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

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About Me

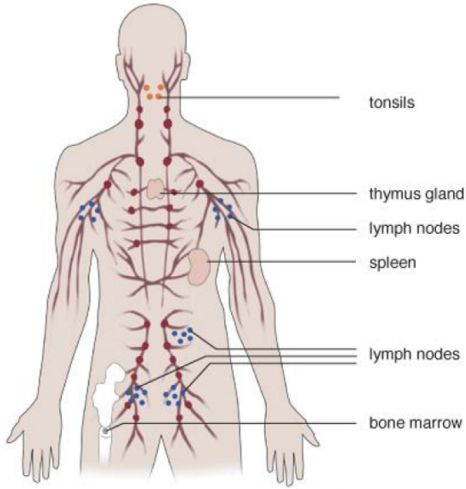
Background:

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

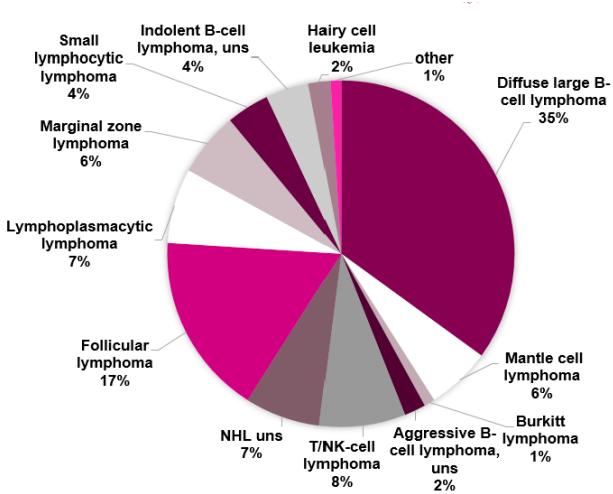
Today:

- 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



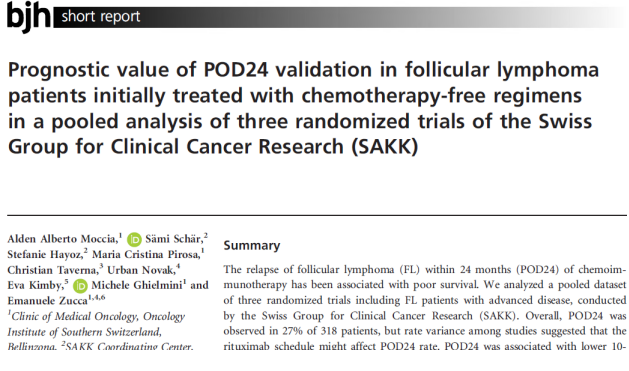
Lymphoma - more than 70 diseases



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.

POD24 in FL patients is well studied



bjh short report

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)

Alden Alberto Moccia,[1] Sämi Schär,[2] Stefanie Hayoz,[2] Maria Cristina Pirosa,[1] Christian Taverna,[3] Urban Novak,[4] Eva Kimby,[5] Michele Ghielmini[1] and Emanuele Zucca[1,4,6]
[1]*Clinic of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona.* [2]*SAKK Coordinating Center.*

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-

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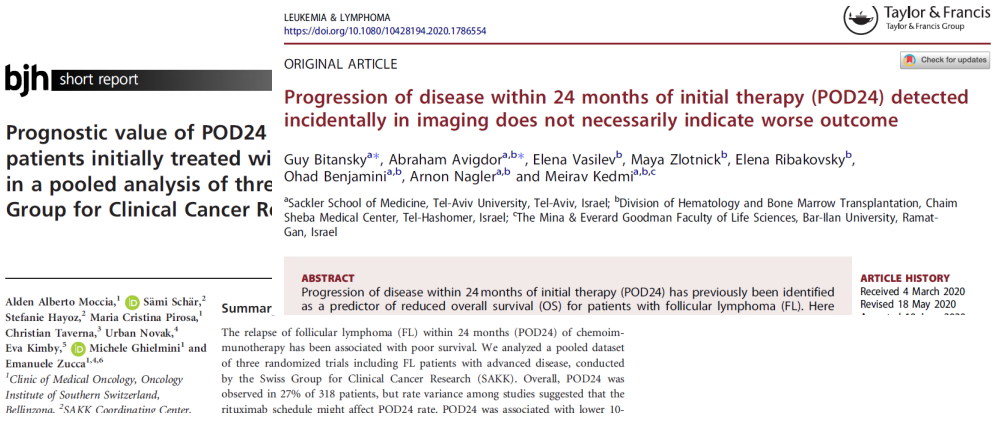

