



**Karolinska  
Institutet**

# Survival by first-line treatment type and timing of progression among follicular lymphoma patients

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*Karolinska Institutet & War on Cancer*

**2022 Northern European Stata Conference**

# About Me

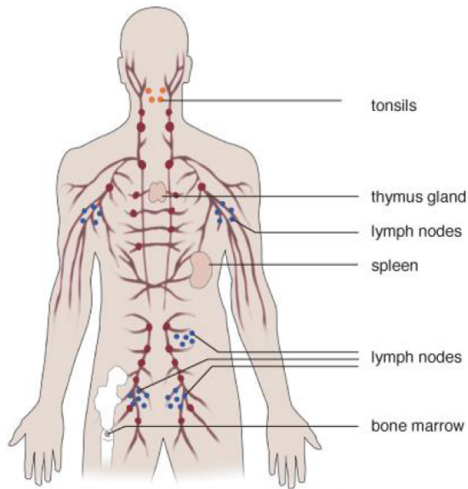
## Background:

- MSc in Mathematical statistics (2009)
- PhD in Medicine (2018)
- Applied biostatistician - cancer epidemiology with a focus on lymphoma

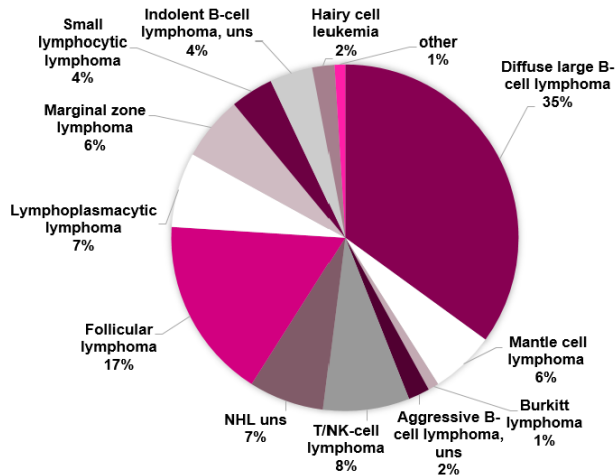
## Today:

- 40% as researcher at the Clinical Epidemiology Unit, Karolinska Institutet
- 60% as lead scientist at War On Cancer (<https://waroncancer.com/>)

# Lymphoma - malignancies that arise in lymphoid tissue





# Lymphoma - more than 70 diseases



# Follicular lymphoma

- Follicular lymphoma (FL) is a mostly indolent malignancy.
- Some patients require treatment, whereas others do not (watch and wait).
- Usually not considered curable, but more of a chronic disease.
- Clinical outcome (prognosis) is highly variable.
- POD24 (progression of disease within 24 months) has been suggested as an important prognostic marker of overall survival (OS).
- Most research on POD24 have been in clinical trial settings and with patients treated with immunochemotherapy.

## Prognostic value of POD24 validation in follicular lymphoma patients initially treated with chemotherapy-free regimens in a pooled analysis of three randomized trials of the Swiss Group for Clinical Cancer Research (SAKK)



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Stefanie Hayoz,<sup>2</sup> Maria Cristina Piroso,<sup>1</sup>  
Christian Taverna,<sup>3</sup> Urban Novak,<sup>4</sup>  
Eva Kimby,<sup>5</sup>  Michele Ghielmini<sup>1</sup> and  
Emanuele Zucca<sup>1,4,6</sup>

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### Summary

The relapse of follicular lymphoma (FL) within 24 months (POD24) of chemoimmunotherapy has been associated with poor survival. We analyzed a pooled dataset of three randomized trials including FL patients with advanced disease, conducted by the Swiss Group for Clinical Cancer Research (SAKK). Overall, POD24 was observed in 27% of 318 patients, but rate variance among studies suggested that the rituximab schedule might affect POD24 rate. POD24 was associated with lower 10-

## Prognostic value of POD24 patients initially treated with rituximab in a pooled analysis of three studies in the Swiss Group for Clinical Cancer Research

Alden Alberto Moccia,<sup>1</sup>  Sämi Schär,<sup>2</sup> Stefanie Hayoz,<sup>2</sup> Maria Cristina Piroso,<sup>1</sup> Christian Taverna,<sup>3</sup> Urban Novak,<sup>4</sup> Eva Kimby,<sup>5</sup>  Michele Ghielmini<sup>1</sup> and Emanuele Zucca<sup>1,4,6</sup>

