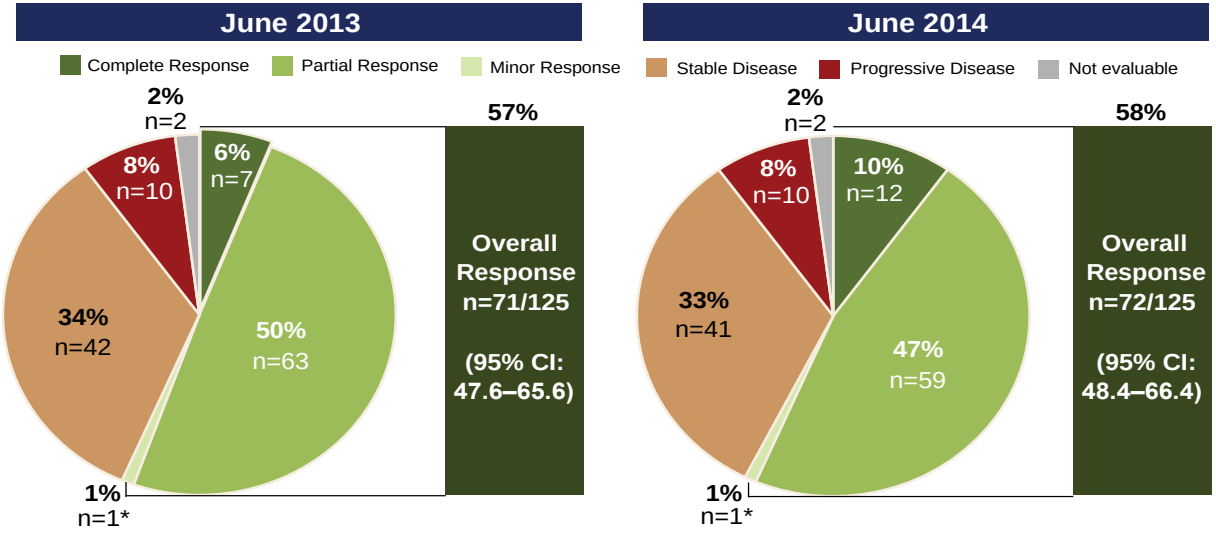
| Prior therapy exposure[1,2] | Patients (N=125) |
|---|---|
| Median (range) prior regimens, n | 4 (2–12) |
| Prior therapy, n (%) | |
| Rituximab | 125 (100) |
| Alkylating agent | 125 (100) |
| R + alkylating agent | 114 (91) |
| Bendamustine | 81 (65) |
| Anthracycline | 79 (63) |
| Purine analogue | 42 (34) |
| Stem cell transplantation | 14 (11) |
| Median time from last regimen to study entry, months | 3.9 |

| Prior therapy refractoriness, n/n (%)[1,2] | Patients (N=125) |
|---|---|
| Rituximab | 125/125 (100) |
| Alkylating agent | 124/125 (99)[a] |
| R + alkylating agent | 108/114 (95) |
| R-CVP | 29/36 (81) |
| R-bendamustine | 47/60 (78) |
| Bendamustine | 61/81 (75) |
| R-CHOP | 40/56 (71) |
| Refractory to ≥2 regimens | 99/125 (79) |
| Refractory to last regimen | 112/125 (90) |

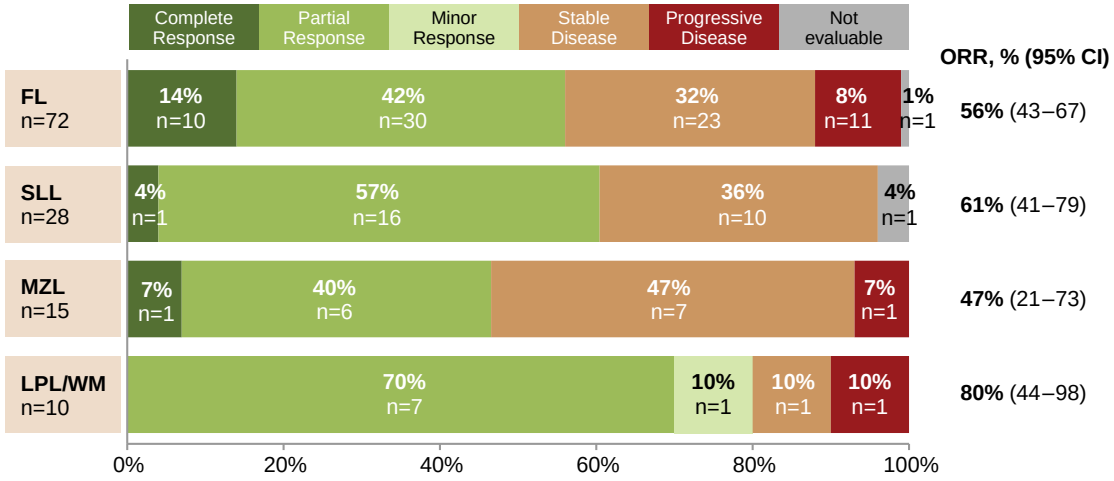
[a] Refractoriness to two cycles required to meet definition but one patient received only one cycle, with no response after that cycle.
CHOP: cyclophosphamide, vincristine, doxorubicin and prednisone; CVP: cyclophosphamide, vincristine and prednisone; R: rituximab

*Gopal et al NEJM 2014*

# Response



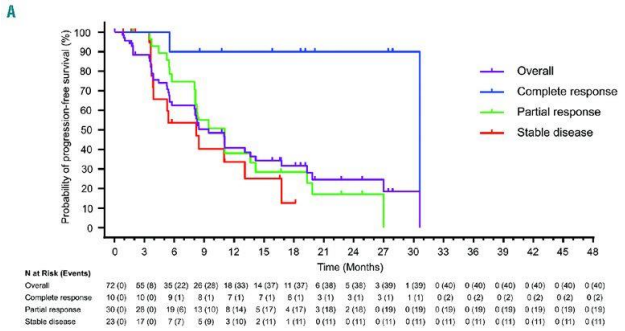

## Overall Response Rate By Disease Subgroups: 2014

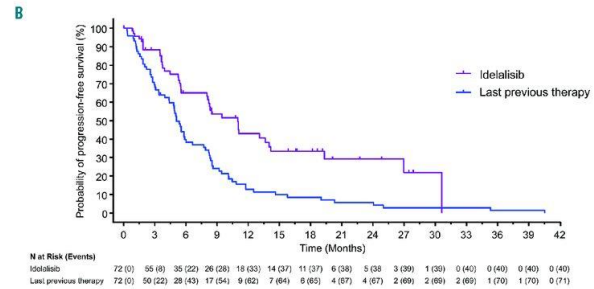


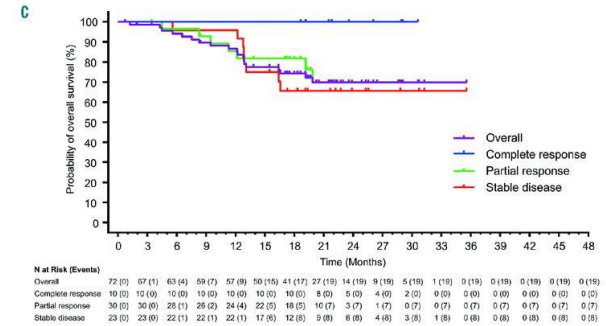

*Gopal et al NEJM 2014*
*Gopal et al ASH 2014*

# Progression-free and overall survival

## Median f-up 20 months



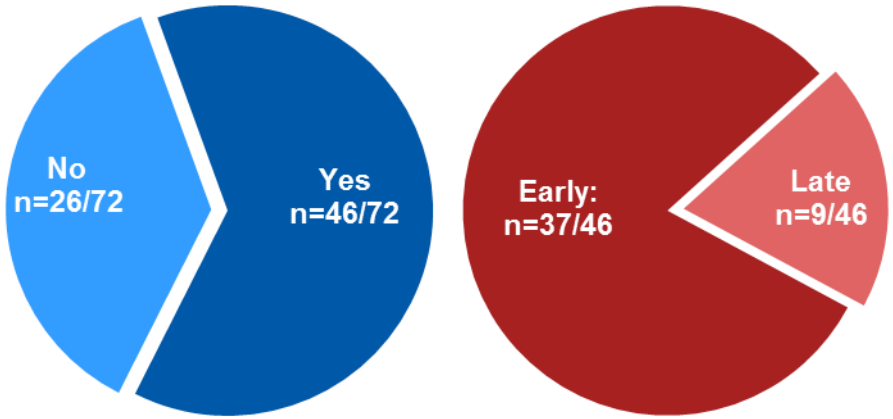

*Salles et al. Haematologica 2017*

# Retrospective subgroup analysis in patients with High-Risk FL

- Retrospective subgroup analysis of data from the Phase 2 trial of idelalisib in patients with FL (Study 101-09; NCT01282424)
- Population
  - Patients with FL who experienced early POD and received first-line (1L) CIT
  - Early POD defined as initiation of 2nd-line chemotherapy within 24 mos of initiating 1L CIT

## Study Population

**1L Chemoimmunotherapy** **Progression of Disease**



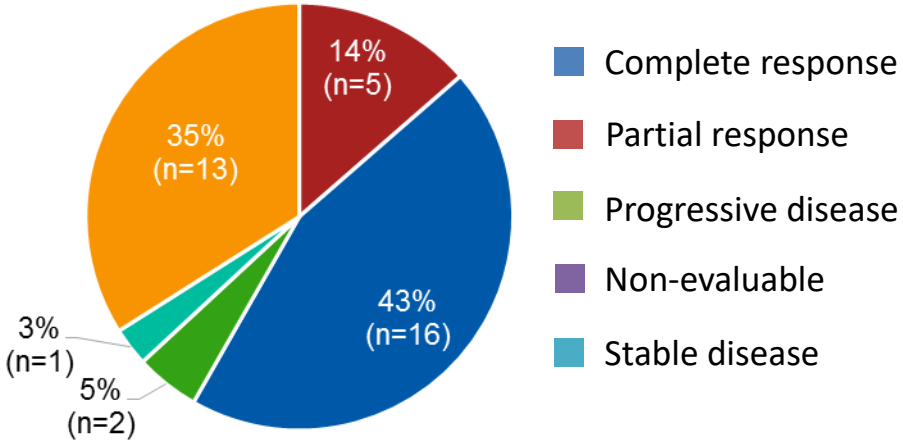

Of pts with FL who received 1L CIT, 37 of 64 experienced early POD

## Demographics and Baseline Characteristics

| Patients with Early POD | | N=37 |
|---|---|---|
| Median age, y (range) | | 64 (33–84) |
| Female, n (%) | | 18 (49) |
| Histologic Grade, n (%) | 1 or 2 | 33 (89) |
| | 3A | 4 (11) |
| FLIPI score ≥3, n (%) | | 21 (57) |
| Mean no. of prior therapies (SD; range) | | 3.4 (1.4; 2–8) |
| Prior therapy, n (%) | R-CHOP | 21 (57) |
| | BR | 7 (19) |
| | R-CVP | 5 (14) |
| Mean intertreatment interval, mos (SD) | 1st and 2nd | 12.5 (6.1) |
| | 2nd and 3rd | 9.7 (9.3) |
| | 3rd and 4th | 11.9 (12.0)* |
| | 4th and 5th | 11.8 (7.6)† |
| Median time to IDL, mo (range)‡ | | 30.3 (8.9–94.7) |

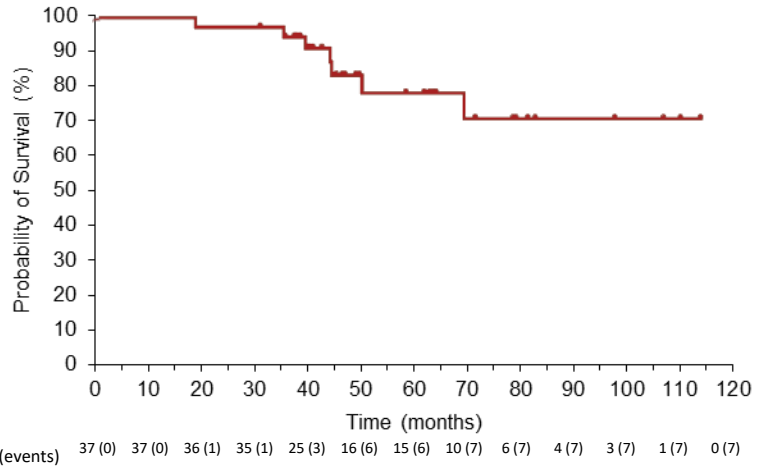
*n=24 (65%); †n=15 (41%); ‡Measured from time of initiation of 1st-line therapy; no patient received idelalisib as 2nd-line therapy. BR, bendamustine-rituximab; CIT: chemoimmunotherapy; FLIPI, FL International Prognostic Index; R-CVP, rituximab-cyclophosphamide-prednisone.

# Results



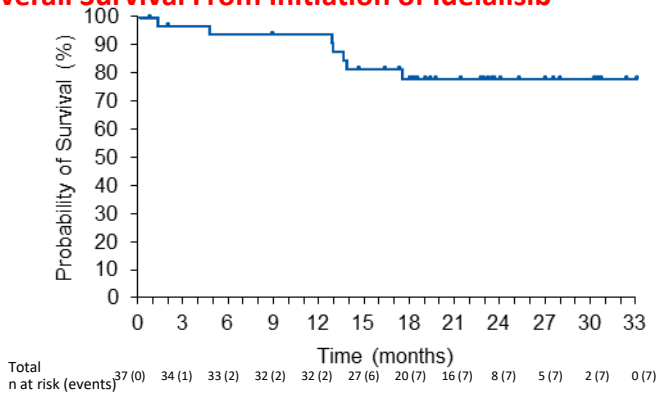

- Median duration of response for patients with complete or partial response was 11.8 months (95% confidence interval [CI] 3.8, not evaluable)

**Overall Survival From Initiation of 1st-line Treatment**



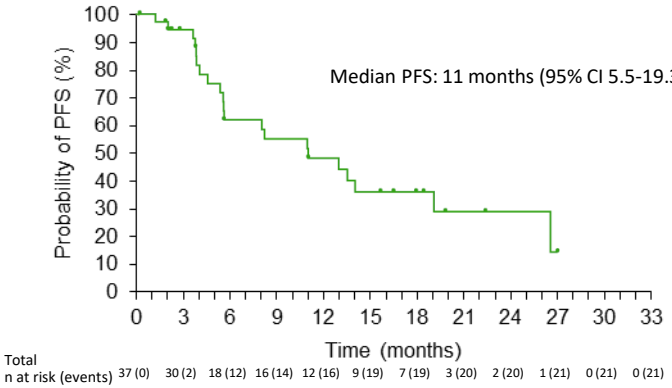

- Median OS following initiation of 1st-line immunochemotherapy was not reached during the course of the study

**Overall Survival From Initiation of Idelalisib**



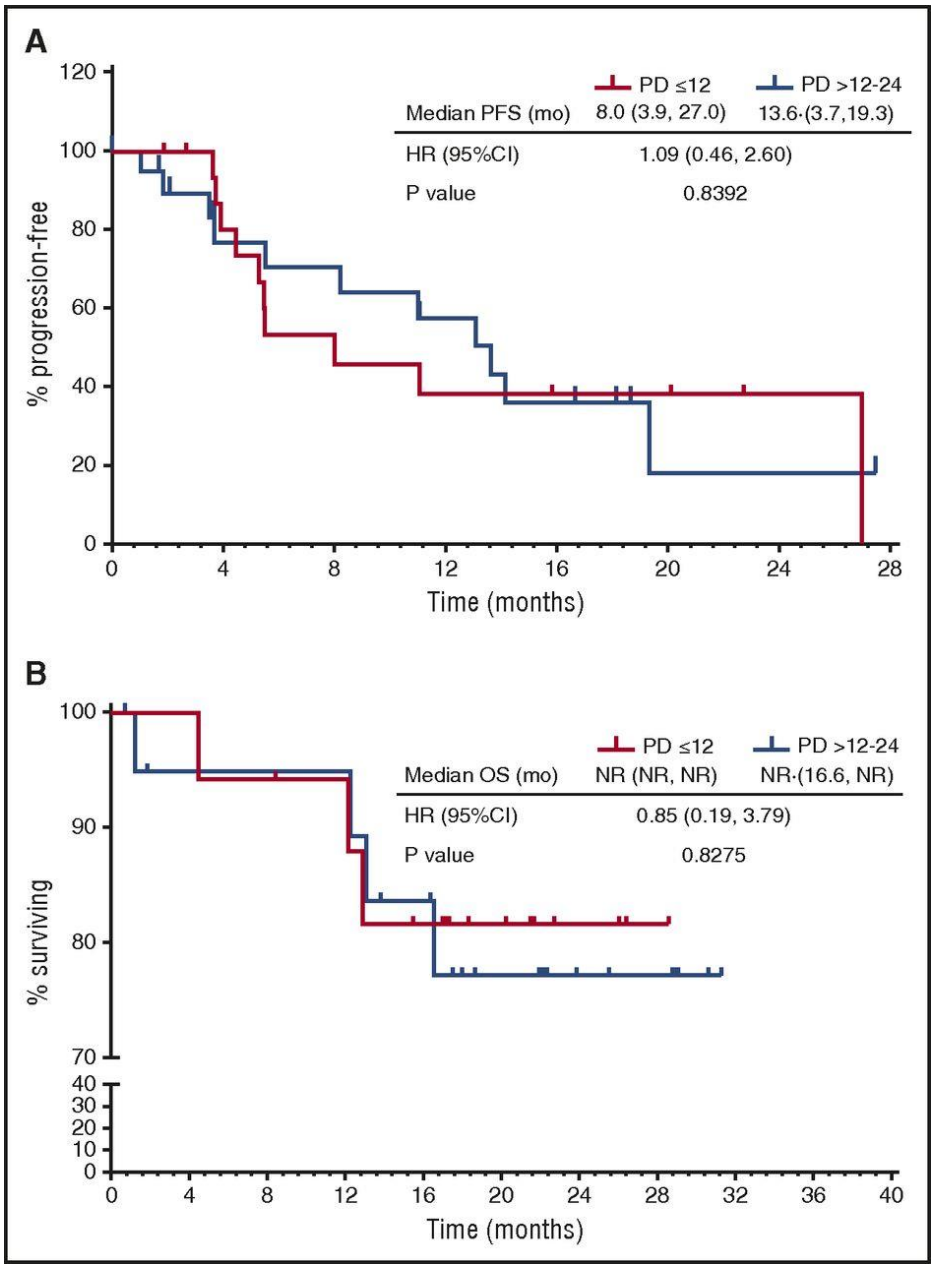

- Estimated probability of survival (±SE) at 2 years following initiation of idelalisib was 79% ± 7%
- Median OS following initiation of idelalisib was not reached during the course of the study

**Progression-Free Survival From Initiation of Idelalisib**




- Estimated probability of survival (±SE) at 2 years following initiation of idelalisib was 29% ± 10%

