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# MEETING SUMMARY
# ASH 2018, San Diego, USA

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# AN UPDATE ON PROGNOSTIC FACTORS IN INDOLENT LYMPHOMAS

# DISCLAIMER

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The views expressed within this presentation are the personal opinion of the author. They do not necessarily represent the views of the author's academic institution or the rest of the LYMPHOMA CONNECT group

# EARLY PROGRESSION AS A PREDICTOR OF SURVIVAL IN MARGINAL ZONE LYMPHOMAS: AN ANALYSIS FROM THE PROSPECTIVE INTERNATIONAL NF10 STUDY BY FONDAZIONE ITALIANA LINFOMI

S. Luminari et al. Abst #393

# BACKGROUND
# NF10 STUDY

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## Unmet need addressed by the research:

- Time to progression is strongly associated with OS in follicular lymphomas (FL)
- However this has never been studied in marginal zone lymphoma (MZL)

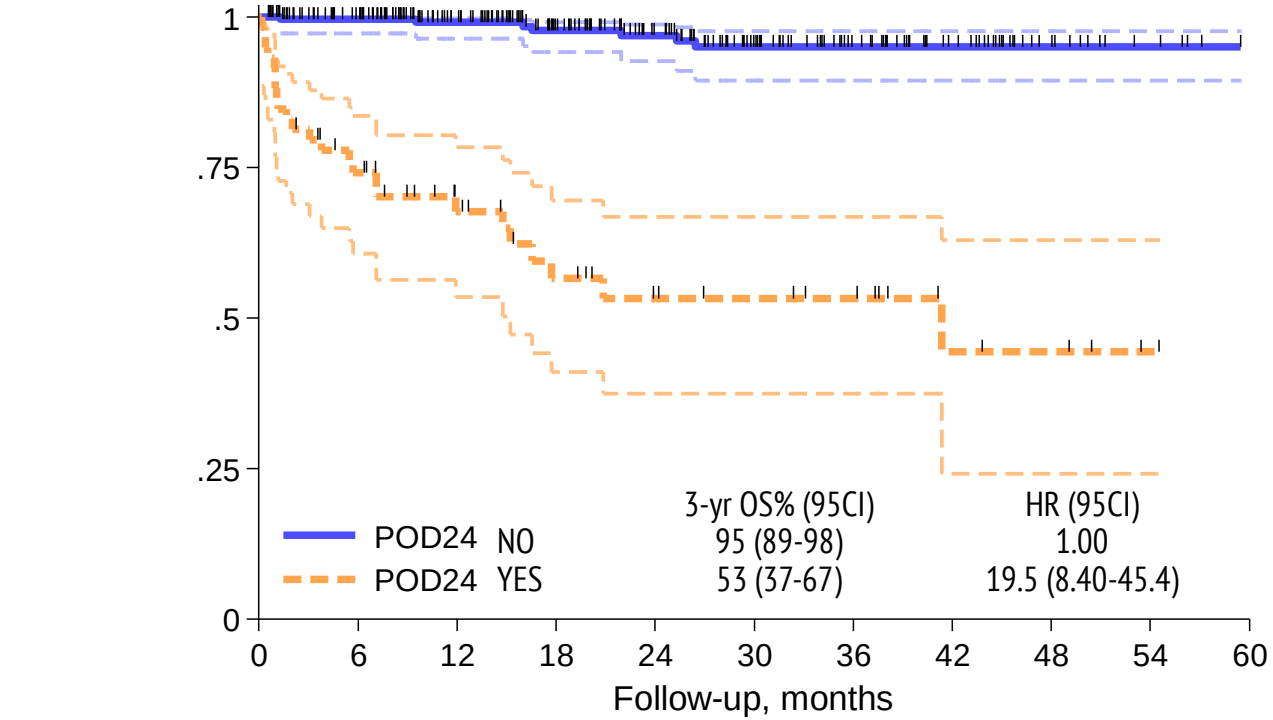
## Study details:

- Observational prospective study on MZL to:
  - Investigate the prognostic role of early progression of disease (POD24)
  - Identify predictive factors for POD24
  - Assess POD24 as surrogate for OS
- N=321* MZL patients - treated with systemic therapy within 3 months from diagnosis