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ORIGINAL ARTICLE



## Progression of disease within 24 months of initial therapy (POD24) detected incidentally in imaging does not necessarily indicate worse outcome

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### ABSTRACT

Progression of disease within 24 months of initial therapy (POD24) has previously been identified as a predictor of reduced overall survival (OS) for patients with follicular lymphoma (FL). Here

### Summary

The relapse of follicular lymphoma (FL) within 24 months (POD24) of chemotherapy has been associated with poor survival. We analyzed a pooled dataset of three randomized trials including FL patients with advanced disease, conducted by the Swiss Group for Clinical Cancer Research (SAKK). Overall, POD24 was observed in 27% of 318 patients, but rate variance among studies suggested that the rituximab schedule might affect POD24 rate. POD24 was associated with lower 10-

### ARTICLE HISTORY

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## Progression of disease within 24 months of initial therapy (POD24) detected incidentally in imaging does not necessarily indicate worse outcome

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<https://doi.org/10.1007/s00277-020-04025-2>

ORIGINAL ARTICLE



### Progression of disease within 2 years (POD24) is a clinically relevant endpoint to identify high-risk follicular lymphoma patients in real life

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#### Abstract

Follicular lymphoma (FL) is an indolent non-Hodgkin's lymphoma with heterogeneous outcomes. Progression or relapse of FL within 2 years (so-called POD24) after diagnosis is associated with a poor outcome for patients treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone) in clinical trials. POD24 needs further validation before it can be used as a relevant endpoint to assess treatment efficacy. In the present retrospective monocentric study, we investigated the predictive value of POD24 in a cohort of 64 (1.2% of 5365) FL patients treated in our institution (Nantes Medical University

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rapy (POD24) has previously been identified  
patients with follicular lymphoma (FL). Here

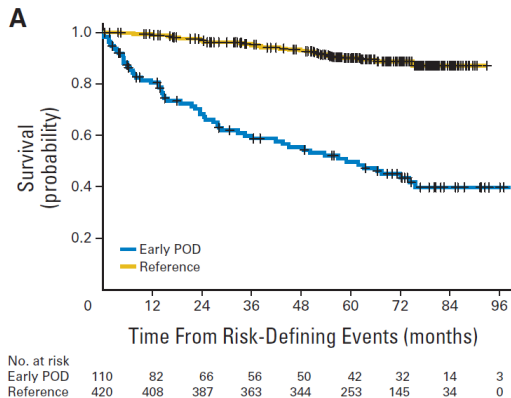
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## However, this measure has some inbuilt issues



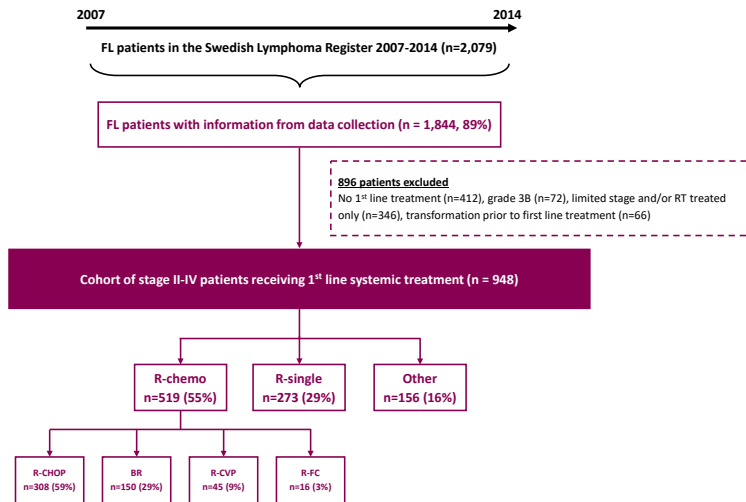
(Casulo C et. al, J Clin Oncol 2015)

- Patients are followed from the “**risk-defining event**” which makes the time scale different for progressed and progression-free patients
- Only progressions within 24 (not 25, 26, ...) months are considered
- Progression-free patients who die before 24 months are excluded from analyses

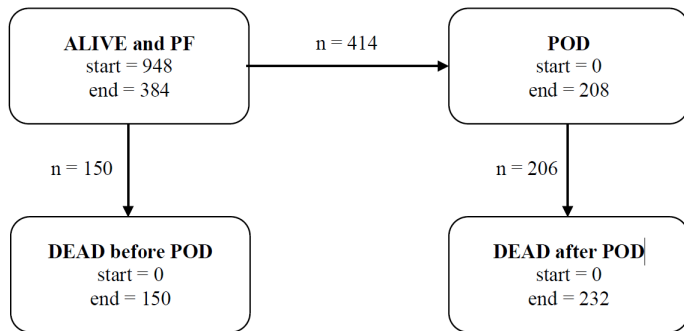
# Aim

What is the impact of POD, and timing thereof, on OS among FL patients treated with immunochemotherapy versus immunotherapy only?