*Gopal et al Blood 2017*




*Gopal et al Blood 2017*

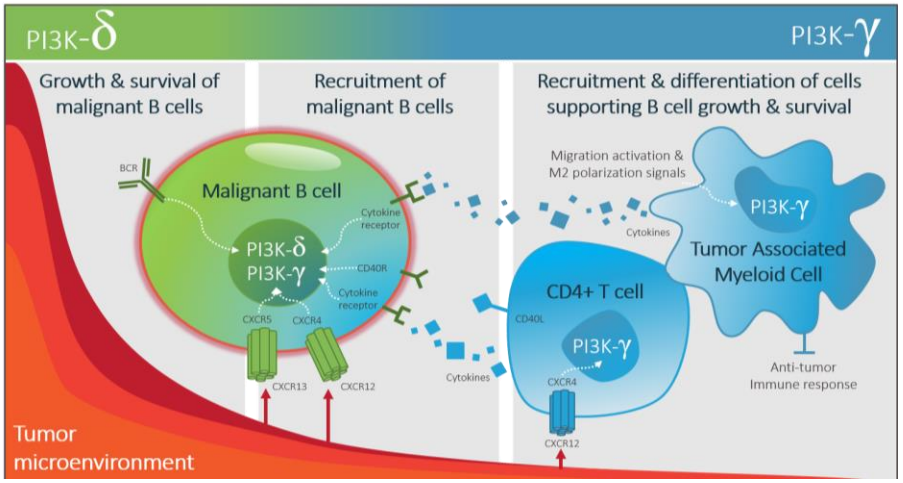
# Other PI3K inhibitors in development

| Agent | Population | Efficacy | Safety |
|---|---|---|---|
| **SAR245409**[1]<br>Pan-Class I PI3K inhibitor | Relapsed or refractory FL (n=24) | • ORR: 50%<br>• PFS ≥24 weeks: 58% | Grade 3/4 TEAEs included<br>• Lymphopenia (13%)<br>• Hyperglycaemia (<10%) |
| BAY 80-6946 (**copanlisib**)[2]<br>PI3Kδ, α inhibitor | FL (n=13) | • ORR: 40%<br>• CR: 20% | Grade 3/4 AEs in 61 patients with lymphoma<br>• Hypertension (31%)<br>• Neutropenia (16%)<br>• Hyperglycaemia (13%)[a] |
| IPI-145 (**duvelisib**)[3]<br>PI3Kδ,γ inhibitor | Advanced haematological malignancies (N=20) | • CR: 9%<br>• PR: 27%<br>• SD: 18% | Grade 3/4 AEs included<br>• Neutropenia (30%)<br>• Thrombocytopenia (5%) |

[a] Hyperglycaemia of any grade occurred in 47% of patients
ORR: objective response rate; PFS: progression-free survival; TEAE: treatment-emergent adverse event; CR: complete response; AE: adverse event; PR: partial response; SD: stable disease

*1. Brown et al. ASH 2013*
*2. Dreyling et al ASH 2013*
*3. Flinn IW, et al. ASH 2012*

# DYNAMO: A PHASE 2 STUDY DEMONSTRATING THE CLINICAL ACTIVITY OF DUVELISIB IN PATIENTS WITH DOUBLE-REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA




Duvelisib synergistically targets both malignant B cells (PI3K-δ) and the supportive microenvironment (PI3K-γ)


FL: 83 pts

> refractory to last two therapies: 81%

> median number of prior regimens: 3 (1-10); more than 2 regimens: 65%

> median time since completion of last therapy: 3 months

*Zinzani PL et al, ICML 2017*

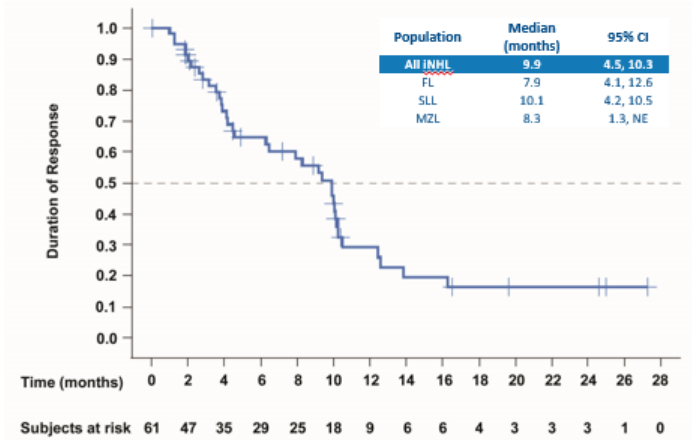
# Results

## OVERALL RESPONSE RATE

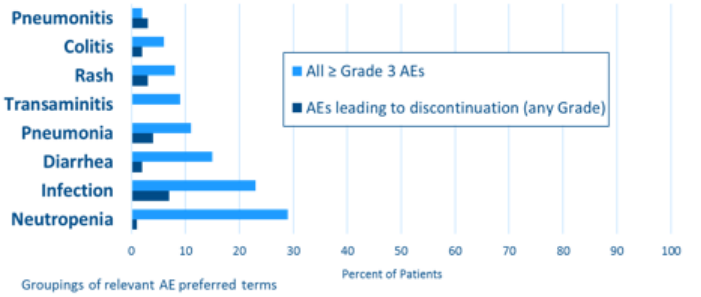
| | OVERALL N = 129 | FL N = 83 | SLL N = 28 | MZL N = 18 |
|---|---|---|---|---|
| **ORR per IRC** | **47%** | **43%** | **68%** | **33%** |
| *P-value* | *p = 0.0001* | -- | -- | -- |
| *95% CI* | *(38-56)* | -- | -- | -- |
| *Complete Response* | *1%* | *1%* | *0* | *0* |
| *Partial Response* | *47%* | *42%* | *68%* | *33%* |
| **ORR per Investigator** | **60%** | **53%** | **86%** | **50%** |
| *Complete Response* | *3%* | *2%* | *4%* | *6%* |
| *Partial Response* | *57%* | *51%* | *82%* | *44%* |

- **Rapid time to response: median 2 months (range: 1.4 – 12)**

## DURATION OF RESPONSE



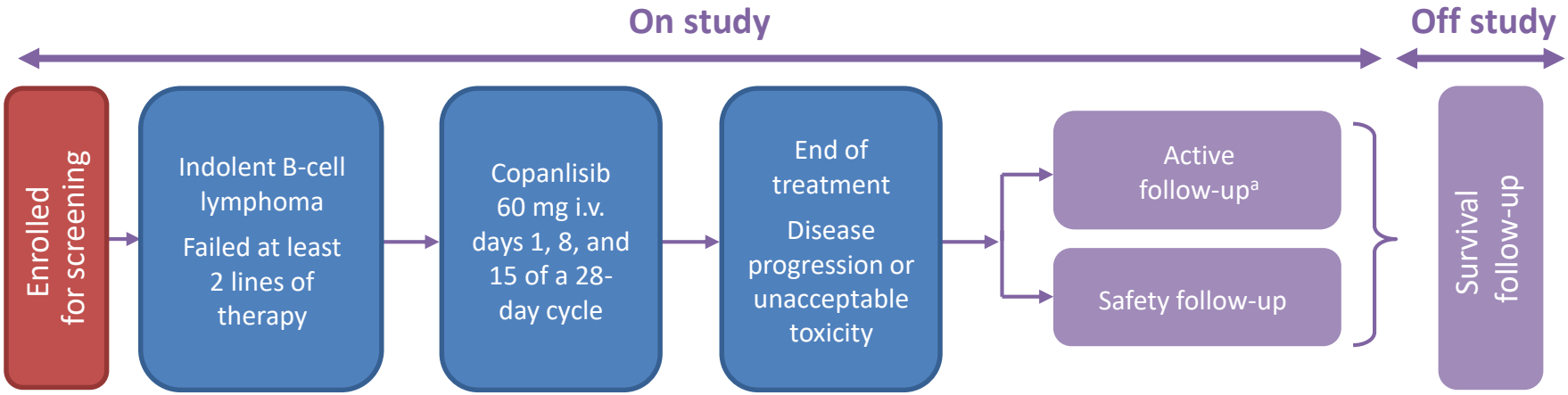

## ADVERSE EVENTS OF INTEREST




*Zinzani PL et al, ICML 2017*

# Chronos 1

## Copanlisib intravenous pan-class I PI3K inhibitor with predominant and potent activity against the PI3K-α and PI3K-δ isoforms




**Lymphoma types**

- FL (grades 1-3a)
- MZL
- SLL
- LPL / WM

**Primary endpoint**

- ORR[1] by central review

**Secondary endpoints**

- PFS
- DoR
- OS
- Safety
- Quality of life

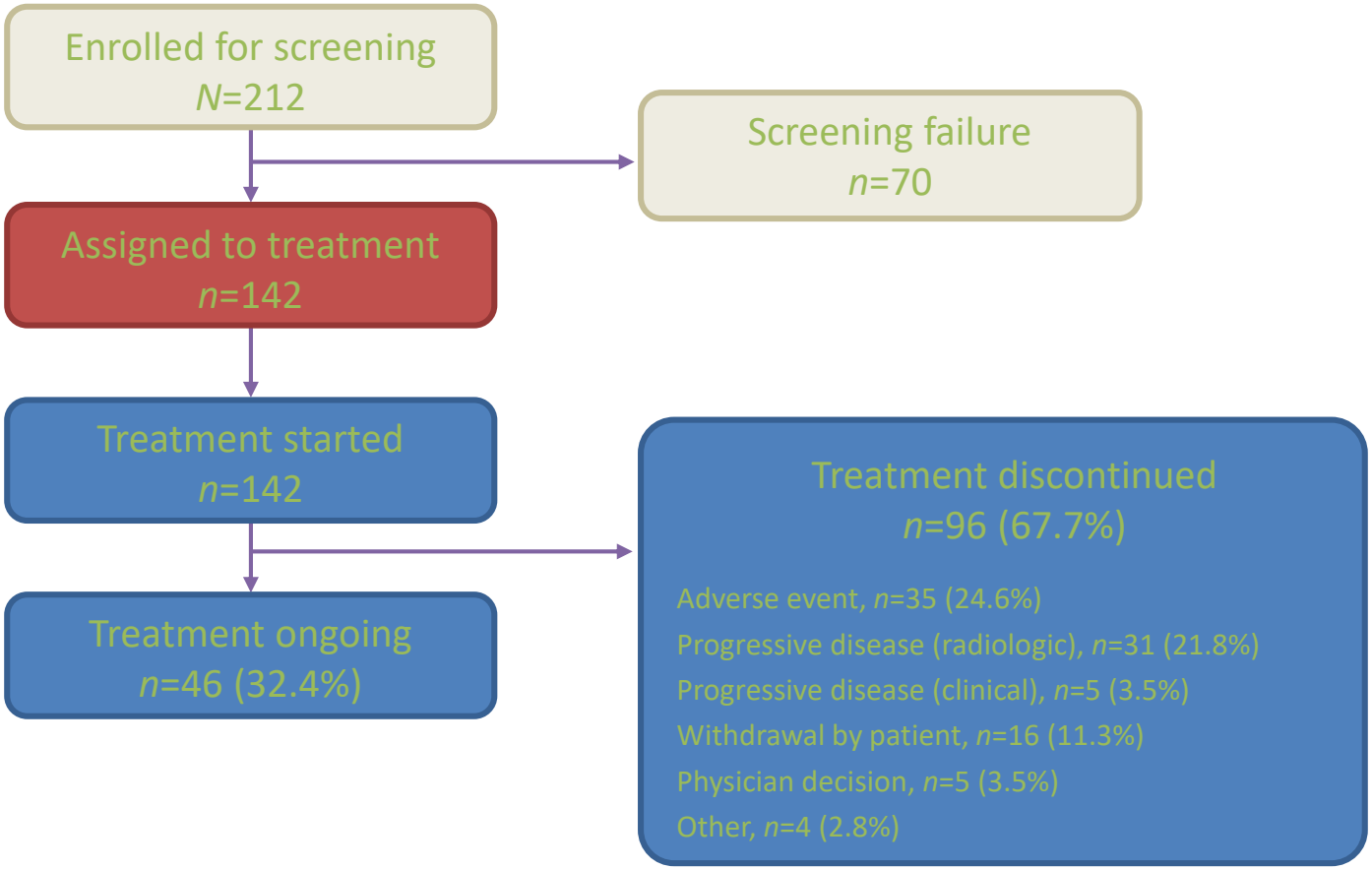
**Tertiary endpoints**

- Disease control rate
- Duration of stable disease
- ECOG scale
- Lesion size
- EQ-5D questionnaire, visual analog scale

•[a]Patients who discontinued treatment for any reason other than progressive disease entered active follow-up
DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQoL five dimensions questionnaire; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

•1. Cheson et al. *J Clin Oncol* 2007; 25: 579-586

# Patient disposition




•Data cut-off date: June 22, 2016

*Dreyling et al JCO 2017*

# Chronos-1 study

Copanlisib e.v. pan-Class I PI3K inhibitor (α and δ)

141 pts with indolent lymphoma (FL/MZL/SLL/LPL-WM: 104/23/8/6)

Median duration of treatment 22 wks (range 1-105), 46 pts on tx

**AEs (all grade/grade 3+)**

- Hyperglycemia (49%/40%)
- Hypertension (29%/23%)
- Neutropenia (25%/19%)
- Diarrhea (18%/4%)
- Lung infection (14%/11%)
- Pneumonitis (7%/1.4%)
- Colitis (0.7%/0.7%)

*Dreyling et al JCO 2017*

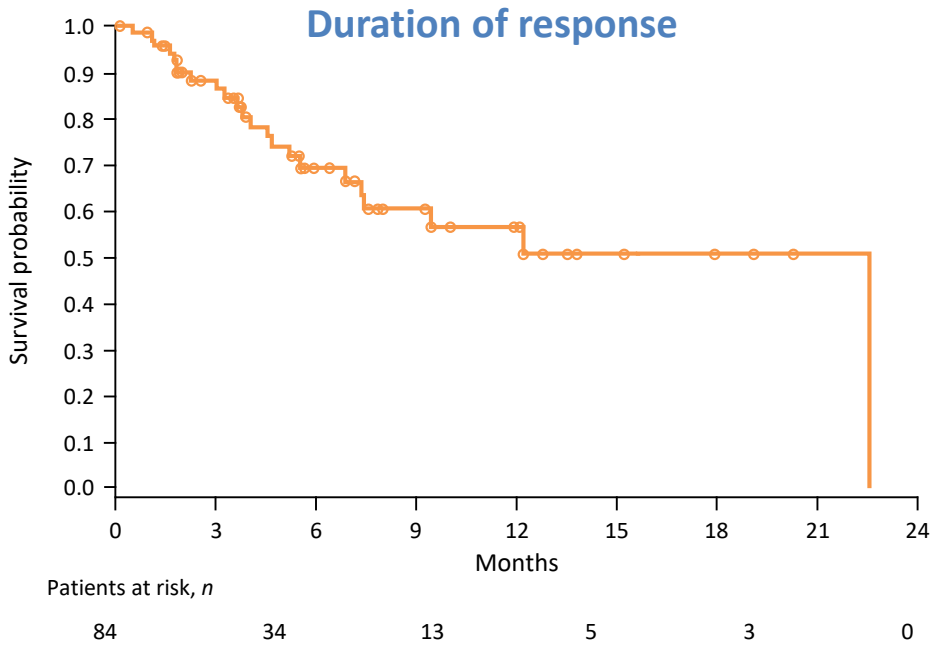
# Primary endpoint: ORR

| | FL (*n*=104) | MZL (*n*=23) | SLL (*n*=8) | LPL / WM (*n*=6) | Total (*N*=142)[a] |
|---|---|---|---|---|---|
| **Best response, *n* (%)** | | | | | |
| Complete response | 15 (14.4%) | 2 (8.7%) | 0 | 0 | 17 (12.0%) |
| Partial response | 46 (44.2%) | 14 (60.9%) | 6 (75.0%) | 1 (16.7%) | 67 (47.2%) |
| Stable disease | 35 (33.7%) | 4 (17.4%) | 1 (12.5%) | 3 (50.0%) | 42 (29.6%) |
| Progressive disease | 2 (1.9%) | 0 | 1 (12.5%) | 0 | 3 (2.1%) |
| NE / NA | 6 (5.8%) | 3 (13.0%) | 0 | 2 (33.3%) | 12 (8.5%) |
| **ORR, *n* (%)** | 61 (58.7%) | 16 (69.6%) | 6 (75.0%) | 1 (16.7%) | 84 (59.2%) |
| 95% CI | 48.6-68.2 | 47.1-86.8 | 34.9-96.8 | 0.4-64.1 | 50.6-67.3 |
| **Disease control rate, *n* (%)** | 91 (87.5%) | 20 (87.0%) | 7 (87.5%) | 4 (66.7%) | 122 (85.9%) |
| 95% CI | 79.6-93.2 | 66.4-97.2 | 47.4-99.7 | 2.3-95.7 | 79.1-91.2 |

- In patients who were refractory to the last regimen, the ORR was 60.5% (95% CI 49.3-70.9)

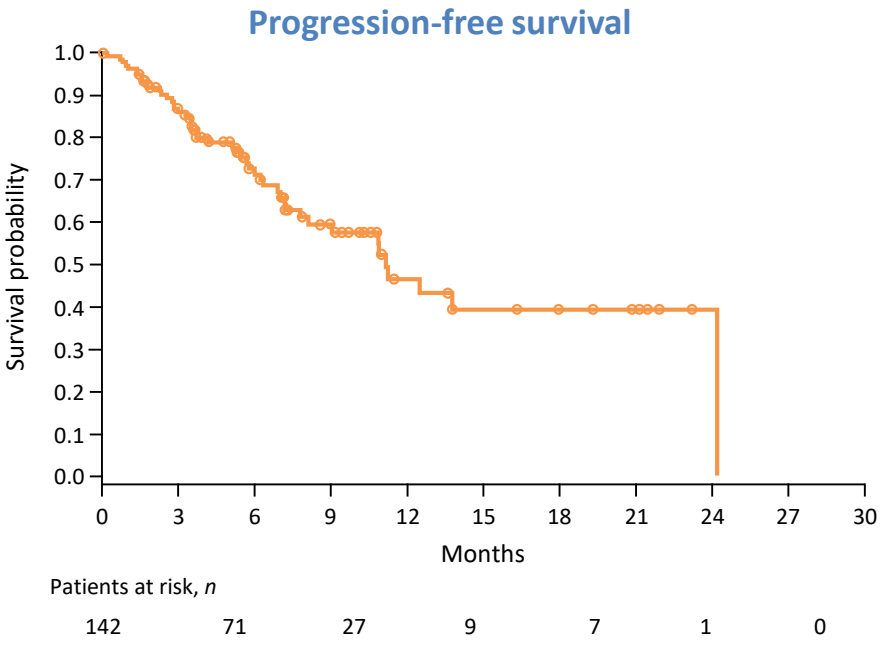
[a]Full analysis set; includes all treated patients
CI, confidence interval; NA, not available; NE, not evaluable

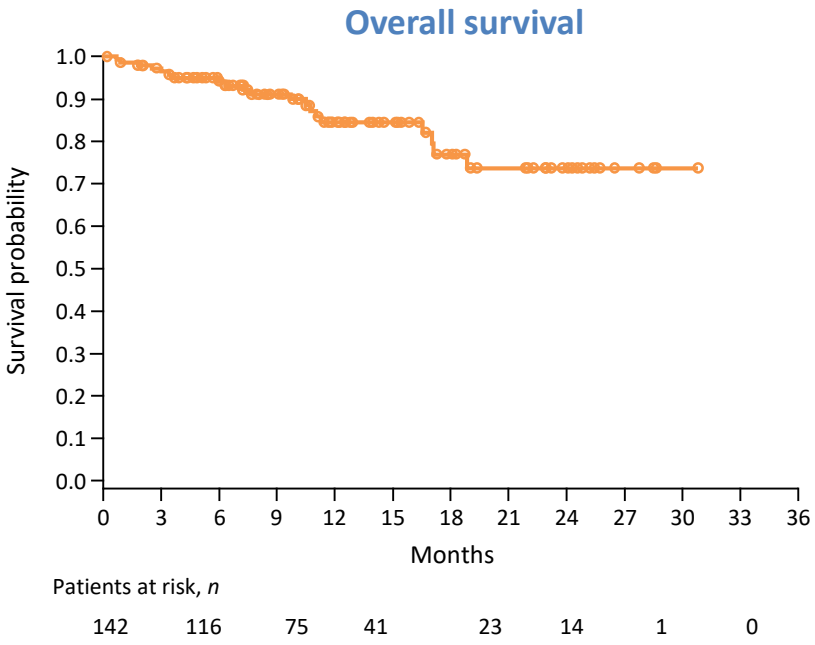
# Additional efficacy endpoints




- Median DoR:
  - Overall: 22.6 months (range 0-22.6; 95% CI 7.4-22.6)
  - Refractory patients: 12.2 months (range 0-22.6; 95% CI 7.4-22.6)
  - FL: 12.2 months (range 0-22.6; 95% CI 6.9-22.6)