*Numbers may differ from the published abstract as the study population has been updated since August 2018
MZL, marginal zone lymphoma; OS, overall survival
Luminari S et al. Presented at ASH 2018 (abstr 393)

# OS BY POD24 IN MZL

## INTERNATIONAL PROSPECTIVE NF10 OBSERVATIONAL STUDY




Patients at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| POD24 No | 262 | 224 | 179 | 138 | 108 | 74 | 52 | 33 | 14 | 7 | 1 |
| POD24 Yes | 59 | 40 | 28 | 20 | 15 | 13 | 11 | 5 | 4 | 1 | 0 |

**POD24 rate: 59/321* (18%)**

*Numbers may differ from the published abstract as the study population has been updated since August 2018

CI, confidence interval; HR, hazard ratio; MZL, marginal zone lymphoma; OS, overall survival; POD24, progression of disease at 24 months

Luminari S et al. Presented at ASH 2018 (abstr 393)

# RESULTS & CONCLUSION
# NF10 STUDY

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## Main results:

- Early progression in 59/321 patients (18%)
  - HR for 3 year OS 19.5
- Factors independently associated with increased risk of POD24:
  - Anemia
  - Thrombocytopenia
  - Lymphocytopenia
- Risk reduced by use of immunochemotherapy
- Compared with other available prognostic scores, POD24 was confirmed as the best surrogate of OS

## What does this research add to current knowledge?

- POD24 is strongly associated and can be suggested as an early surrogate of OS also in MZL who require systemic therapy
- The risk of early failure can be predicted and can be modified by initial treatment choice

CI, confidence interval; HR, hazard ratio; MZL, marginal zone lymphoma; OS, overall survival; POD24, progression of disease at 24 months
Luminari S et al. Presented at ASH 2018 (abstr 393)

# FRONTLINE THERAPY WITH BENDAMUSTINE AND RITUXIMAB IN FOLLICULAR LYMPHOMA: PROGNOSIS AMONG PATIENTS WITH PROGRESSION OF DISEASE BY 24 MONTHS IS POOR WITH MAJORITY HAVING TRANSFORMED LYMPHOMA

C.L. Freeman et al. Abst #2873

# BACKGROUND
# FRONTLINE THERAPY WITH BR IN FL

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**Unmet need addressed by the research:**

- Incidence of transformation and outcomes of patients with early progression within 24 months (POD24) after BR remain poorly documented in patients with follicular lymphoma

**Study details:**

- Population-based analysis evaluating outcomes following the introduction of BR, including the incidence of transformation and POD24
- Outcomes were compared with a historical cohort of patients treated with frontline RCVP
  - N=296 BR-treated patients
  - Historical control of 347 RCVP-treated patients

BR, Bendamustine and Rituximab; FL, Follicular Lymphoma; POD24, progression of disease at 24 months; RCVP, rituximab, cyclophosphamide, vincristine, prednisolone
Freeman C.L et al. Presented at ASH 2018 (abstr 2873)