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Summar

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2020.1786554

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ORIGINAL ARTICLE

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

Guy Bitansky[a*], Abraham Avigdor[a,b*], Elena Vasilev[b], Maya Zlotnick[b], Elena Ribakovsky[b], Ohad Benjamini[a,b], Arnon Nagler[a,b] and Meirav Kedmi[a,b,c]

[a]Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [b]Division of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer, Israel; [c]The Mina & Everard Goodman Faculty of Life Sciences, Bar-Ilan University, Ramat-Gan, Israel

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

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-

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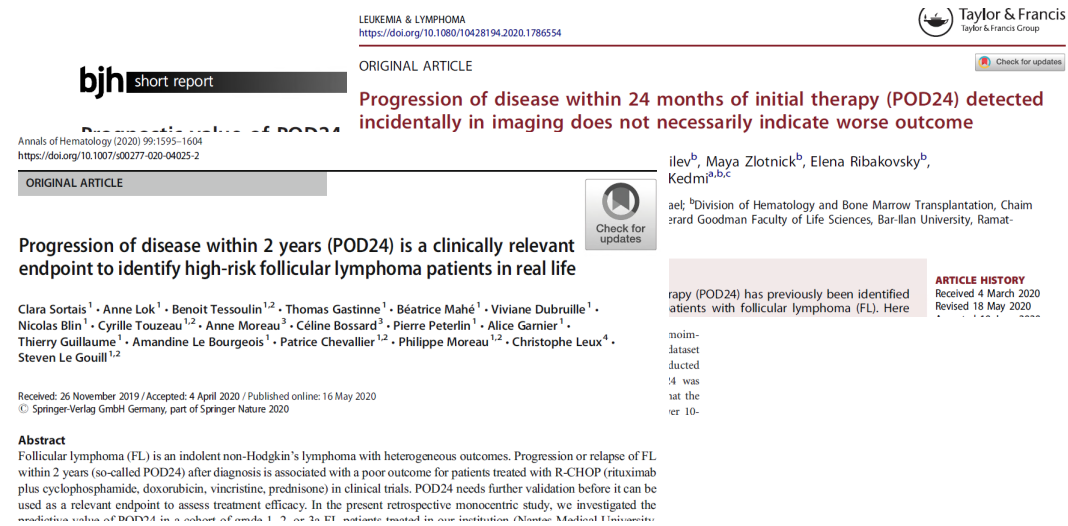
POD24 in FL patients is well studied



bjh short report

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ORIGINAL ARTICLE

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

Clara Sortais[1] · Anne Lok[1] · Benoit Tessoulin[1,2] · Thomas Gastinne[1] · Béatrice Mahé[1] · Viviane Dubruille[1] · Nicolas Blin[1] · Cyrille Touzeau[1,2] · Anne Moreau[3] · Céline Bossard[3] · Pierre Peterlin[1] · Alice Garnier[1] · Thierry Guillaume[1] · Amandine Le Bourgeois[1] · Patrice Chevallier[1,2] · Philippe Moreau[1,2] · Christophe Leux[4] · Steven Le Gouill[1,2]

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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 grade 1, 2, or 3a FL patients treated in our institution (Nantes Medical University