# Additional efficacy endpoints

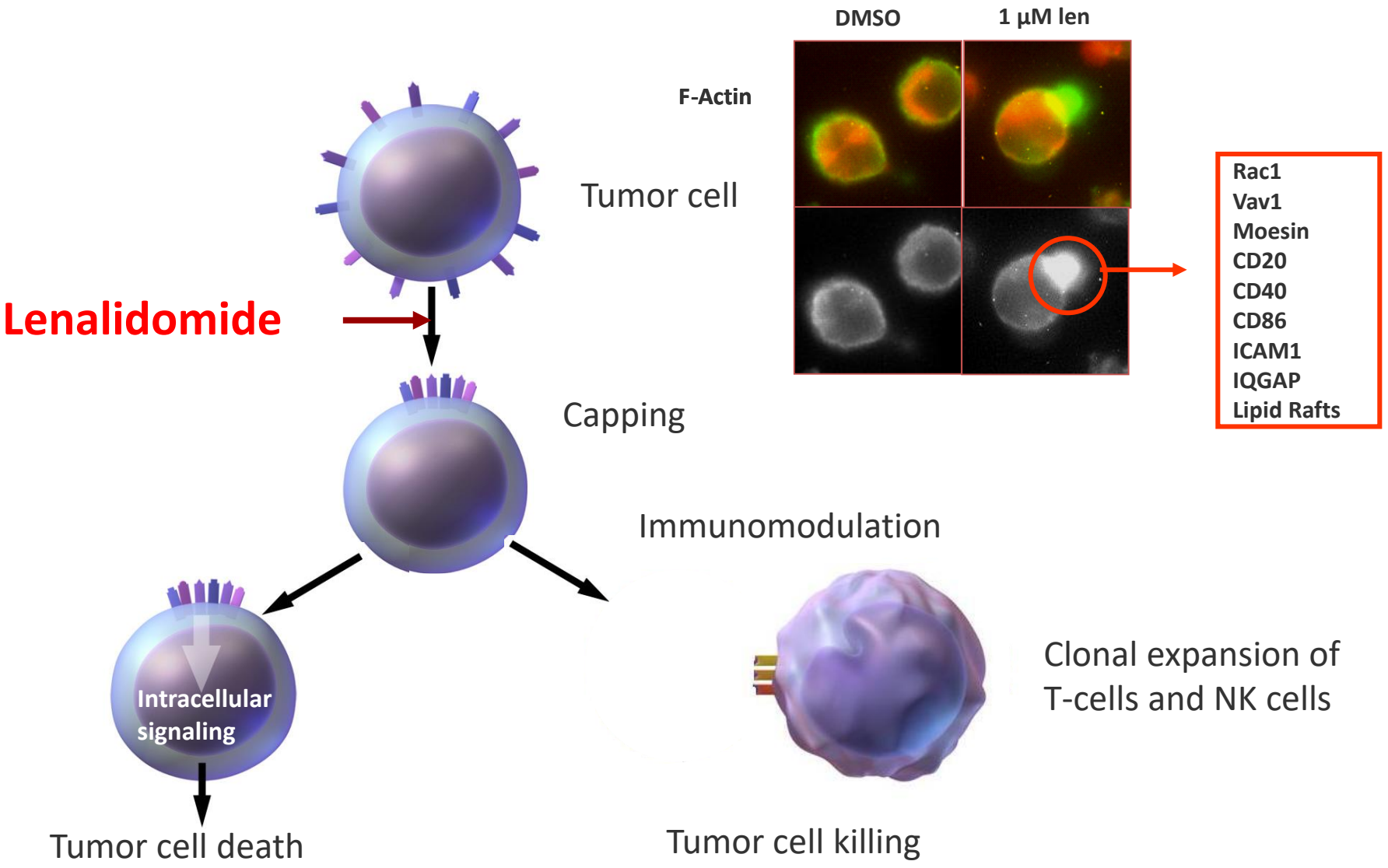



- Median PFS:
  - Overall: 11.2 months (95% CI 8.1-24.2)
  - FL:11.2 months (95% CI 7.8-24.2)
- Median OS was not yet reached

# Immunomodulations

# Lenalidomide couples tumoricidal & immunomodulatory activity



# Lenalidomide + R in R/R Indolent NHL

- Lena for 21 days in 28-d cycles and weekly R for 4 wks
- Lena continued until progression or unacceptable toxicity
- 27 evaluable for response
- ORR 74%; CR 44%
- Median PFS 12.4 mo
- 13 R refractory pts: ORR 61,5%
- FL: ORR 77%
- At a median f-up of 43 mo, median DOR 15·4 and TTNT 37·4 mo
- Grade 3/4 lymphopenia 45%, neutropenia (55%), fatigue (23%)
- Lena may improve R in low-affinity FCGR3A polymorphisms pts

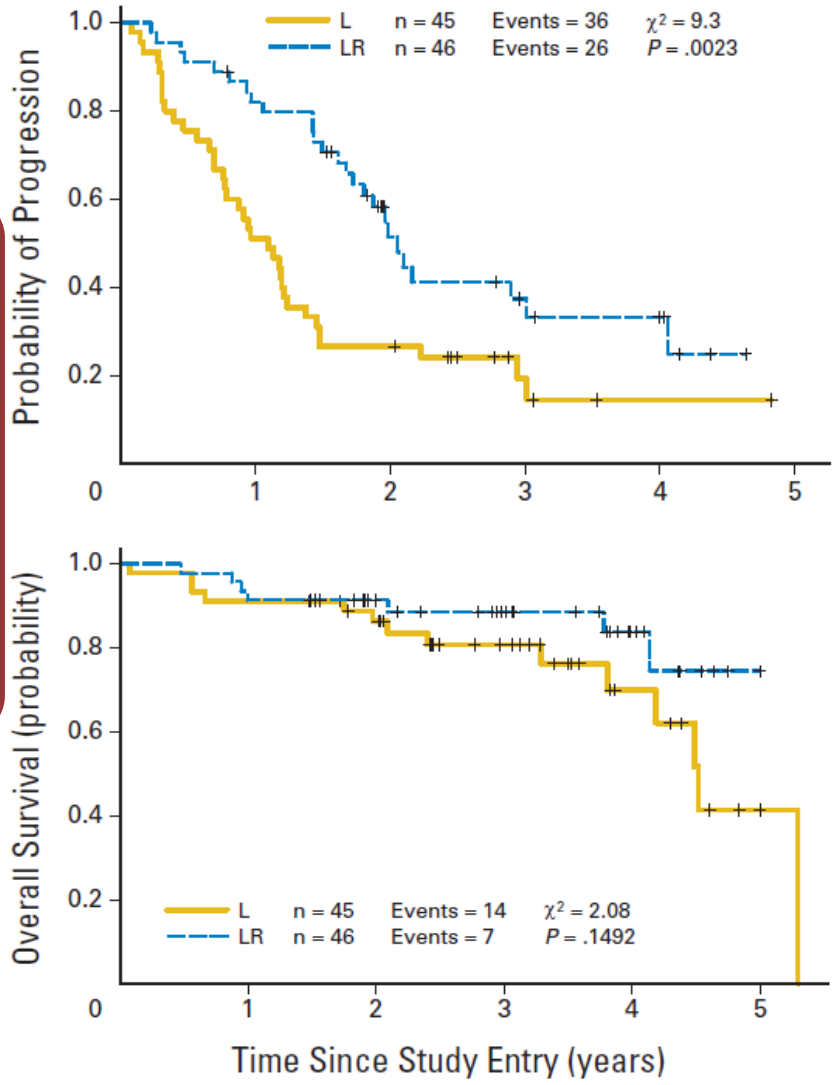
*Tuscano et al BJH 2014*

# CALGB (Alliance) 50401: R-squared

**Lenalidomide: 15 mg per day on days 1 to 21**

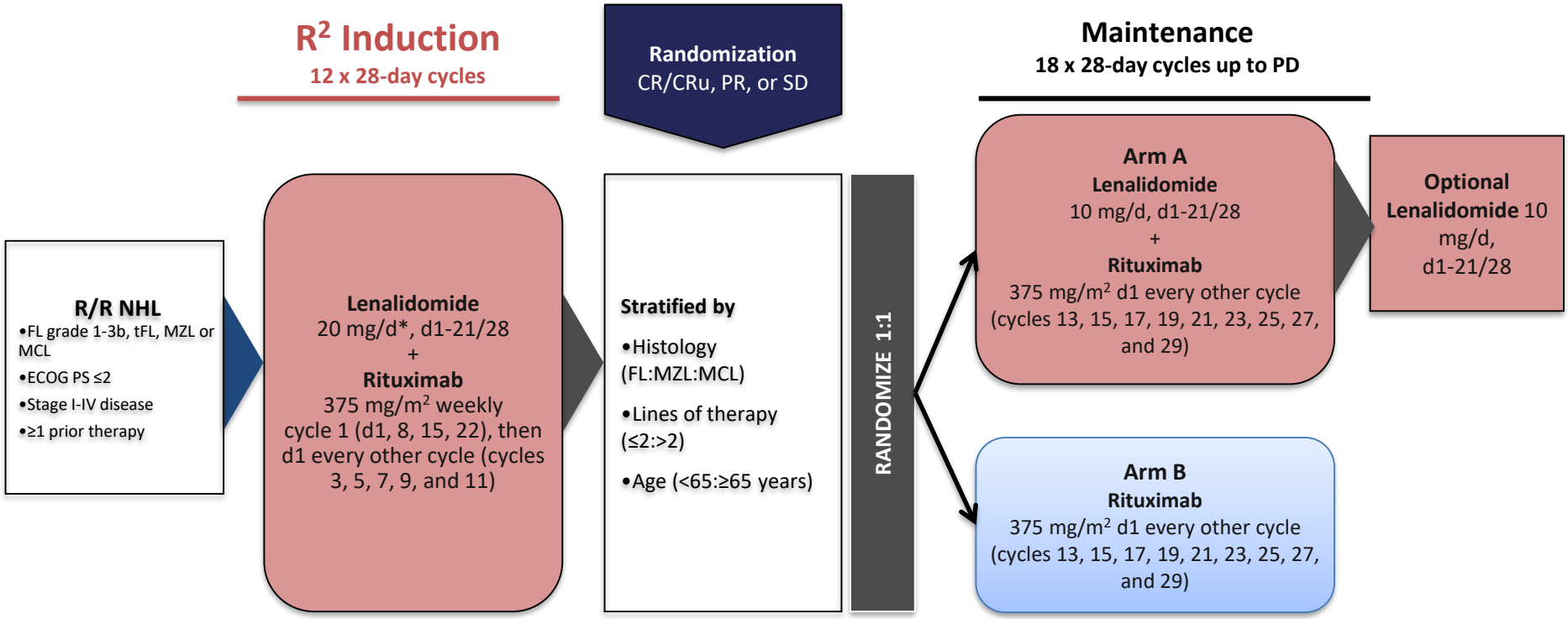
| Outcome | L Arm (n = 45) | LR Arm (n = 4 |
|---|---|---|
| Overall response | | |
| No. of patients | 24 | 35 |
| % | 53.3 | 76.1 |
| 95% CI* | 37.9 to 68.3 | 61.2 to 87.4 |
| Complete response | | |
| No. of patients | 9 | 18 |
| % | 20.0 | 39.1 |
| 95% CI | 9.6 to 34.6 | 25.1 to 54.6 |
| Partial response rate, % | 33.3 | 37.0 |
| Median TTP, years | 1.1 | 2.0 |
| 2-Year TTP, % | 27 | 52 |

| | |
|---|---|
| Neutropenia | 16% v 20% |
| Fatigue | 9% v 13% |
| Rash | 4% v 4% |
| Thrombosis | 16% v 4% |




*Leonard et al JCO 2015*

# Phase III randomized, open-label, multicenter study of $R^2$ induction therapy followed by $R^2$ maintenance vs. rituximab (R) maintenance in patients with R/R NHL, including MZL - NHL-008 study (MAGNIFY)




**Primary endpoint:** PFS (maintenance; 2-sided test a=0.05 and HR=0.67)†
**Secondary endpoints:** OS, IOR, ORR, CR, DOR, DOCR, TTNLT, TTHT, safety†
**Exploratory:** subgroup analysis of efficacy and safety by histology and QOL

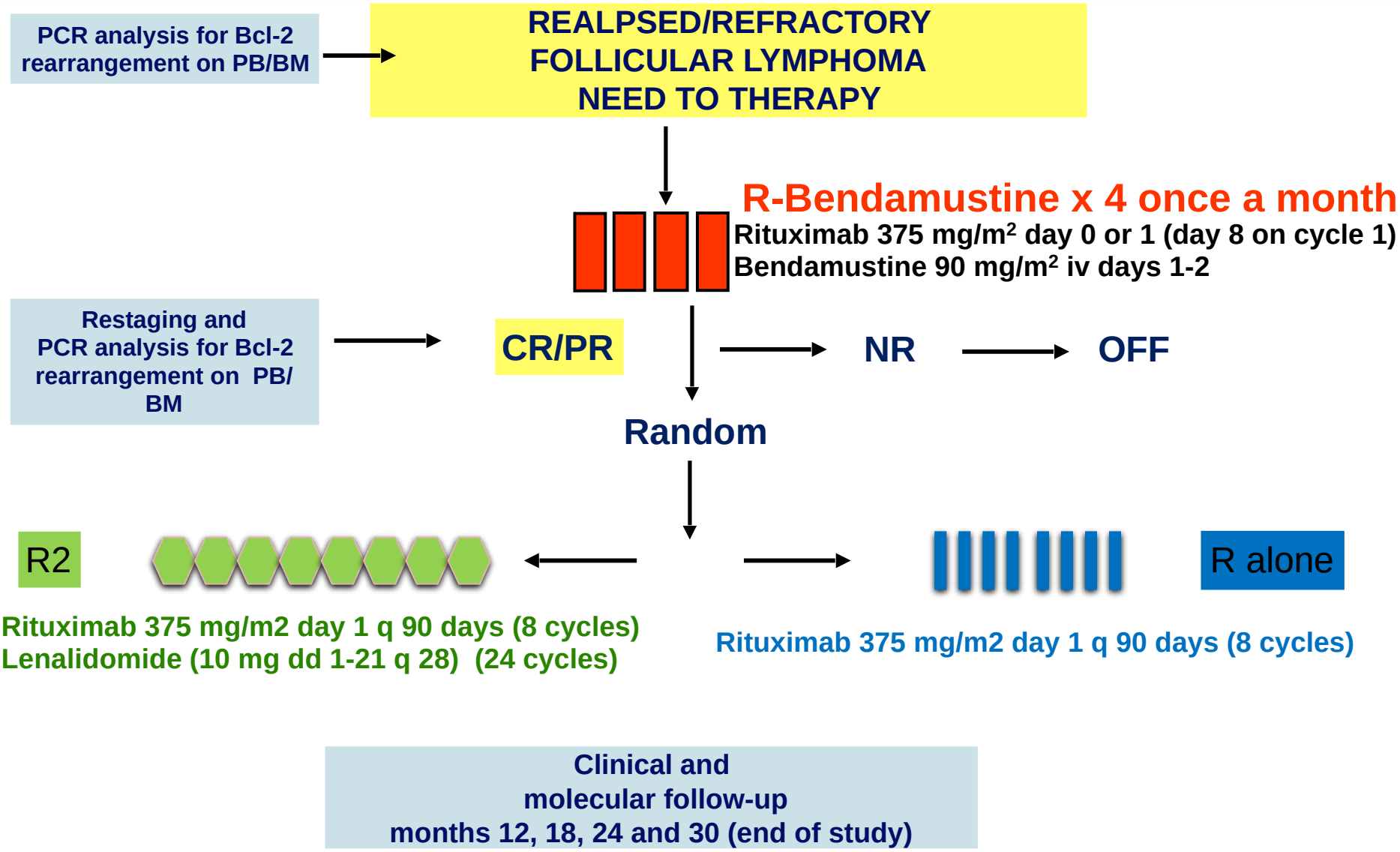
*Coleman et al ICML 2017*

# MAGNIFY FL Population: Efficacy

| Outcome | All FL (n = 160) | DR (n = 50) | ER (n = 52) |
|---|---|---|---|
| 1-yr PFS, % | 70 | 65 | 49 |
| Best response (efficacy evaluable pts), n (%)<br>▪ ORR<br>• CR/CRu<br>• PR<br>▪ SD<br>▪ PD | (n = 128)<br>85 (66)<br>49 (38)<br>36 (28)<br>31 (24)<br>12 (9) | (n = 42)<br>19 (45)<br>9 (21)<br>10 (24)<br>15 (36)<br>8 (19) | (n = 43)<br>20 (47)<br>9 (21)<br>11 (26)<br>17 (40)<br>6 (14) |
| Median follow-up, mos | 10.2 | 9.0 | 12.1 |
| Median time to response, mos | 2.8 | 2.8 | 2.7 |
| Median treatment duration, mos | 6.0 | 5.6 | 6.2 |
| Median duration of response, mos | NR | NR | NR |

- 1-yr PFS in ER subgroup similar for pts who did (n = 39) vs did not (n = 13) receive first-line rituximab-based therapy (52% vs 44%, respectively)

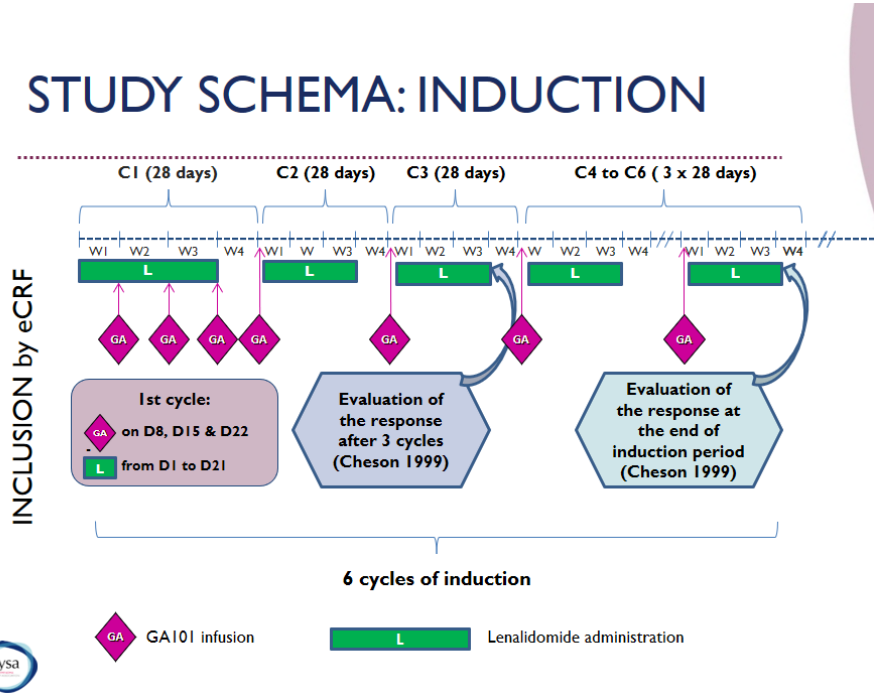
# RENOIR trial FIL

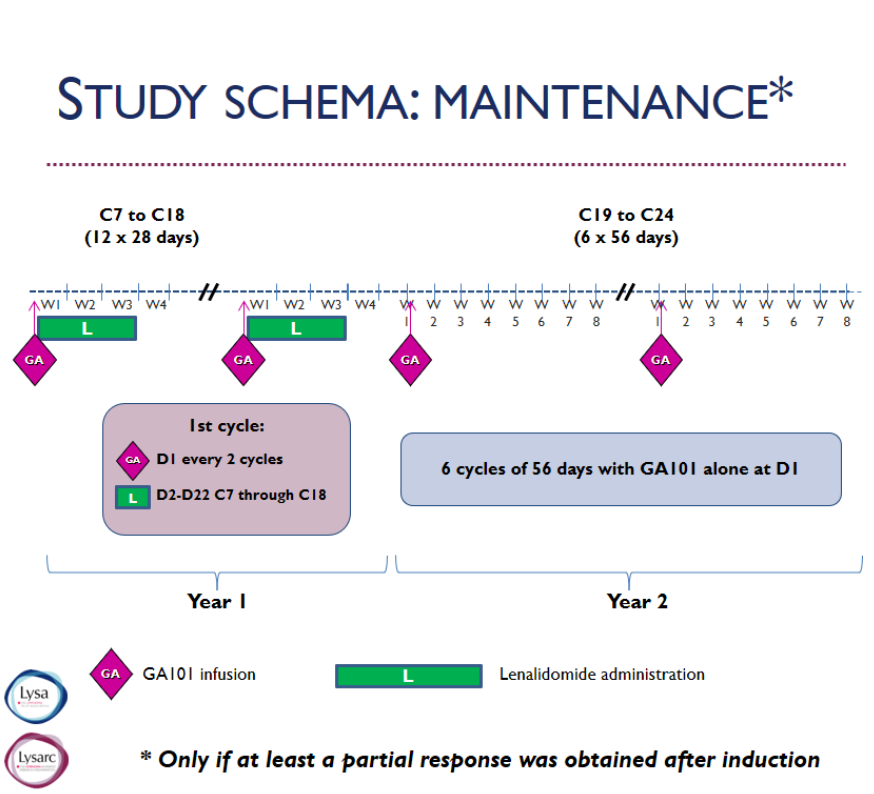


# Obinotuzumab + lenalidomide

# A Phase II LYSA Study of Obinutuzumab Combined with Lenalidomide (GALEN) for Relapsed or Refractory Follicular B-Cell Lymphoma