# Population-based study



# An illness-death modelling approach



*PF, progression-free; POD, progression of disease*

# Modelling and predictions

- Modelling of transition rates:
  - Flexible parametric survival models
  - Treatment group (R-chemo, R-single, other), time-varying effects
  - Adjusting for time of entry to POD (semi-Markov)
  - Package `merlin`
- Prediction of transition probabilities:
  - 5-year OS conditional on time of POD/PF
  - Package `multistate`

# Modelling transition rates with merlin

```
// Transition 1
stmerlin tr2 tr3          /// main effects
        if _trans==1     /// fl -> dead
        , dist(rp) df(3)  /// flexible parametric model
        tvc(tr2 tr3) dftvc(2) // time-varying effects
est store m1
```

```
// Transition 2
stmerlin tr2 tr3          /// main effects
        if _trans==2     /// fl -> POD
        , dist(rp) df(3)  /// flexible parametric model
        tvc(tr2 tr3) dftvc(2) // time-varying effects
est store m2
```

```
// Transition 3
stmerlin tr2 tr3          /// main effects
        _t0              /// semi-Markov
        if _trans==3     /// POD -> dead
        , dist(rp) df(3)  /// flexible parametric model
        tvc(tr2 tr3) dftvc(2) // time-varying effects
est store m3
```

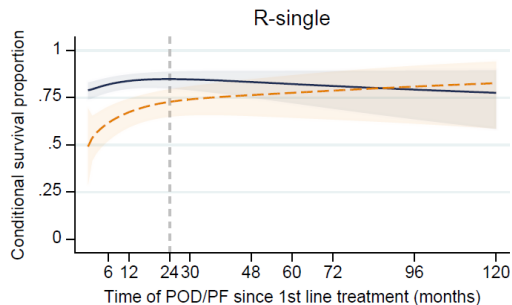
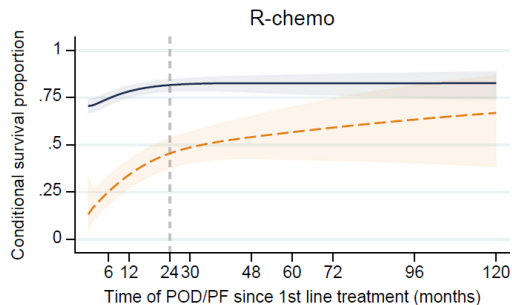
# Predicting conditional 5-year OS with predictms

```
range ptime 0 10 100
gen tvar5 = 5 + ptime

// Predict the conditional 5-year overall survival
forvalues ptime = 1/100 {
    cap drop temptime
    gen temptime = tvar5[`ptime'] in 1

    predictms, transmat(tmat)
        models(m1 m2 m3)
        from(1 2)
        at1(_t0 `=ptime[`ptime']' tr1 1)
        at2(_t0 `=ptime[`ptime']' tr2 1)
        at3(_t0 `=ptime[`ptime']' tr3 1)
        timevar(temptime)
        ltruncated(`=ptime[`ptime']')
        probability
}
/// specify transition matrix
/// specify models
/// starting states
/// R-chemo treated patients
/// R-single treated patients
/// Patients treated with other
/// prediction time
/// entry time
// transition probability
```

## 5-year OS by time of POD/PF: R-CHEMO vs R-Single



Conditional 5-year overall survival for FL patients treated with R-chemo (left) and R-single (right). The dashed line represents POD/PF-24.



# Conclusions

- Progression mainly before, but also after 24 months, is associated with a worse 5-year overall survival among immunochemotherapy treated patients.
- This inferior survival remained for patients progressing at least within four years after treatment initiation .
- Among patients selected for immunotherapy only, progression of disease did not have a strong effect on the 5-year overall survival.

## Thank you and some references below

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