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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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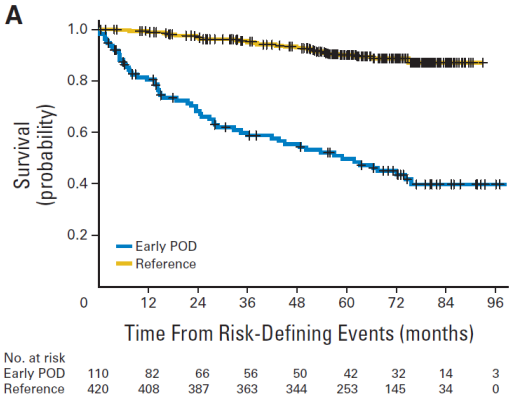


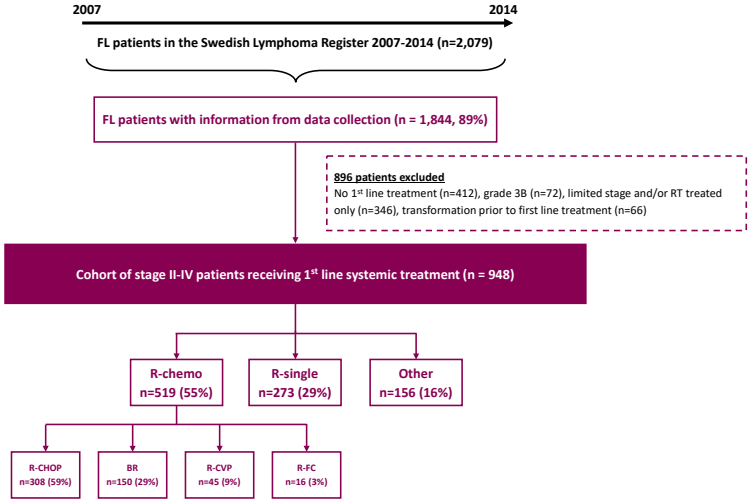
(Casulo C et. al, J Clin Oncol 2015)

- 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

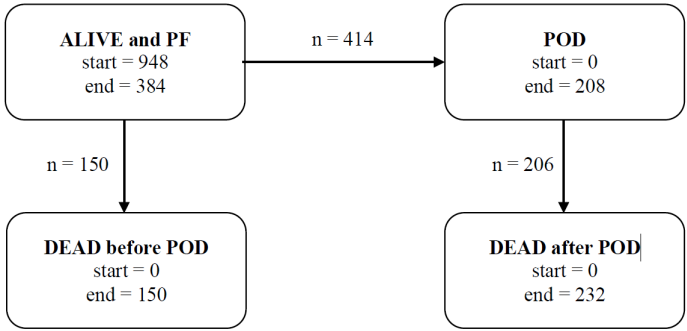
Aim

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
```

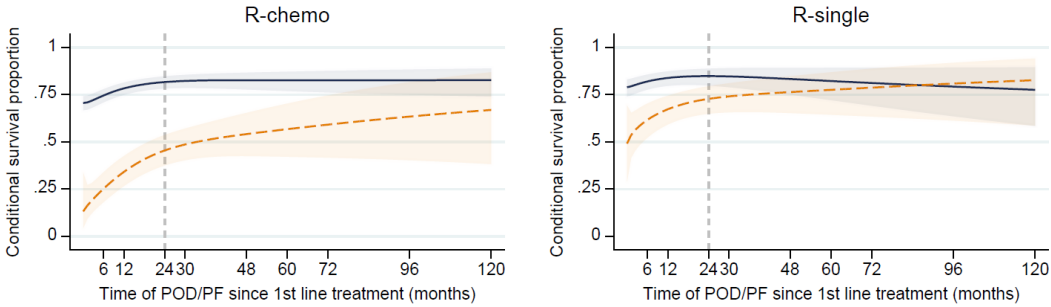
Predicting conditional 5-year OS with `predictms`

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

// Predict the conditional 5-year overall survival
forvalues ptindex = 1/100 {
    cap drop temptime
    gen temptime = tvar5[‘ptindex’] in 1

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