*Morschhauser et al ICML 2017*




**GA-101: 1000 mg; Lena: 20 mg (ph I)**

# Primary endpoint

- ORR at end of induction by IWG criteria (Cheson 1999)
- Hypothesis: ORR increase from 50% to 70%

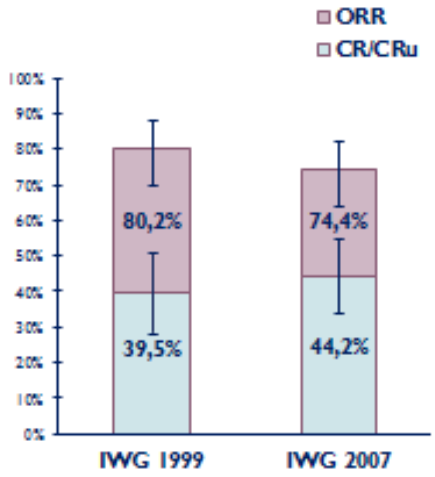
## Patients characteristics

| | All pts (N=86) |
|---|---|
| Median age (min-max) | 64 (39-87) |
| Sex (M/F) | 62.8% / 37.2% |
| Histological grade at inclusion (WHO)<br>Gr 1-2<br>Gr 3a | <br>73.2%<br>15.5% |
| Performance status 0/1/2 | 72.1% / 24.4% / 3.5% |
| Ann Arbor stage I-II/III-IV | 14 (16.3%) / 72 (83.7%) |
| B-symptoms | 14 (16.3%) |
| Bulk (≥ 5cm/≥ 7cm) | 30 (34.9%) / 11(12.8%) |
| Increased LDH | 26 (31.0%) |
| Time between biopsy of initial diagnosis and inclusion (mo) | 73.7(12-254) |
| Median number of prior therapies (min-max) | 2 (1-7) |
| Progression of disease within 24 mo of 1st line start (POD24) | 24 (27.9%) |
| Refractory to R-containing and/or last treatment | 23 (26.7%) |

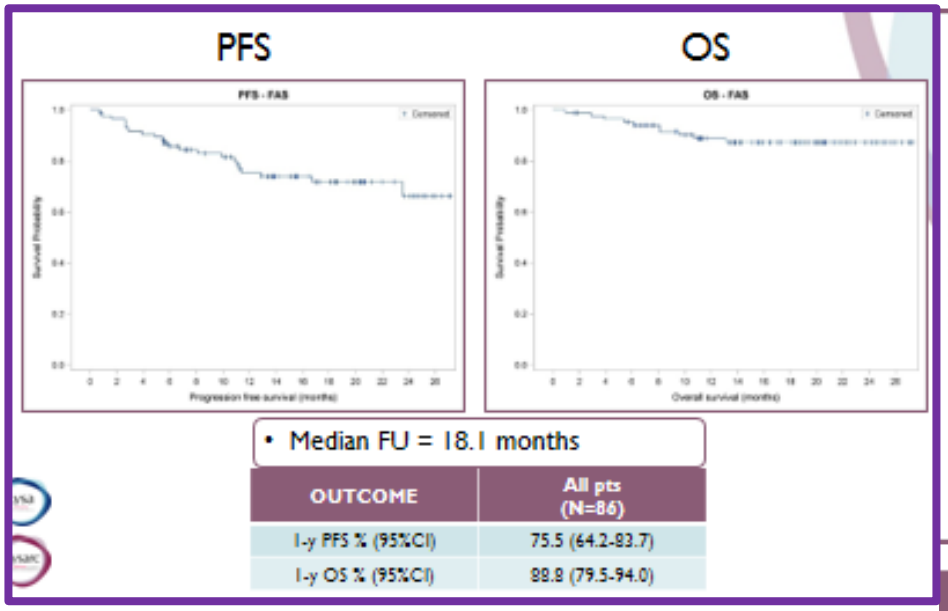
## Safety (AEs grade ≥ 3)

- Neutropenia 28.4%
- Thrombocytopenia 11.4%
- Infections: 6.8%

## Response

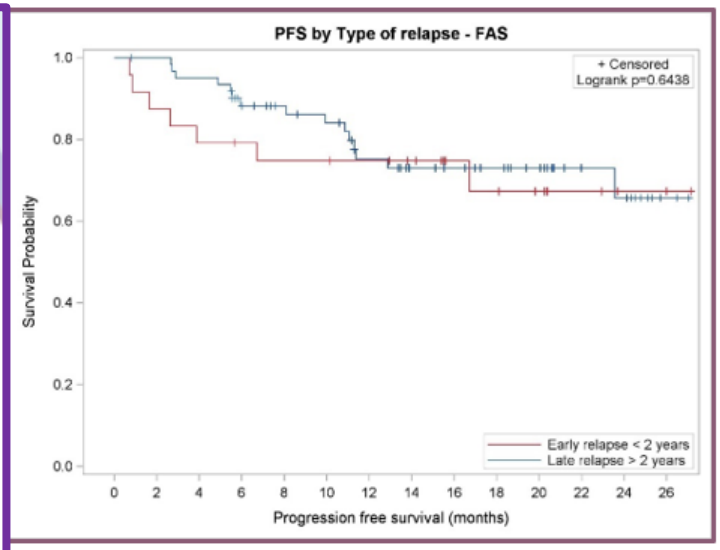


# GALEN: OUTCOME




| OUTCOME | All pts (N=86) |
|---|---|
| 1-y PFS % (95%CI) | 75.5 (64.2-83.7) |
| 1-y OS % (95%CI) | 88.8 (79.5-94.0) |

PFS




| | POD24 (N=24) | POD>24m (N=62) | All pts (N=86) |
|---|---|---|---|
| 1-y PFS % (95%CI) | 74.8 52.2-87.8 | 75.3 60.9-85.0 | 75.5 64.2-83.7 |

**GALEN:**

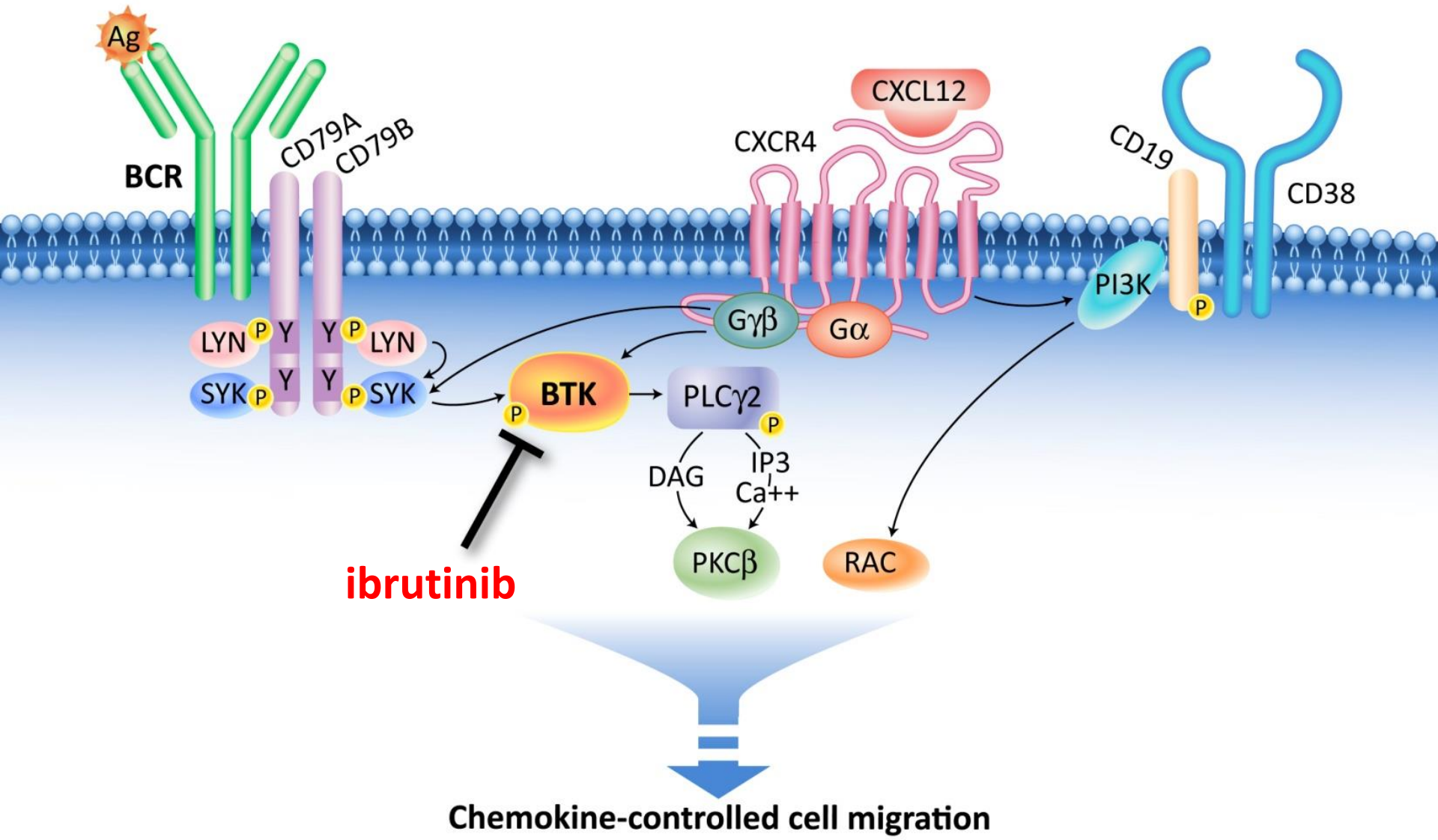
seems superior to R2 especially in patients with POD24 based on historical comparison with MAGNIFY

appears safe with no unexpected toxicity

*Morschhauser F et al, abs 037*

# Ibrutinib

# Btk signaling pathways



# Phase II Consortium: Ibrutinib Monotherapy in Relapsed/Refractory FL

- **Key eligibility criteria:**
  - Grade 1, 2, 3a relapsed/refractory FL
  - ≥ 1 prior chemotherapy
  - ECOG PS 0-2
  - No anticoagulation requirements (ie, warfarin, vitamin K)
  - No previous ASCT


*Bartlett et al. Blood 2018*

# BTK inhibition in FL

- 40 patients with relapsed or refractory FL that had progressed during or after ≥1 prior chemotherapy regimens
- Median age 64 years,
- **Median 3 prior regimens**
- **45% rituximab refractory**
- Patients received the BTK inhibitor ibrutinib 560 mg daily until progression or unacceptable toxicity

*Bartlett et al. Blood 2018*

# Phase II Consortium: Ibrutinib Monotherapy in R/R FL

- Single-agent ibrutinib associated with antitumor responses in relapsed/refractory FL
  - ORR: 37.5 %
  - CR: 12.5 %
  - Median PFS 14 mo

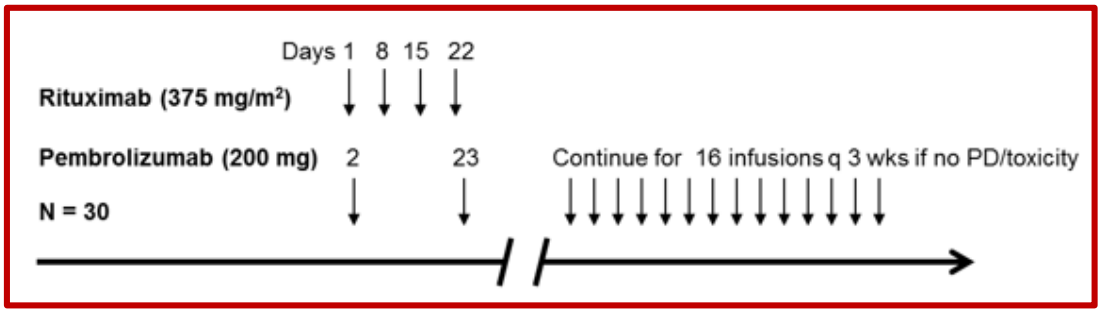
*Bartlett et al. Blood 2018*

# Pembrolizumab

# High Response Rates with Pembrolizumab in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma: Interim Results of an Open-label, Phase II Study

**Background:**

- Follicular lymphoma tumors are infiltrated with antitumor T cells, however, their function is impaired by immune checkpoints such as PD-1/PD-ligand pathway.
- Blocking PD-1 enhances the function of antitumor T cells in FL.
- Blocking PD-1 on NK cells has been shown to enhance the ADCC effect of NK cells.
- Therefore, the combination of pembrolizumab, an anti-PD-1 antibody, and rituximab, an anti-CD20 antibody that induces tumor cell killing by ADCC, is likely to be synergistic through activation of both the innate and adaptive immune systems




**Primary Objective**

- To determine the ORR in subjects with relapsed FL treated with rituximab plus pembrolizumab
  - The two-drug combination was expected to improve ORR to 60% as compared with historical controls of ORR of 40% with rituximab retreatment

*Nastoupil et al ICML 2018*

| Characteristic | | N (% or Range) |
|---|---|---|
| **Age** | Median | 64 (43-84) yrs |
| **Sex** | Male | 17 (57%) |
| | Female | 13 (43%) |
| **ECOG PS** | 0 | 22 (73%) |
| | 1 | 8 (27%) |
| **FLIPI** | Low | 8 (27%) |
| | Intermediate | 16 (53%) |
| | High | 6 (20%) |
| **Stage** | II | 4 (13%) |
| | III/IV | 8/18 (27%/60%) |
| **GELF** | High | 15 (50%) |
| **Prior Therapy** | Median | 2 (1-4) |
| | Prior chemo | 22 (73%) |
| **PFS from last therapy** | Median | 28 (3-162) months |
| | PFS < 2 yrs, last line | 13 (43%) |
| | PFS < 1 yr, last line | 5 (17%) |

4 subjects discontinued drug due to immune related adverse events (IR-AE)

- Grade 2 diarrhea, N=2
- Grade 2 rash, N=1
- Grade 2 pneumonitis, N=1

# Efficacy

- 20 evaluable for response
- **ORR was 65%**

  (CR N=10/PR N=3)
- **CR rate was 50%**
- 3 patients with stable disease and 4 with progressive disease as best response


| AE (N=30) | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) |
|---|---|---|---|
| Fatigue | 13 (43) | 3 (10) | |
| Eye pain/blurred vision/watery eye | 12 (40) | 1 (3) | |
| N/V | 6 (20) | 3 (10) | 2 (7) |
| Diarrhea | 6 (20) | 3 (10) | |
| Dyspnea | 3 (10) | 1 (3) | |
| Rash | 3 (10) | 4 (13) | |
| Cough | 2 (7) | 2 (7) | |
| Lymphopenia | 2 (7) | 3 (10) | 1 (3) |

# Tazemetostat

# Interim report from a Phase 2 multicenter study of Tazemetostat, an EZH2 inhibitor: clinical activity and favorable safety in patients with relapsed or refractory B-cell Non-Hodgkin Lymphoma

- **EZH2** is an epigenetic regulator of gene expression and plays a critical role in multiple forms of cancer

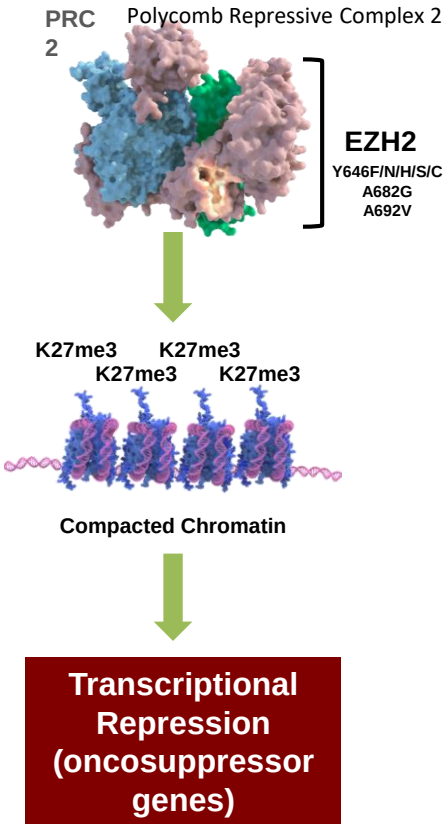
  -Activating mutations of EZH2 can act as an oncogenic driver for cancers, especially in FL and GCB-DLBCL, present in ~20% of patients

- **Tazemetostat**

  - First-in-class, potent and selective oral inhibitor of mutated and wild-type EZH2

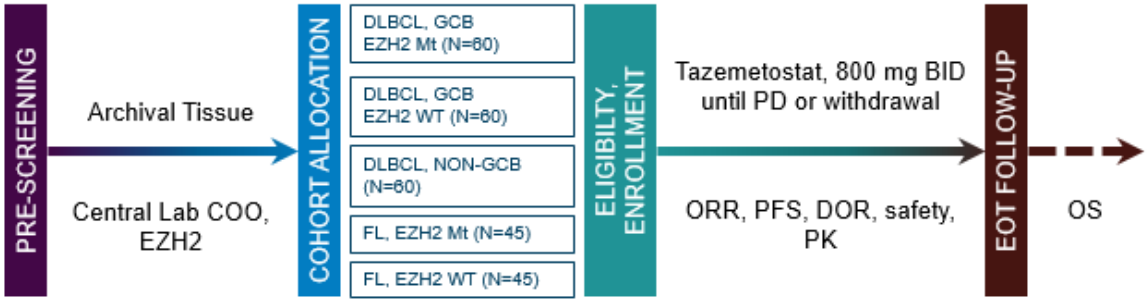
  - Preclinical activity in DLBCL cells lines, with greater activity in EZH2 mutant models

  - Monotherapy activity and favorable safety in phase 1 studies in patients with relapsed or refractory (R/R) NHL, as well as certain genetically defined solid tumors