# RESULTS
# FRONTLINE THERAPY WITH BR IN FL

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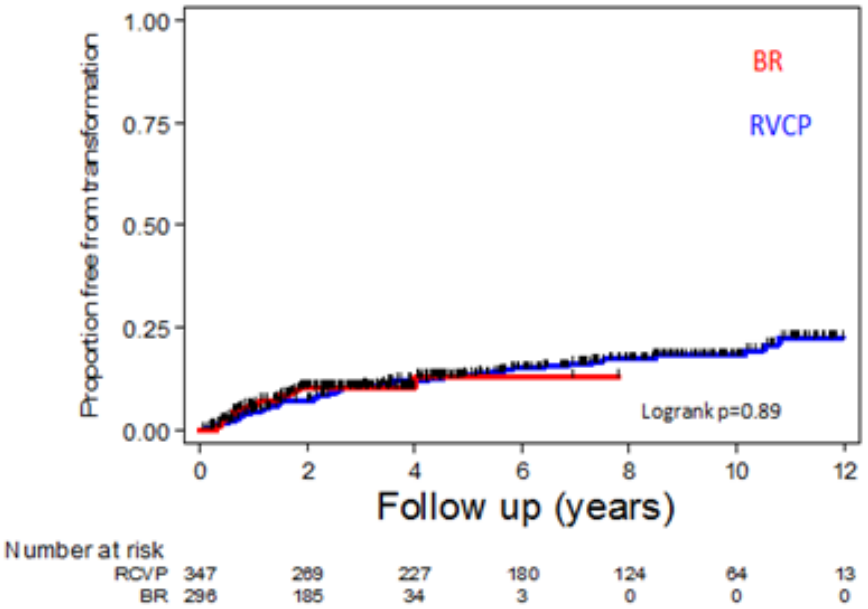
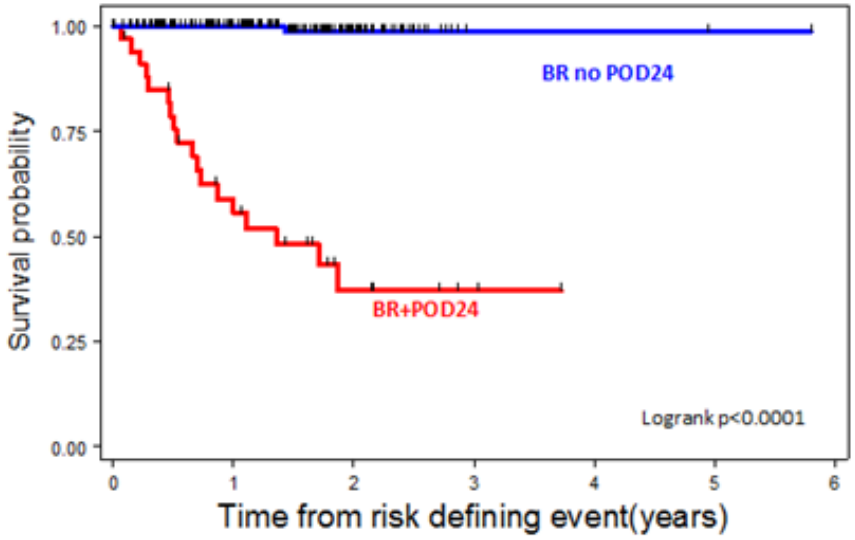
## FIGURE 1:

## TIME TO TRANSFORMATION BY TREATMENT GROUP




## FIGURE 2:

## OVERALL SURVIVAL BY TREATMENT GROUP**




**post progression for POD24 or from 24 months post-initiation of BR for reference group

BR, Bendamustine and Rituximab; POD24, progression of disease at 24 months; RCVP, rituximab, cyclophosphamide, vincristine, prednisolone
Freeman C.L et al. Presented at ASH 2018 (abstr 2873)

# RESULTS & CONCLUSION
# FRONTLINE THERAPY WITH BR IN FL

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## Main results

- Median follow-up for living patients of 2.8 year (range 0.2-7.6)
- Use of BR was associated with an improvement in EFS compared with RCVP (2-y EFS 76% [95% CI 71-80%], p=0.001), but no difference in OS with current follow-up
- Early progression (POD24) occurred in 35/296 (12%) of BR-treated patients
  - The majority of these, 27 (77%), had transformed lymphoma
- POD24 occurred in 77/347 (22%) of RCVP-treated patients comprising 31 (40%) transformed lymphoma

## What does this research add to current knowledge?

The occurrence of early progression (POD24) may be decreasing following the introduction of BR, but the majority of POD24 patients now have transformed lymphoma

BR, Bendamustine and Rituximab; CI, confidence interval; EFS, event free survival; FL, Follicular Lymphoma; OS, overall survival; POD24, progression of disease at 24 months; RCVP, rituximab, cyclophosphamide, vincristine, prednisolone
Freeman C.L et al. Presented at ASH 2018 (abstr 2873)

# PROGNOSTIC BIOMARKERS CONVERGE ON A GERMINAL CENTRE DARK ZONE PHENOTYPE AS A DETERMINANT OF ADVERSE OUTCOME IN FOLLICULAR LYMPHOMA PATIENTS TREATED WITH RITUXIMAB AND CHEMOTHERAPY

A. Silva et al. Abst #4095

# BACKGROUND
# PROGNOSTIC BIOMARKERS

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**Unmet need addressed by the research:**