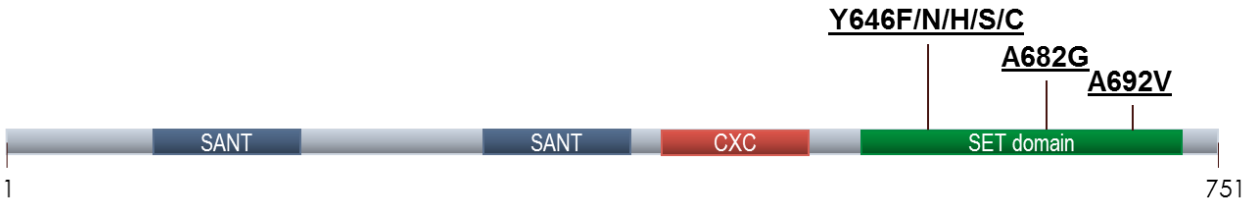



*Morschhauser et al, ICML 2017*

# Tazemetostat for the Treatment of B-cell NHL




- R/R DLBCL and FL
- ≥ 2 prior lines
- Primary endpoint: ORR




**Prospective testing: required for cohort allocation**
**Allele specific PCR test for EZH2 hot spot mutations**

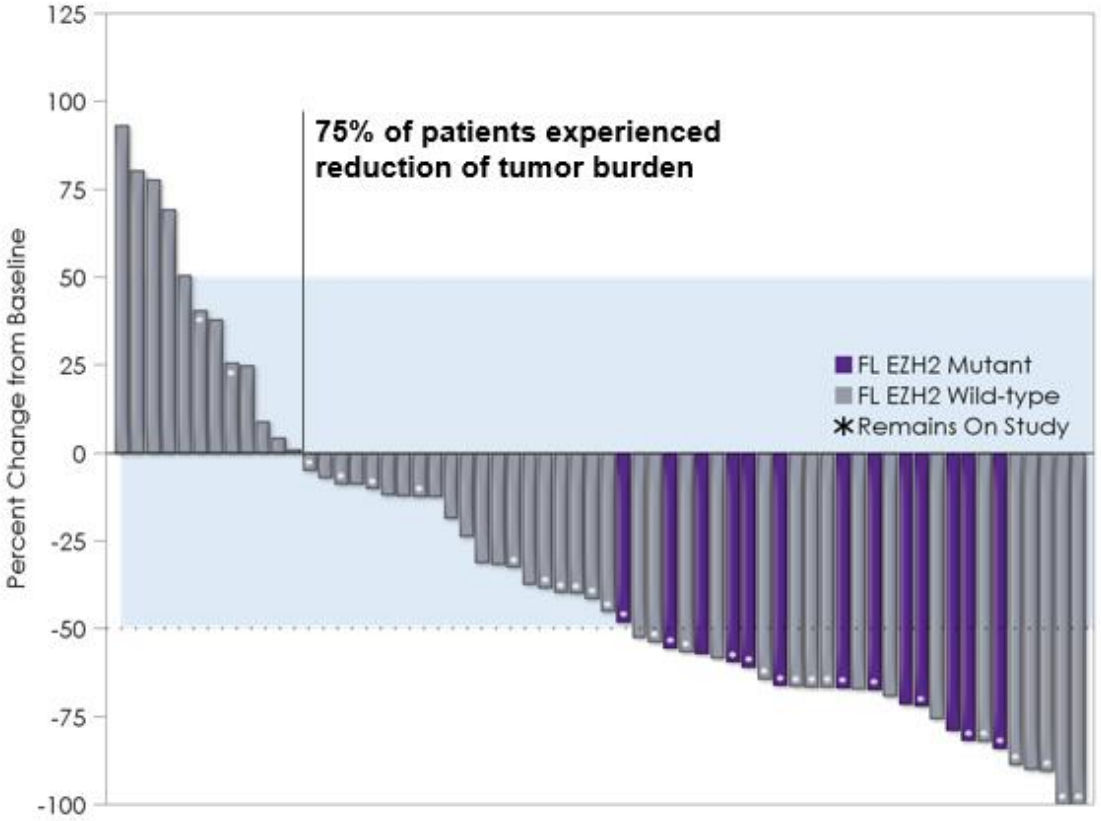
*Morschhauser et al, ICML 2017*

# Tazemetostat for the Treatment of B-cell NHL

| Characteristic | | Follicular Lymphoma | | DLBCL | |
|---|---|---|---|---|---|
| EZH2 Status | | Mutant | Wild-type | Mutant | Wild-type |
| n | | 13 | 54 | 17 | 120 |
| Age, median | years | 62 | 61 | 61 | 69 |
| Males | | 46% | 63% | 53% | 58% |
| ECOG PS, median (range) | | 0 (0 - 2) | 0 (0 - 2) | 1 (0 - 2) | 1 (0 - 2) |
| Prior lines of therapy, n (%) | 1 | 1 ( 8%) | 0 | 0 | 3 ( 3%) |
| | 2 | 2 (15%) | 11 (20%) | 4 (24%) | 40 (33%) |
| | 3 | 3 (23%) | 9 (17%) | 7 (41%) | 28 (23%) |
| | 4 | 1 ( 8%) | 14 (26%) | 3 (18%) | 18 (15%) |
| | ≥ 5 | 6 (46%) | 20 (37%) | 3 (18%) | 31 (26%) |
| | median | 4 | 4 | 3 | 3 |
| Refractory to last regimen, n (%) | | 7 (54%) | 26 (48%) | 14 (82%) | 75 (63%) |
| Prior HSCT | | 23% | 41% | 41% | 24% |
| Median time from initial diagnosis | years | 7.4 | 4.9 | 1.0 | 2.0 |
| Median time from last prior therapy | weeks | 13.0 | 41.3 | 8.6 | 11.6 |

*Morschhauser et al, ICML 2017*

# Tazemetostat: safety and efficacy




| | FL EZH2 MT (n=13) | FL EZH2 WT (n=54) | DLBCL EZH2 MT (n=17) | DLBCL EZH2 WT (n=119) |
|---|---|---|---|---|
| CR + PR) | 12 (92%) | 14 (26%) | 5 (29%) | 18 (15%) |
| | 1 (8%) | 3 (6%) | 0 | 10 (8%) |
| | 11 (85%) | 11 (20%) | 5 (29%) | 8 (7%) |

**Higher RR in mutated EZH2 NHL**

*Morschhauser et al, ICML 2017*

# Safety warning

# *Safety warning*

**Phase 2 study of idelalisib and entospletinib: pneumonitis limits combination therapy in relapsed refractory CLL and NHL**

Paul M. Barr,[1] Gene B. Saylors,[2] Stephen E. Spurgeon,[3] Bruce D. Cheson,[4] Daniel R. Greenwald,[5] Susan M. O'Brien,[6] Andre K. D. Liem,[7] Rosemary E. McIntyre,[8] Adarsh Joshi,[9] Esteban Abella-Dominicis,[9] Michael J. Hawkins,[9] Anita Reddy,[9] Julie Di Paolo,[9] Hank Lee,[9] Joyce He,[9] Jing Hu,[9] Lyndah K. Dreiling,[9] and Jonathan W. Friedberg[1]

Lenalidomide, idelalisib, and rituximab are unacceptably toxic in patients with relapsed/refractory indolent lymphoma

Chan Yoon Cheah, Loretta J. Nastoupil, Sattva S. Neelapu, Sheryl G. Forbes, Yasuhiro Oki and Nathan H. Fowler

Blood 2015 125:3357-3359; doi:10.1182/blood-2015-03-633156

Phase I trial of rituximab, lenalidomide, and ibrutinib in previously untreated follicular lymphoma: Alliance A051103

Chaitra S. Ujjani, Sin-Ho Jung, Brandelyn Pitcher, Peter Martin, Steven I. Park, Kristie A. Blum, Sonali M. Smith, Myron Czuczman, Matthew S. Davids, Ellis Levine, Lionel D. Lewis, Scott E. Smith, Nancy L. Bartlett, John P. Leonard and Bruce D. Cheson

Blood 2016 :blood-2016-06-718106; doi:10.1182/blood-2016-06-718106

factors prior to enrollment. Given the increased toxicity and required dose modifications, as well as the apparent lack of additional clinical benefit to the rituximab-lenalidomide doublet, further investigation of the regimen in this setting seems unwarranted. The study was registered with www.ClinicalTrials.gov (NCT01829568).

# Lenalidomide, idelalisib and rituximab

**Lenalidomide** 5 mg (d 8-21 C1, d 1-21 thereafter)

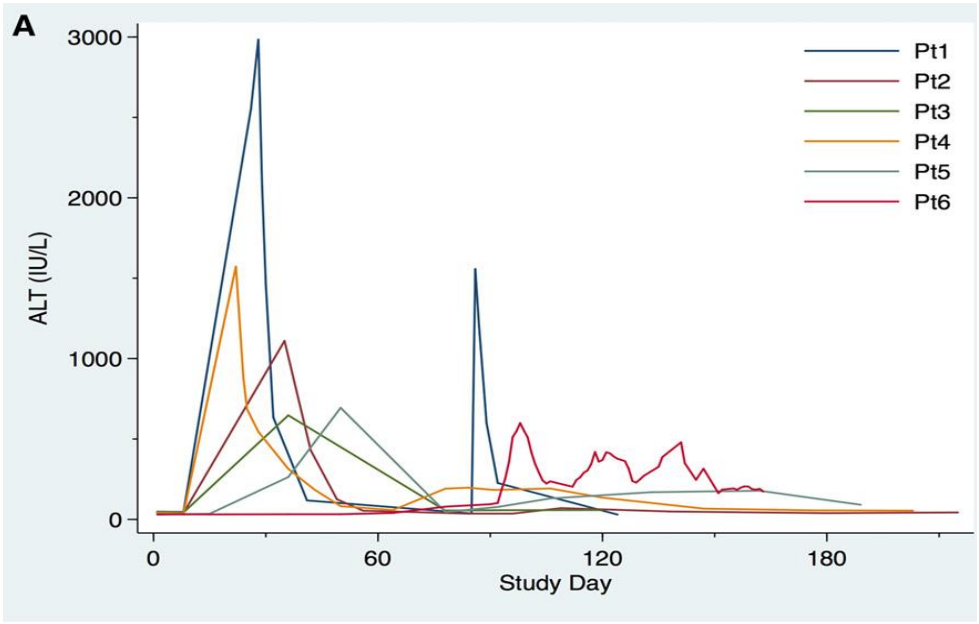
**R** 375 mg/m2 d 1

**Idelalisib** 150 mg BID from d 1 (C1, 35 d; subsequent cycles, 28 d)

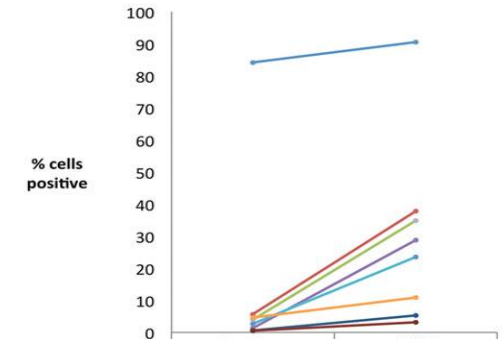
7 pts enrolled in the initial cohort (5 FL, 1 SLL, 1 MZL)

In 6 pts hepatic toxicity (1 death for liver failure)

*Cheah et al. Blood 2015*

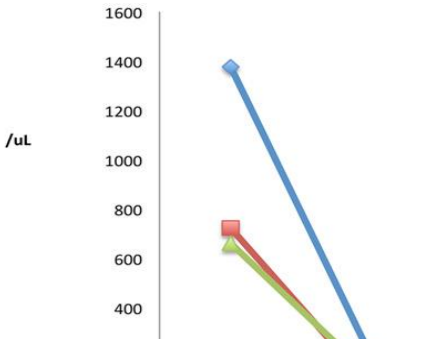



**B** T-cell activation markers pre- and post-treatment




| | baseline | D116 |
|---|---|---|
| CD4+OX40+ | 84.2 | 90.6 |
| CD8+CD69+ | 5.7 | 37.8 |
| CD8+OX40+ | 3.9 | 34.8 |
| CD8+ICOS+ | 1.3 | 28.8 |
| CD8+41BB+ | 2.7 | 23.5 |
| CD4+CD69+ | 4.6 | 10.8 |
| CD4+ICOS+ | 0.6 | 5.3 |
| CD4+41BB+ | 0.5 | 3.2 |

**C** Lymphocyte subsets pre- and post-treatment

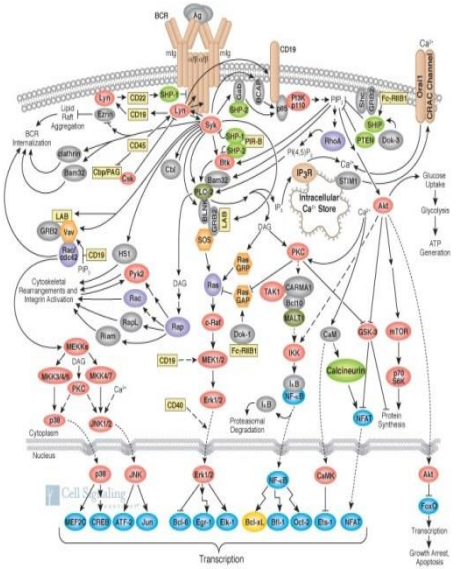



| | baseline | D116 |
|---|---|---|
| CD3+ T-cells | 1376 | 194 |
| CD4+ T-cells | 722 | 76 |
| CD8+ T-cells | 661 | 117 |
| CD56+ NK cells | 36 | 11 |
| Foxp3+ Tregs | 15 | 21 |

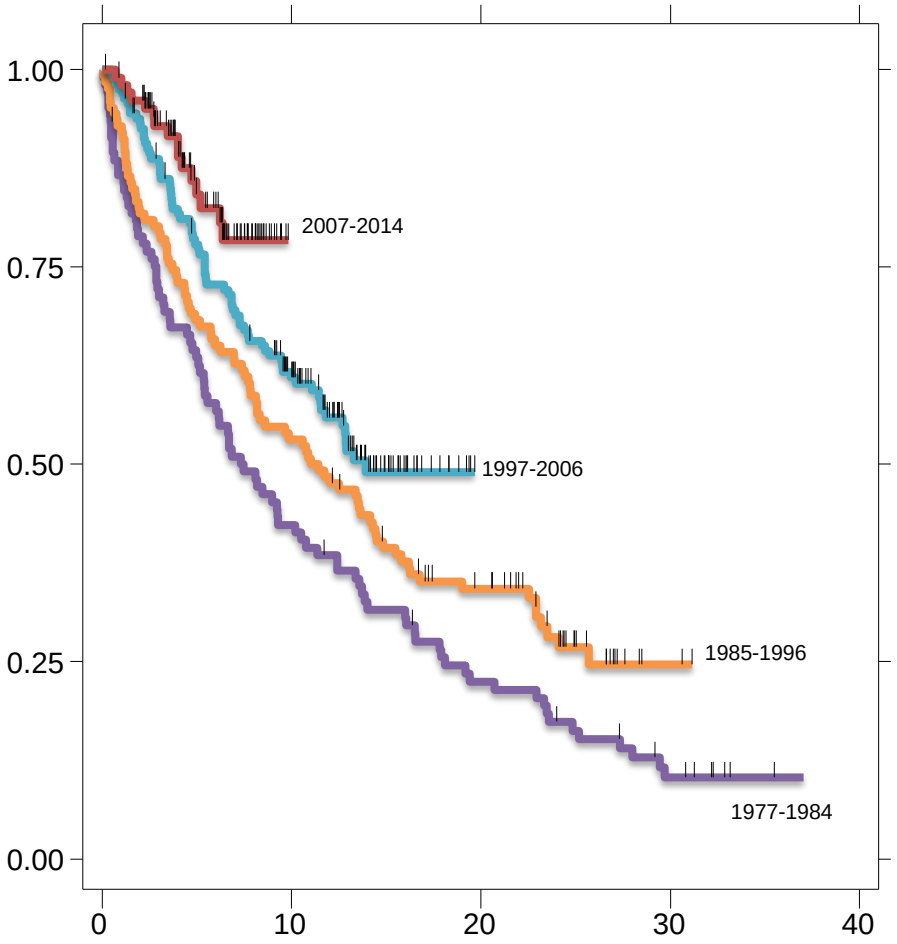
*Cheah et al. Blood 2015*
*Smith et al ASH 2014*

# Transplantation

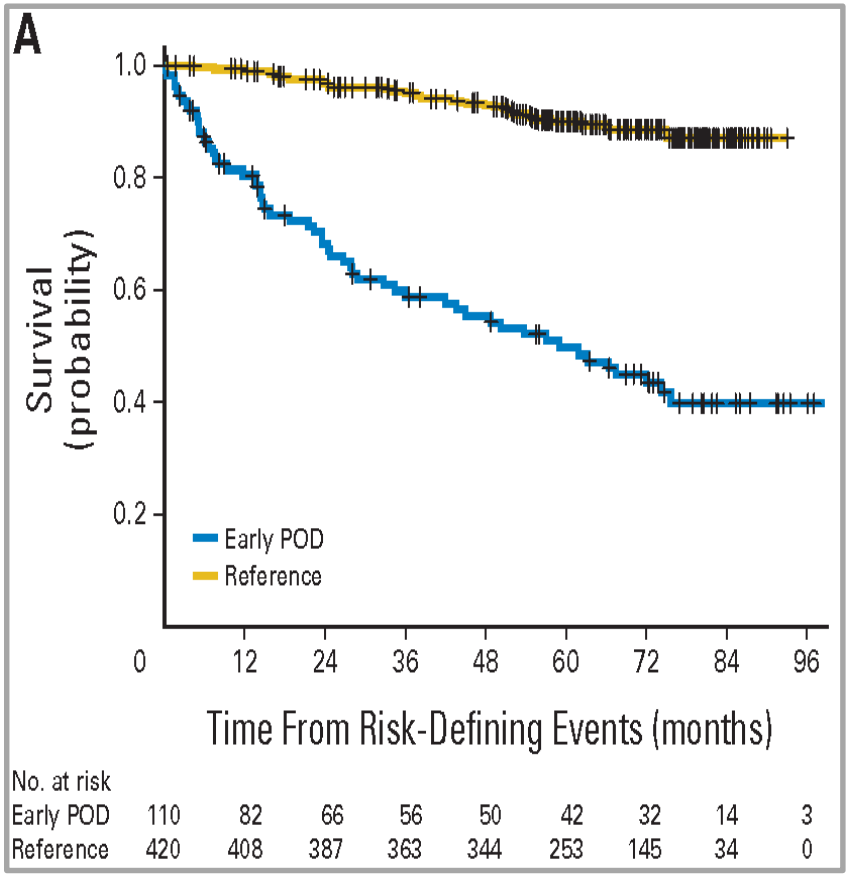
# *Patients want to be cured*



# Setting the scene: the disease



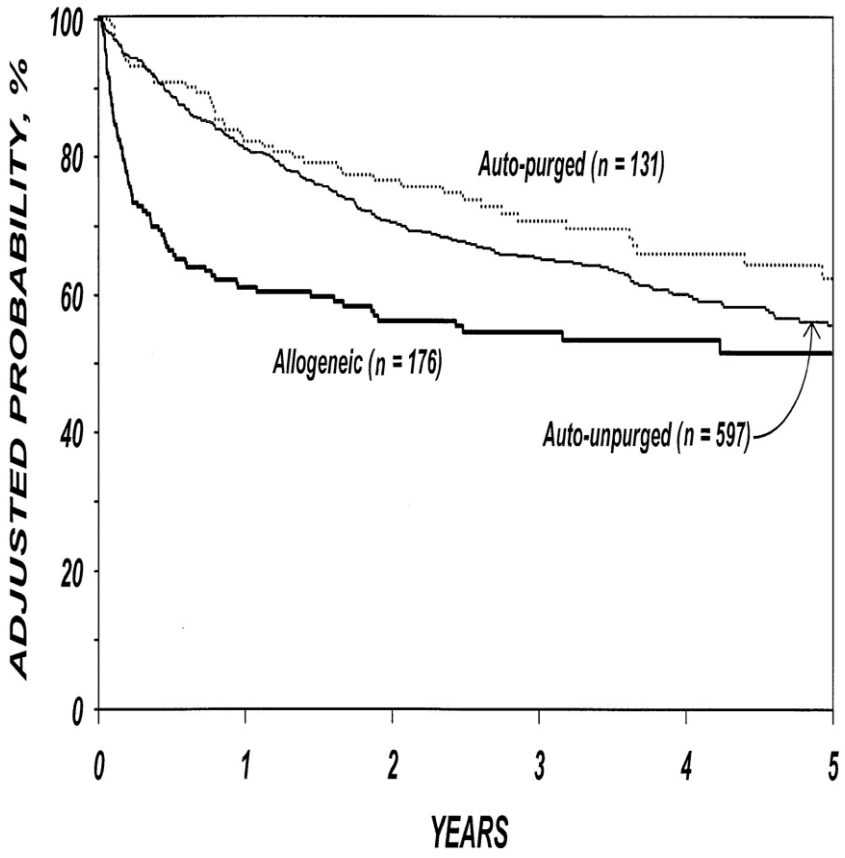

*St Bartholomew's Hospital, 1977-2014*



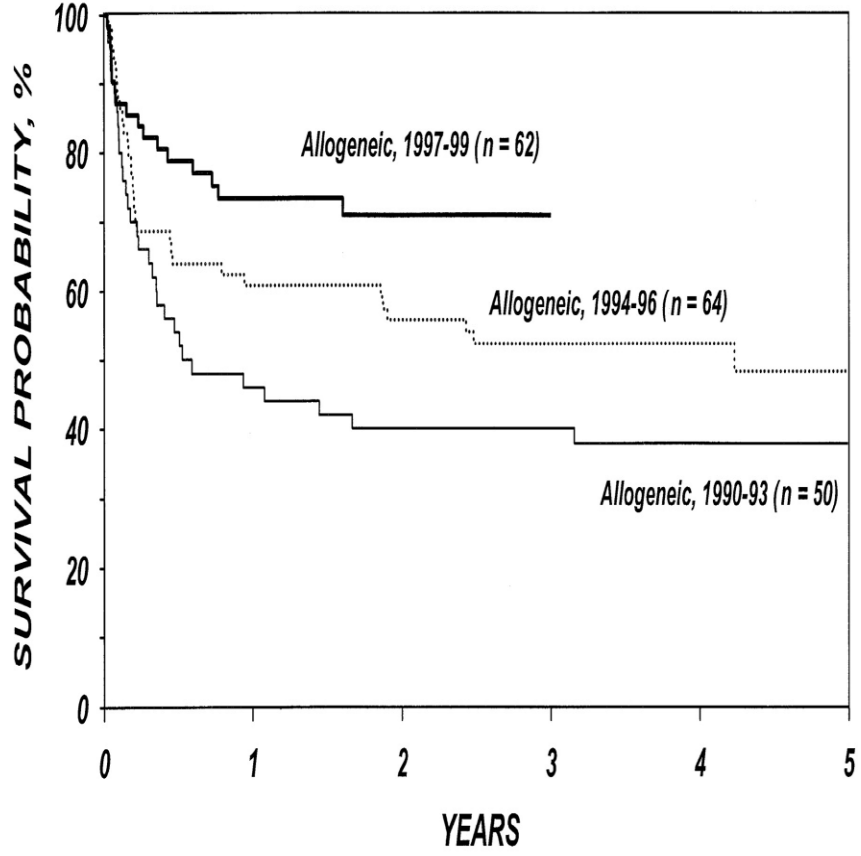

*Casulo C et al, J Clin Oncol 2015*

# Auto vs allo transplant for FL

**OS by type of transplant**




**OS by time of transplant**




**904 case of IBMTR , 20 % transplanted in first year after diagnosis**

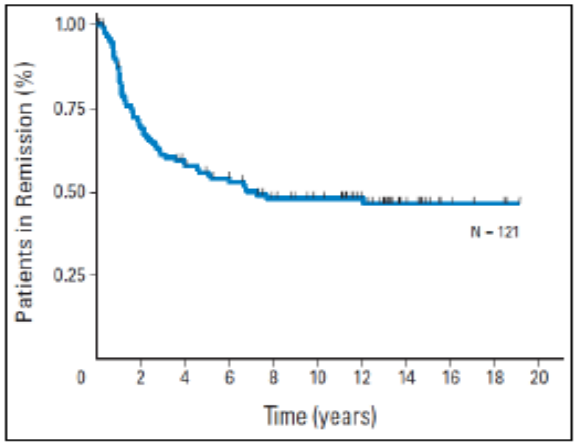
*Van Besien et al, Blood, 2003*

# Long term efficacy

VOLUME 25 · NUMBER 18 · JUNE 20 2007
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Myeloablative Therapy With Autologous Bone Marrow Transplantation for Follicular Lymphoma at the Time of Second or Subsequent Remission: Long-Term Follow-Up

*Ana Z.S. Rohatiner, Lee Nadler, Andrew J. Davies, John Apostolidis, Donna Neuberg, Janet Matthews, John G. Gribben, Peter M. Mauch, T. Andrew Lister, and Arnold S. Freedman*



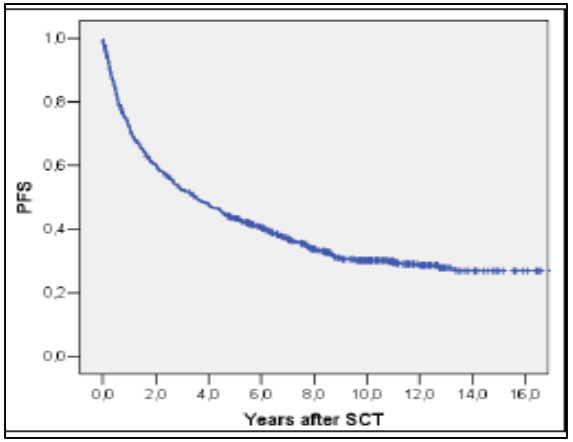

Leukemia (2007) 21, 2324–2331

www.nature.com/leu

ORIGINAL ARTICLE

Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study

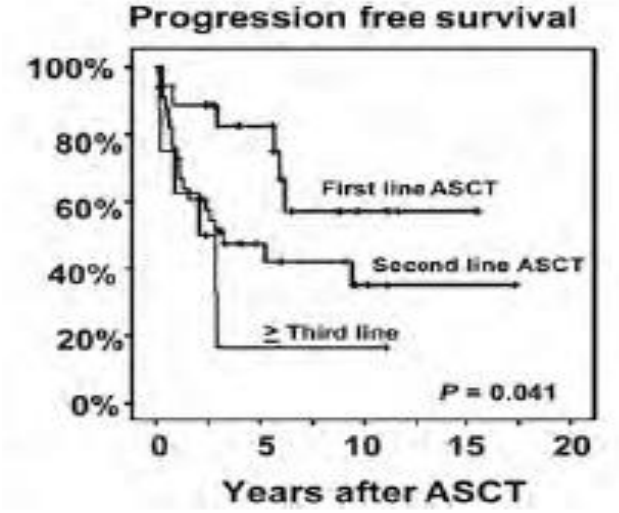
S Montoto[1], C Canals[2], AZS Rohatiner[1], G Taghipour[3], A Sureda[2], N Schmitz[4], C Gisselbrecht[5], L Fouillard[6], N Milpied[7], C Haioun[8], S Slavin[9], E Conde[10], C Fruchart[11], A Ferrant[12], V Leblond[13], H Tilly[14], TA Lister[1] and AH Goldstone[15], for the EBMT Lymphoma Working Party




Long-term clinical and molecular remissions in patients with follicular lymphoma following high-dose therapy and autologous stem cell transplantation

B. Metzner[1*], C. Pott[2], T. H. Müller[3], W. Gebauer[3], J. Casper[1], D. Kraemer[1], B. Rosien[1], S. Schumann-Binarsch[1], R. Thole[1] & C. H. Köhne[1]

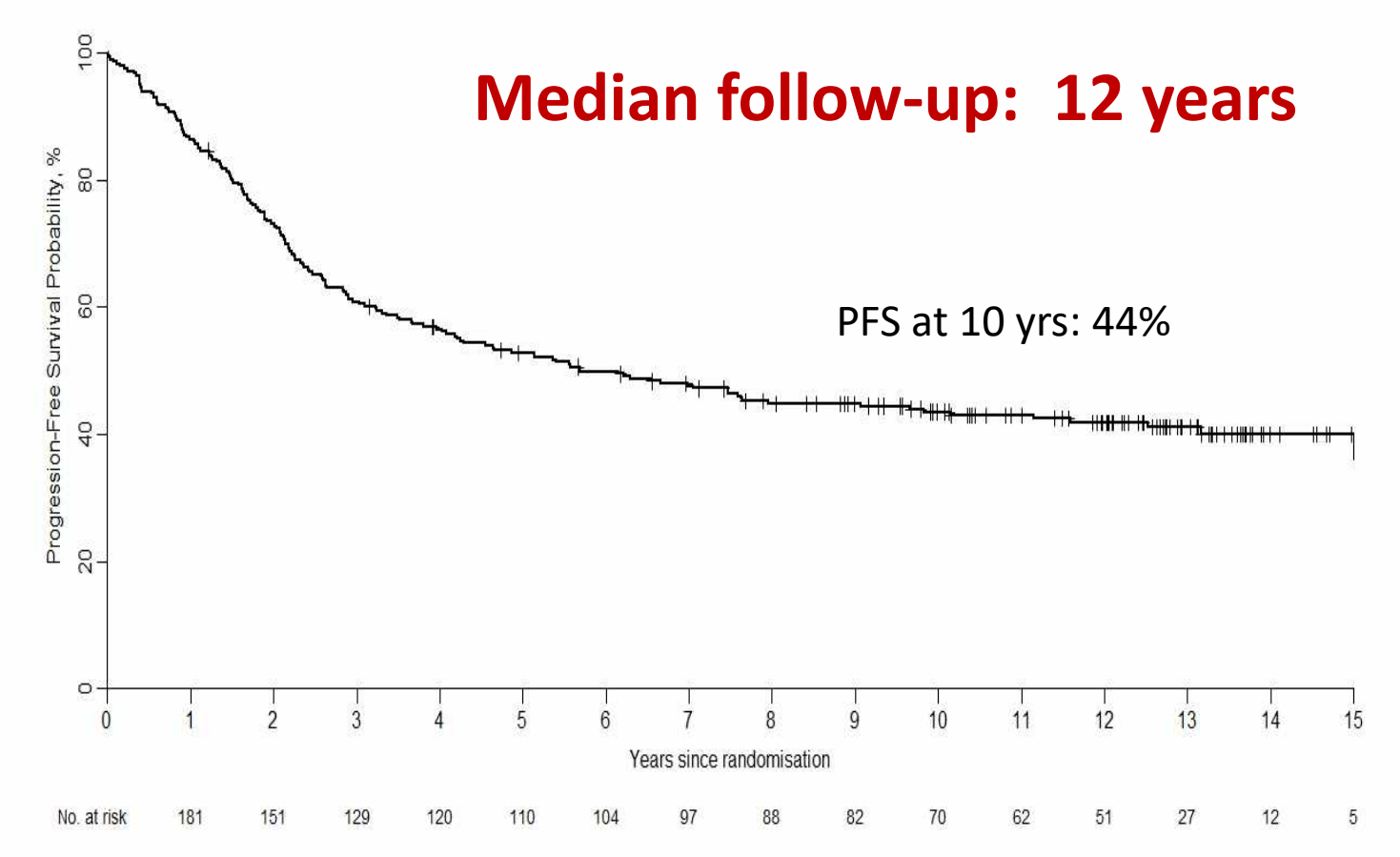
[1]*Department of Oncology and Haematology, Klinikum Oldenburg, University Hospital, Oldenburg;* [2]*Department of Medicine II, University of Schleswig-Holstein, Kiel;* [3]*Blood Transfusion Service German Red Cross, Oldenburg, Germany*