Reliable and accurate baseline prognostic factors for follicular lymphomas are missing and biological basis of aggressiveness in FL is poorly understood

**Study details:**

- The 23 gene prognostic model proposed by Huet et al (Lancet 2017) was tested on 137 newly diagnosed FL treated with R-CVP, and was compared with the m7-FLIPI, *EZH2* mutation status and FOXP1 expression

EZH2, enhancer of zeste H2; FL, follicular lymphoma; FOXP1, forkhead box P1; m7-FLIPI, modified-7 follicular lymphoma international prognostic index 1 a clinicogenetic risk model; OS, overall survival; PFS progression free survival; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone
A. Silva et al. Presented at ASH 2018 (abstr 4095)

# RESULTS
# PROGNOSTIC BIOMARKERS

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**Main results:**

- All poor-risk genes from the 23-gene predictor were associated with poor PFS and **calculated risk scores were significantly associated with PFS** in the univariate Cox regression analysis (*P*=0.007)
- Dichotomizing the distribution of risk scores identified **68% of cases with high risk score** who had inferior PFS and OS compared to **32% of cases with low risk score** (5-year PFS 54% vs. 77%, *P*=0.004; 5-year OS 73% vs. 86%, *P*=0.04)
- The mean risk score was significantly higher in cases with high expression of **FOXP1** (*P*<0.001) and in cases with high **m7-FLIPI** risk score (*P*=0.023)
- Genes with positive weight and coefficients were **enriched in the FOXP1-high phenotype** that is typically expressed in a germinal centre dark zone signature
- The **ICA13 signature** reported by Huet et al. as being highly expressed in centroblasts was also associated with higher expression of FOXP1

EZH2, enhancer of zeste H2; FL, follicular lymphoma; FOXP1, forkhead box P1; m7-FLIPI, modified-7 follicular lymphoma international prognostic index 1 a clinicogenetic risk model; OS, overall survival; PFS progression free survival; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone
A. Silva et al. Presented at ASH 2018 (abstr 4095)

# CONCLUSION
# PROGNOSTIC BIOMARKERS

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**What does this research add to current knowledge?**

- Robustness of the 23 gene predictor model by Huet et al. is **confirmed**
- FOXP1 expression, *EZH2* wild-type status and expression of dark zone-related genes characterize a subset of FL cases with adverse outcome following rituximab and chemotherapy

EZH2, enhancer of zeste H2; FL, follicular lymphoma; FOXP1, forkhead box P1
A. Silva et al. Presented at ASH 2018 (abstr 4095)

# MINIMAL RESIDUAL DISEASE RESPONSE AT END OF INDUCTION AND DURING MAINTENANCE CORRELATES WITH UPDATED OUTCOME IN THE PHASE III GALLIUM STUDY OF OBINUTUZUMAB- OR RITUXIMAB-BASED IMMUNOCHEMOTHERAPY IN PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA PATIENTS

C. Pott et al. Abst #396

# BACKGROUND
# PROGNOSTIC ASSESSMENT OF MRD RESPONSE (GALLIUM)

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**Unmet need addressed by the research:**

- Molecular response to induction immunochemotherapy has shown to predict PFS in patients with advanced stage FL but needs further **validation**

**Study details:**

- N=634 out of 1202 FL patients enrolled in the GALLIUM trial were studied for Minimal residual disease analysis (MRD) by real-time quantitative (RQ)-PCR assays
- MRD assessed at:
  - mid-induction in peripheral blood
  - EOI in PB and bone marrow
  - 4-monthly intervals during maintenance in PB
  - 6-monthly intervals during follow-up in PB

  and was defined as negative (MRD response) if RQ-PCR and subsequent nested PCR were negative in all samples analysed at the respective time point

EOI, end of induction; FL, follicular lymphoma; MI, mid-induction; MRD, minimal residual disease; PB, peripheral blood; PCR, polymerase chain reaction; PFS, progression-free survival
Pott C et al. Presented at ASH 2018 (abstr 396)

# RESULTS
# PROGNOSTIC ASSESSMENT OF MRD RESPONSE (GALLIUM)

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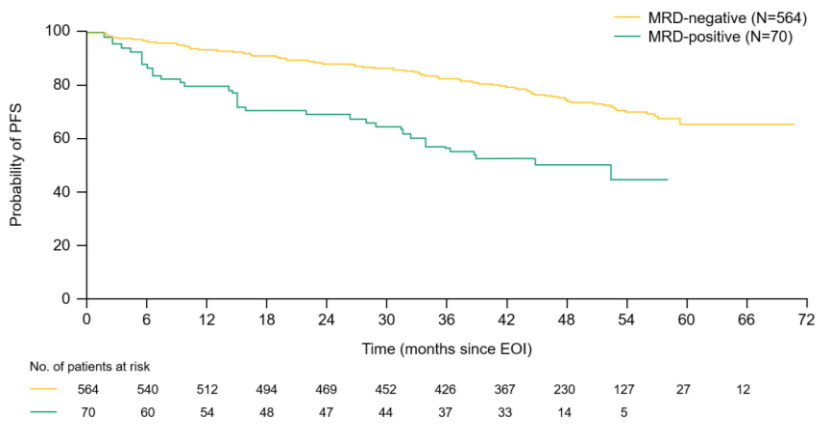
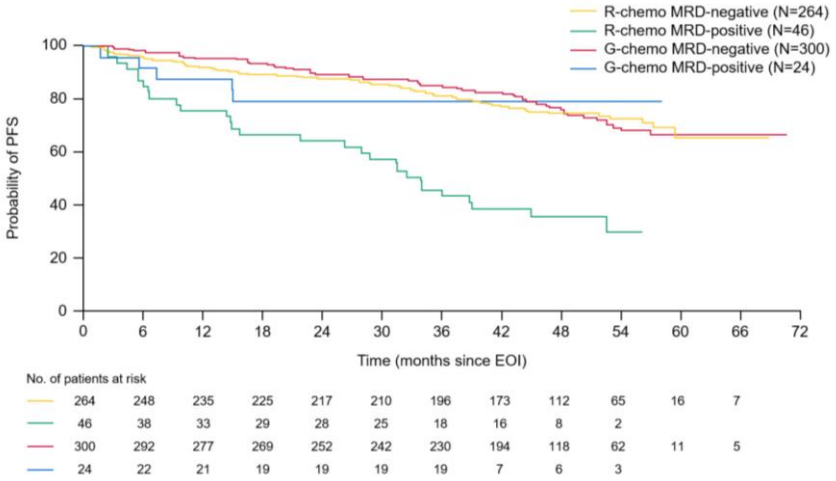
## FIGURE 1:

### PFS FROM DATE OF EOI SAMPLE BY MRD STATUS IN PB AND/OR BM




## FIGURE 2:

### PFS FROM DATE OF EOI SAMPLE BY MRD STATUS IN PB AND/OR BM AND TREATMENT ARM




BM, bone marrow; EOI, end of induction; FL, follicular lymphoma; MI, mid-induction; MRD, minimal residual disease; PB, peripheral blood; PCR, polymerase chain reaction; PFS, progression-free survival

Pott C et al. Presented at ASH 2018 (abstr 396)

# RESULTS & CONCLUSION
# PROGNOSTIC ASSESSMENT OF MRDR (GALLIUM)

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## Main results:

- After 57 months median follow-up
  - MRD evaluable patients who had a MRD-negative response at EOI (n=564) continued to have a longer PFS than those who had a MRD-positive response at EOI (n=70; hazard ratio 0.38; 95% confidence interval 0.26, 0.56; p<0.0001; (**Figure 1**)
  - This was irrespective of treatment arm (**Figure 2**)
- The majority of MRD-negative patients remained negative during maintenance
- No difference in the MRD relapse rate (conversion to MRD positivity) was observed between patients treated with G or R maintenance (6.3% vs 6.1%, respectively)

## What does this research add to current knowledge?

- These data confirm the **prognostic value of MRD status at EOI** in previously untreated FL patients receiving immunochemotherapy and with similar results achieved with metabolic response provide the rationale for response adapted therapy in FL

EOI, end of induction; FL, follicular lymphoma; G, obinutuzumab; MI, mid-induction; MRD, minimal residual disease; PB, peripheral blood; PCR, polymerase chain reaction; PFS, progression-free survival; R, rituximab
Pott C et al. Presented at ASH 2018 (abstr 396)

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