Plateau tra 10-15 anni dopo ASCT

1/3 – 1/4 dei pazienti può considerarsi curata dopo ASCT

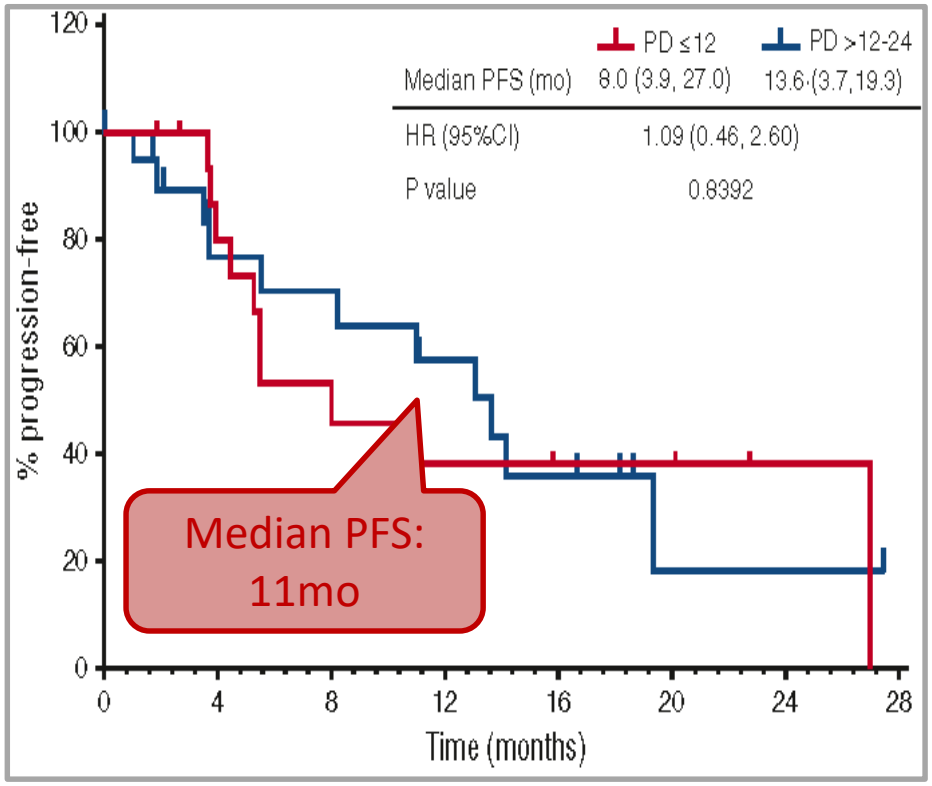
# *FL incurable with ASCT? LYM1*




*Pettengell R et al, ICML 2017*

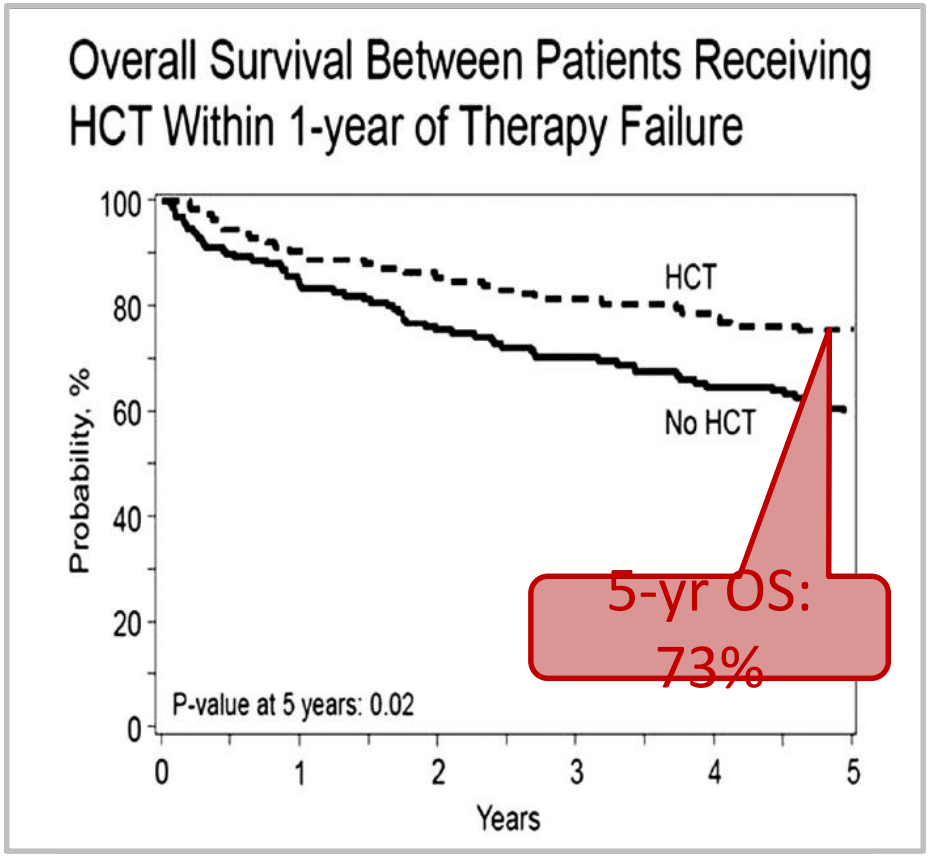
# PFS in high-risk FL

## Idelalisib




*Gopal et al. Blood 2017*

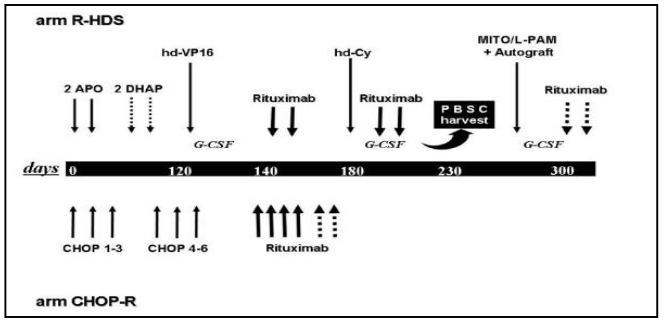
## ASCT

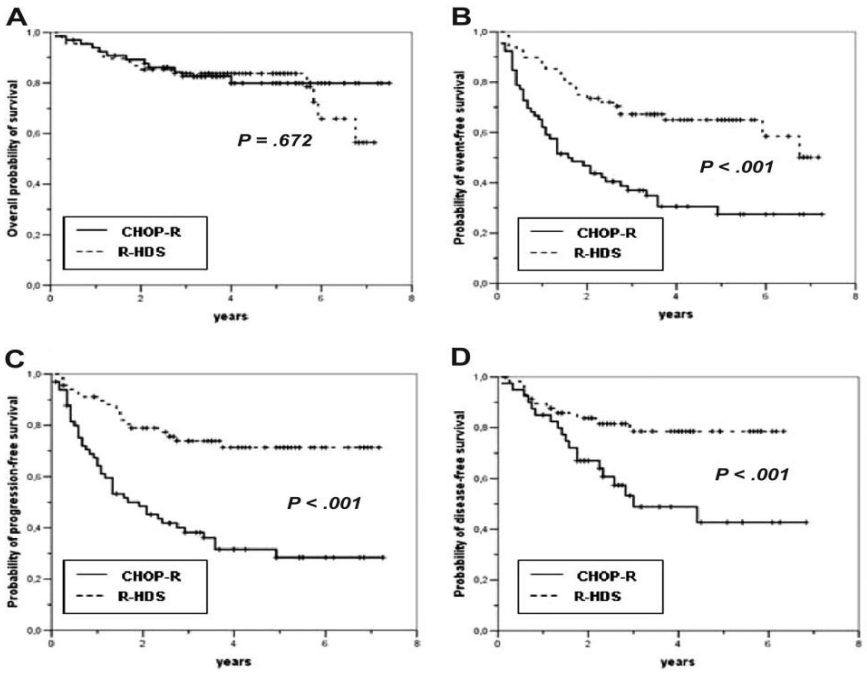


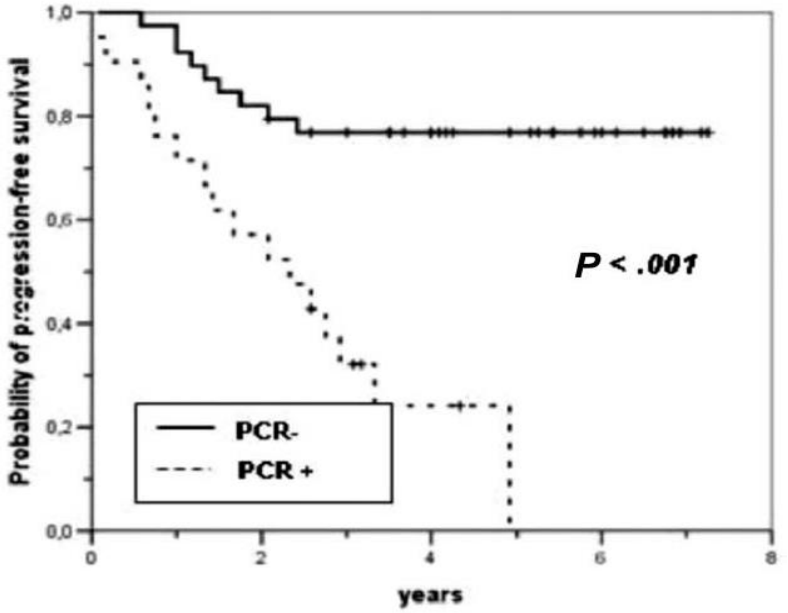

*Casulo C et al. ICML, 2017*

# ASCT in first remission

# GITMO/IIL trial



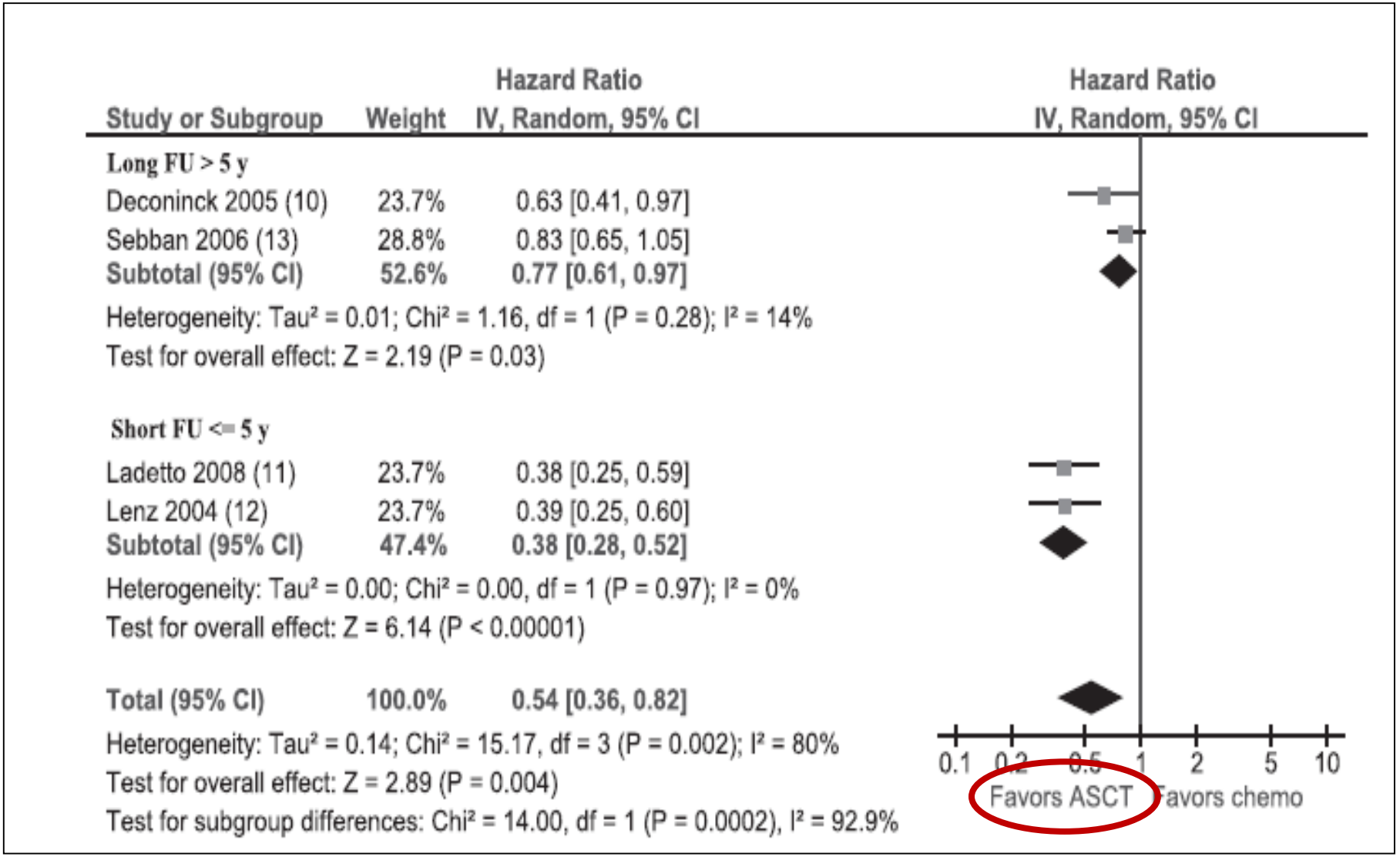




- R-HDS assicura miglior outcome molecolare rispetto a CHOP-R ma non determina un vantaggio in termini di OS
- Le recidive dopo CHOP-R possono ottenere nuovamente la remissione dopo terapia di salvataggio con R-HDS, identificando il subset della malattia recidivata/refrattaria come il più appropriato per la terapia ad alte dosi

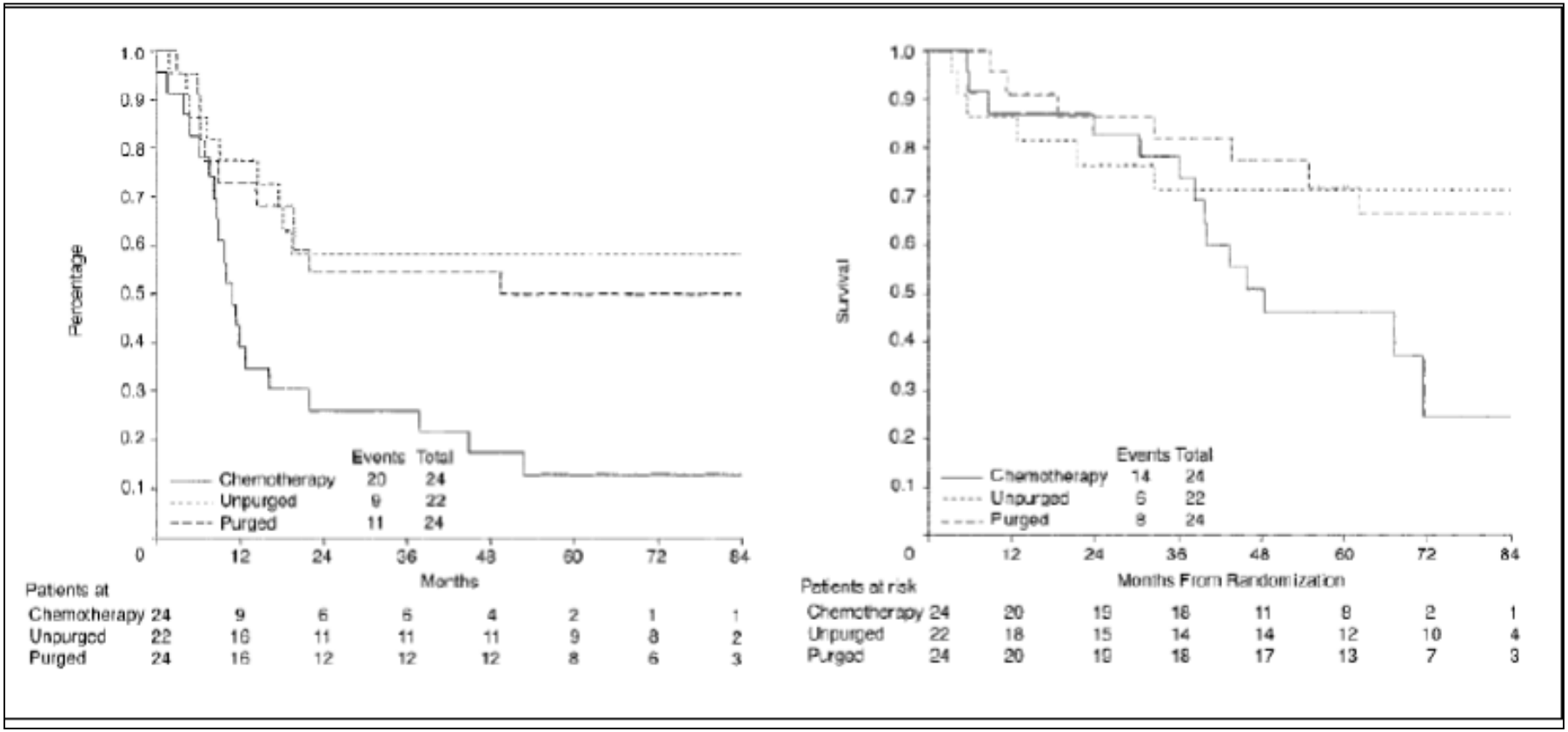
*Ladetto et al Blood 2008*

# Meta-analysis: ASCT in first remission




Al Khabouiri et al. Autologous stem cell transplantation in follicular lymphoma: a systematic review and metanalysis. J Natl Cancer Inst 2012;104:18-28.

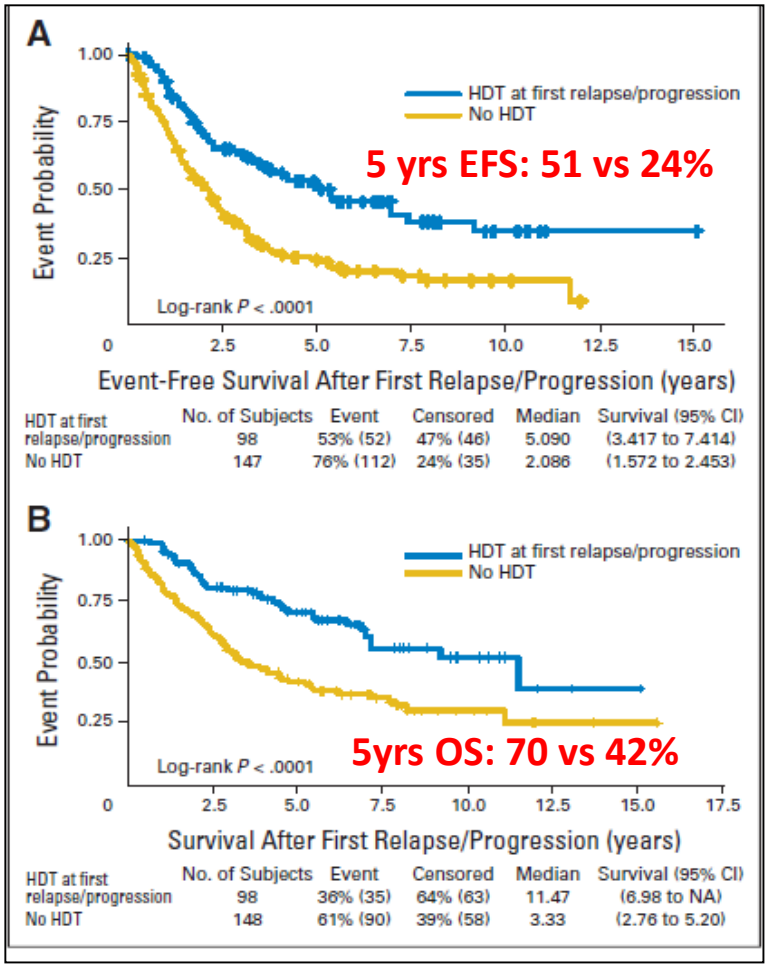
# ASCT in first relapse – CUP trial

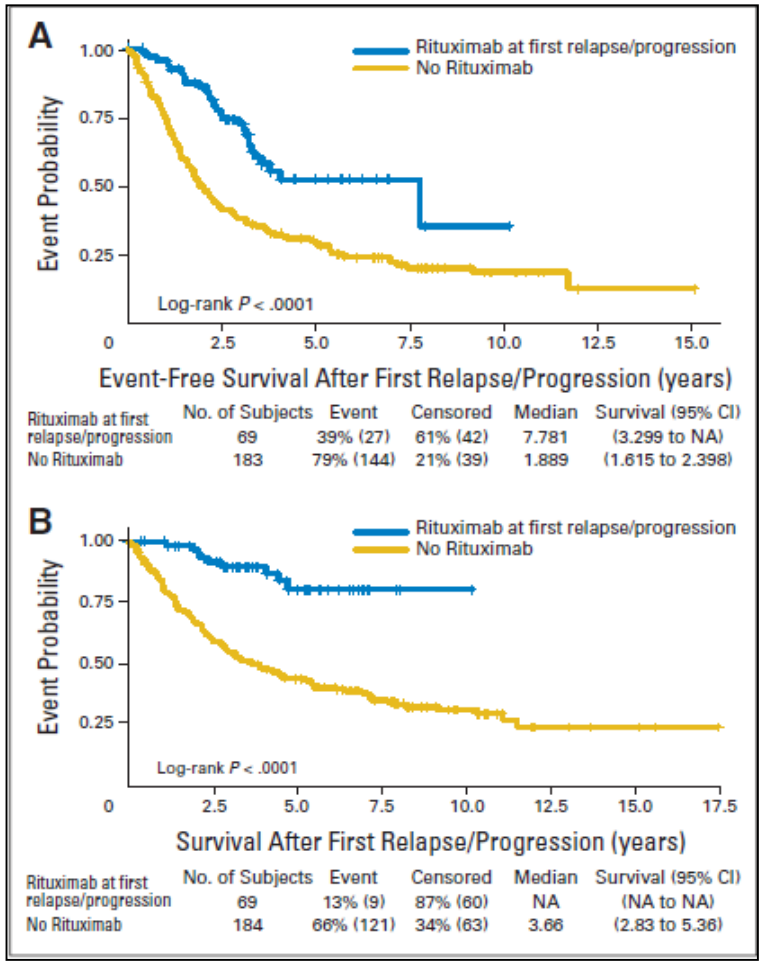



- Studio prospettico randomizzato
- PFS a 2 anni: 55-58 vs 26%
- OS a 4 anni: 71-77% vs 46%
- Limiti: numerosità, era pre rituximab, OS inferiore all'atteso

*Schouten et al JCO 2003*

# R - ASCT in first relapse – GELA trial




- Studio retrospettivo (GELF 86 – GELF 94), 254 pazienti
- HDT sono associate ad un vantaggio in termini di EFS e SAR
- R in terapia di salvataggio + HDT mostrano una SAR maggiore del 90%

*Sebban et al JCO 2008*

# ASCT outcome according to R use GELA/GOELAMS FL2000 study

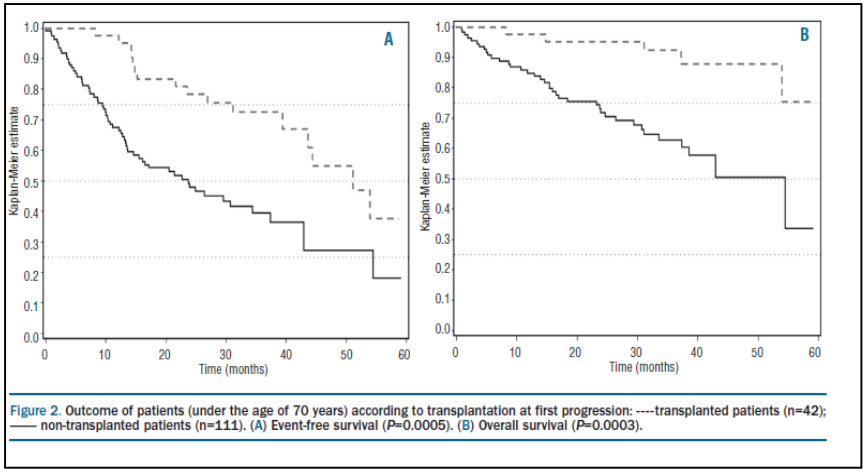



Figure 2. Outcome of patients (under the age of 70 years) according to transplantation at first progression: ----transplanted patients (n=42); —— non-transplanted patients (n=111). (A) Event-free survival (*P*=0.0005). (B) Overall survival (*P*=0.0003).

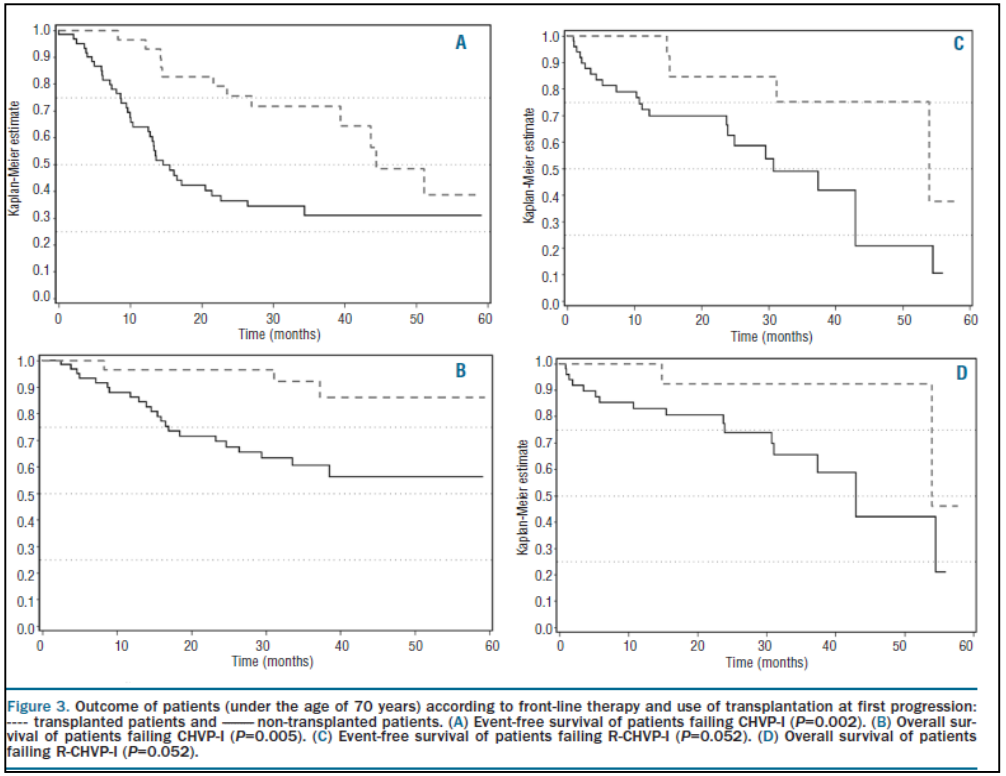


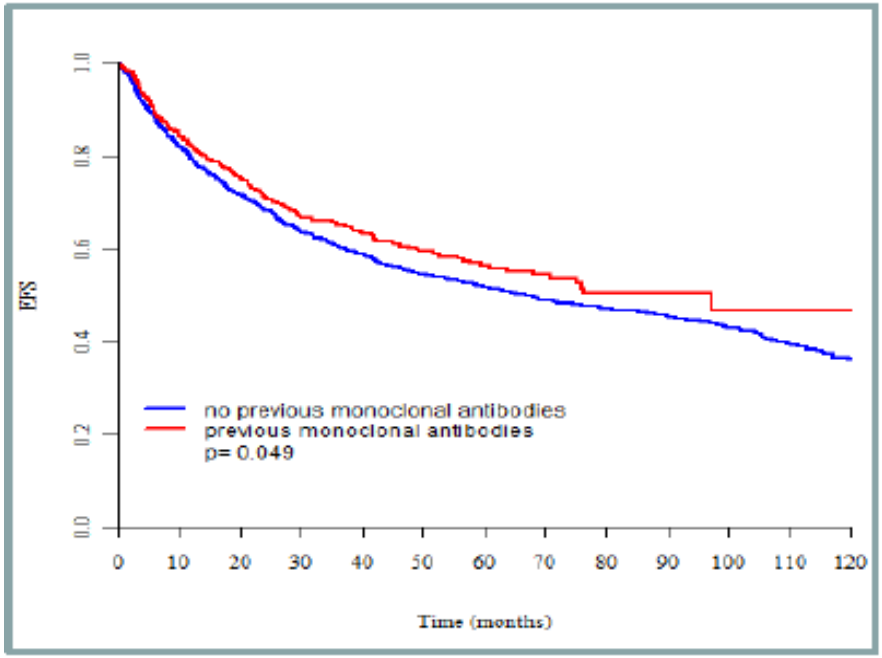

Figure 3. Outcome of patients (under the age of 70 years) according to front-line therapy and use of transplantation at first progression: ---- transplanted patients and —— non-transplanted patients. (A) Event-free survival of patients failing CHVP-I (*P*=0.002). (B) Overall survival of patients failing CHVP-I (*P*=0.005). (C) Event-free survival of patients failing R-CHVP-I (*P*=0.052). (D) Overall survival of patients failing R-CHVP-I (*P*=0.052).

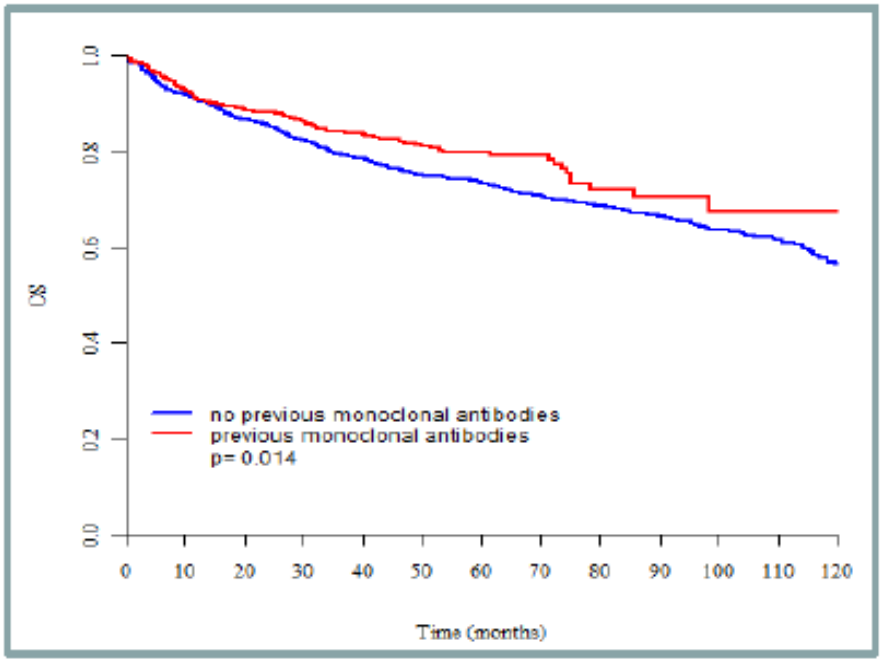
- Studio retrospettivo, 175 pazienti

- Indipendentemente dall'esposizione a R, ASCT conferisce un vantaggio in termini di outcome

*Le Gouill et al Haematologica 2011*

# R pre ASCT

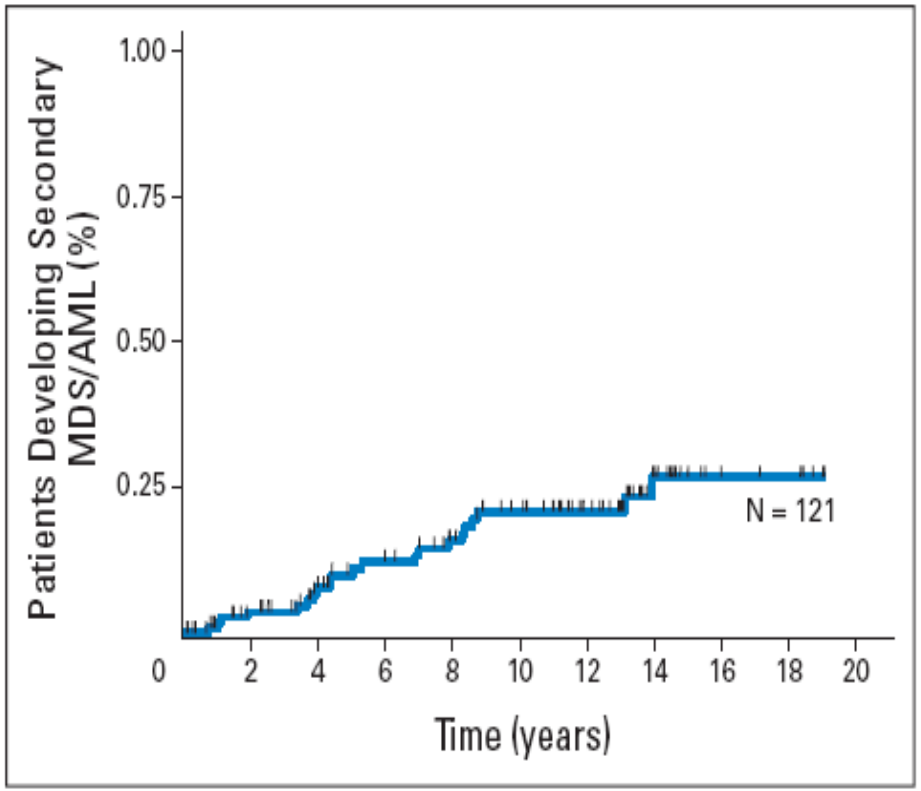


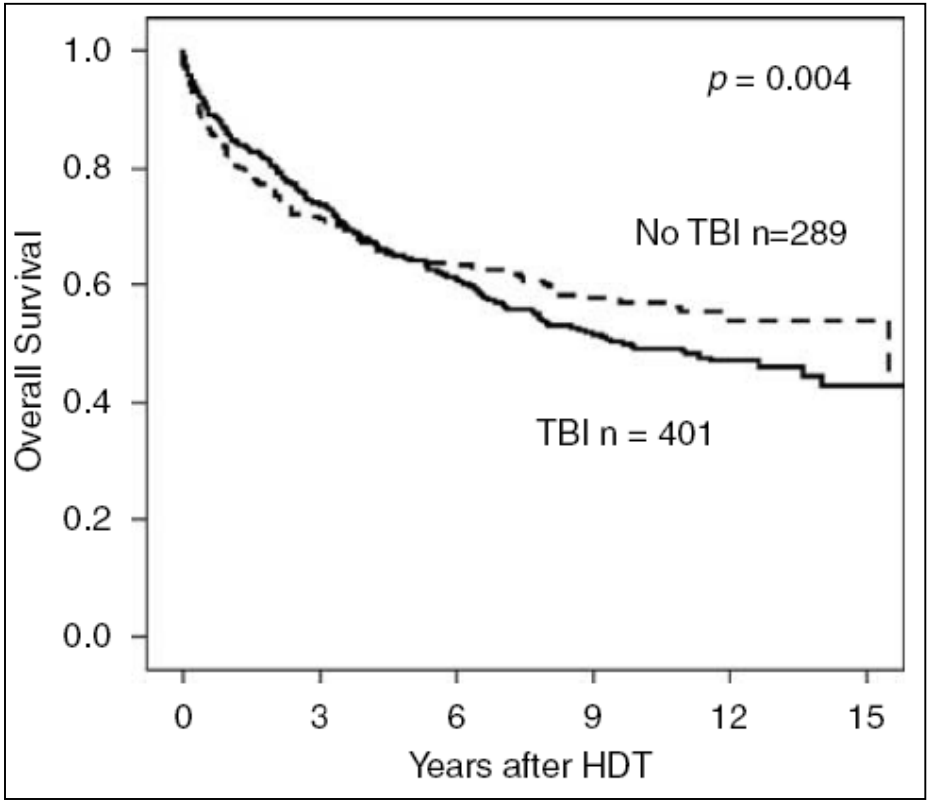




- R non altera l'efficacia del HDT-ASCT ma l'outcome è significativamente migliore nei pazienti che hanno ricevuto R prima della terapia ad alte dosi

*El Najjar et al. Ann Oncol.2014*

# *Late toxicity: risk of MDS*



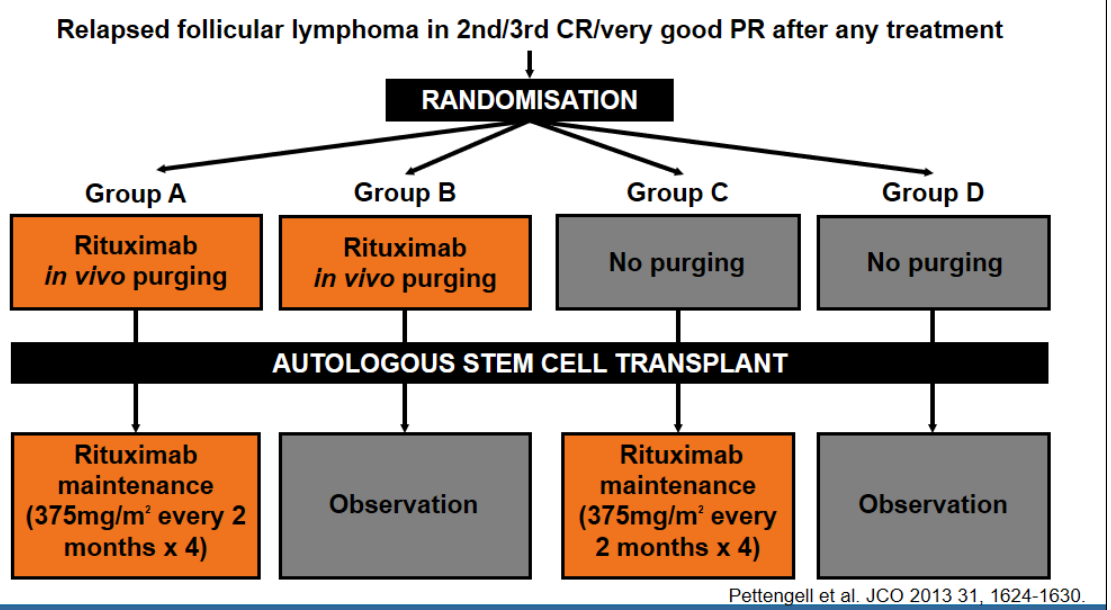




*Rohatiner et al, JCO, 2007*

*Montoto et al, Leukemia, 2007*

# Rituximab EBMT-LYM-1 trial: Protocol

Accrual Oct 1999–Apr 2006




Pettengell et al. JCO 2013 31, 1624-1630.

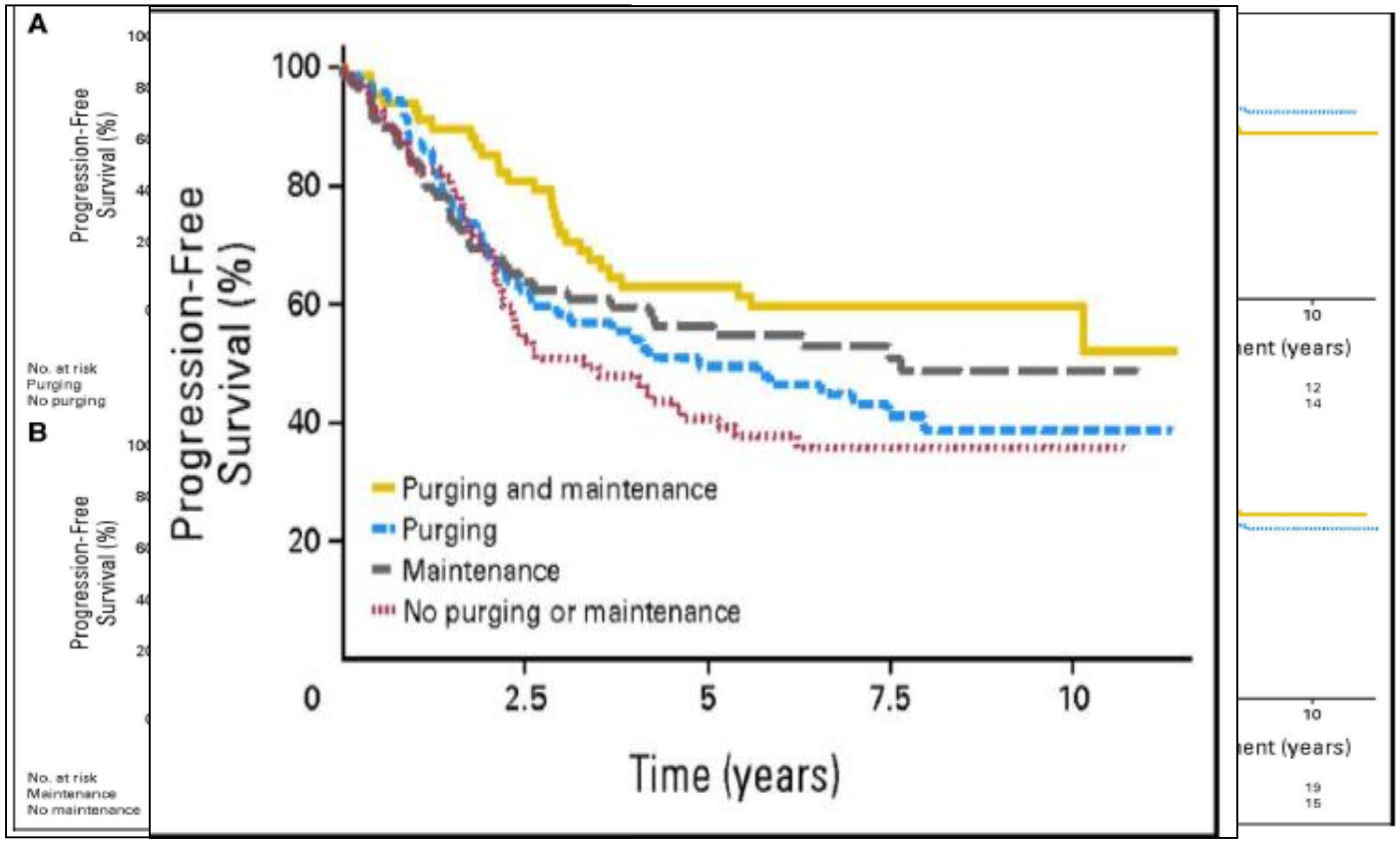
*The European Group for Blood and Marrow Transplantation*

**Median Follow-up**
**12 years (range 10-13)**

| Total | (n=280) |
|---|---|
| Median age (range) | 51.6 (26–70) |
| LDH > ULN (%) | 37.1 |
| ECOG > 1 (%) | 22.4 |
| Stage III/IV (%) | 78.3 |
| Hb <12 g/dL (%) | 21.9 |
| B2 M (range) | 2 (0–7.3) |
| Extranodal involvement (%) | 34.1 |
| Bulky disease (%) | 21.8 |
| BCL2 positive (%) | 58.8 |
| unknown (%) | 25.4 |
| BM involvement (%) | 33.1 |
| Months from diagnosis (range) | 44.1 (3.4–464) |
| Prior lines of chemo (%) | |
| 1 | 0.5 |
| 2 | 40 |
| 3 | 59.5 |
| FLIPI (%) | |
| Low | 26.4 |
| Intermediate | 26.4 |
| High | 25.4 |
| Response to induction (%) | |
| CR | 30 |
| VG PR (>90%) | 70 |

*Pettengel R et al. ICML 2017*

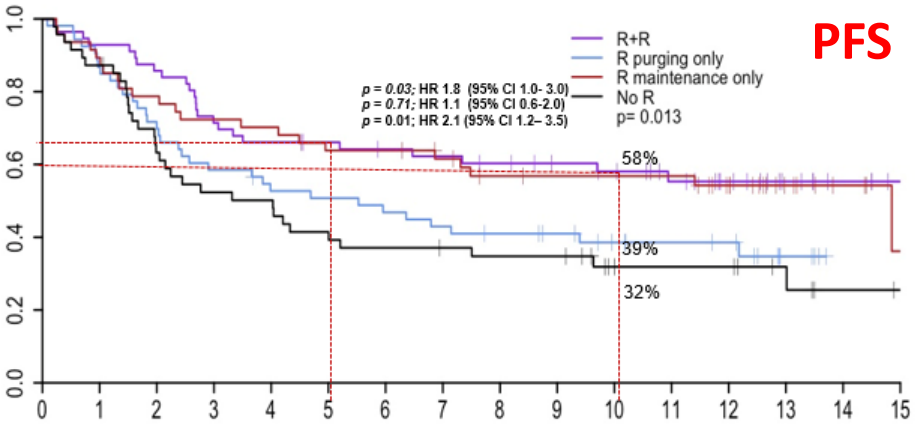
# Rituximab purging e/o mantenimento post ASCT

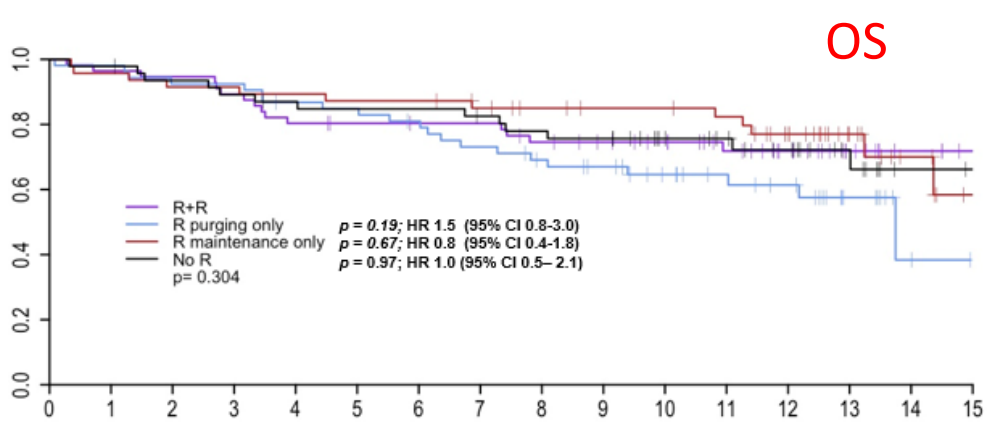



- 280 pazienti; random a purging con R (375 mg/m2/week for 4 weeks) vs obs (NP) e a RM (M; 375 mg/m2 ogni 2 mesi per 4 somministrazioni) vs obs
- RM è sicuro e prolunga la PFS ma non OS
- In vivo purging con R non ha impatto sull'outcome nemmeno nei R-naive

*Pettengel et al. JCO 2013*

# Rituximab EBMT-LYM-1 trial: Protocol




- The benefit of R maintenance after ASCT on PFS in patients with chemosensitive relapsed FL is sustained at 12 years

*Pettengel R et al. ICML 2017*

# Allotransplant

| Series | Preparative Regimen (N) | Matched Related Donor (%) | Prior Rituximab | NRM (%) | PFS/EFS (%) | OS (%) |
|---|---|---|---|---|---|---|
| IBMTR [13] | MA (176) | 100 | NR | 30 (5Y) | 45% (5Y) | 51% (5Y) |
| CIBMTR [58] | MA (120) | 100 | 26 | 25 (3Y) | 67 (3Y) | 62 (3Y) |
| | RIC (80) | 100 | 45 | 28 | 55 | 71 |
| EBMT [54] | RIC ATG (46) | 100 | NR | 18 (3Y) | 55 (3Y) | 70 (3Y) |
| | RIC Alemtuz (42) | | | 18 p=NS | 44 p=0.015 | 68 p=NS |
| | RIC no TCD (76) | | | 17 | 67 | 74 |
| NCCN [44] | Allo (48) | 63 | 100 | 24 (3Y) | 52 (3Y) | 61 (3Y) |
| EBMT [53] | RIC (149) | 80 | 62 | 22 (3Y) | 57 (5Y) | 67 (5Y) |
| CIBMTR/EBMT FL1/2 [39] | RIC (268) | 53 | 100 | 26 (5Y) | 58 (5Y) | 66 (5Y) |
| CIBMTR/EBMT FL3 [40] | RIC (61) | 59 | 100 | 27 (5Y) | 51 (5Y) | 54 (5) |

*Kuruvilla et al Blood 2016*

# Final results: consensus IN FAVOUR

1. HDT-ASCR **non** è una opzione terapeutica appropriata per consolidare una prima remissione in paziente trattato con immuno-chemioterapia al di fuori di trial clinici.

2. HDT-ASCR è una appropriata opzione terapeutica per consolidare la remissione in prima recidiva:

    - con malattia chemiosensibile;

    - recidiva precoce (<3 anni)

    - elevato FLIPI alla ricaduta

    - precedentemente esposto a rituximab

3. In seconda o successive recidive in malattia chemiosensibile

4. Il trapianto allogenico va considerato in pazienti selezionati recidivati dopo ASCT

5. Nell'ambito del trapianto allogenico vanno considerati regimi di condizionamento ad intensità ridotta.

*Montoto et al. Haematologica 2013*

# FLAZ-12: STUDY DESIGN