

Prognostic impact of POD24 across different treatment strategies in Waldenström Macroglobulinemia treated with bendamustine-rituximab, dexamethasone-rituximab-cyclophosphamide and BTK inhibitors.

F. Autore(1), AM. Frustaci(2), G. Benevolo(3), N. Danesin(4), D. Giannarelli(1), R. Rizzi(5), M. Nicolosi(6), E. Cencini(7), R. Pasquale(8), C. Conticello(9), S. Steffanoni(10), M. Bullo(11), D. Marino(12), M. Gentile(13), I. Innocenti(1), L. Stirparo(1), F. Piazza(4), G. D'Uva(3), A. Tedeschi(2), L. Laurenti(1)

(1)Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma; (2)Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milano; (3)Ematologia Universitaria A.O.U. Città della Salute e della Scienza di Torino, Torino; (4)Dipartimento di Medicina - Università degli Studi di Padova e UOC di Ematologia - Azienda Ospedale Università Padova, Padova; (5)Università degli Studi "Aldo Moro," A.O.U. Consorziale Policlinico di Bari, Bari; (6)SC Ematologia, AOU Città della Salute e della Scienza, Torino; (7)A.O.U. Senese e Università di Siena, Siena; (8)Azienda Sanitaria Universitaria Friuli Centrale, Udine; (9)Divisione di Ematologia e Trapianto di Midollo Osseo, Policlinico Gaspare Rodolico di Catania, Catania; (10)Ospedale Valduce di Como, Como; (11)A.O. Ordine Mauriziano di Torino, Torino; (12)Istituto Oncologico Veneto IOV-IRCCS, Padova; (13)Azienda Ospedaliera di Cosenza, Cosenza.

Progression of disease within 24 months (POD24) is a validated dynamic prognostic marker in patients with follicular lymphoma receiving frontline immunochemotherapy, whereas its prognostic role in Waldenström Macroglobulinemia (WM) across different treatment settings, including relapsed disease, remains poorly defined.

Our aim was to evaluate the prognostic impact of POD24 in WM and to compare its discriminatory value with IPSSWM and mutational status.

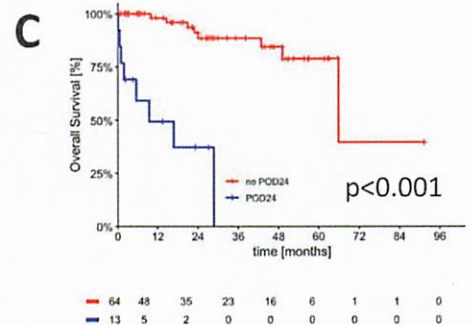
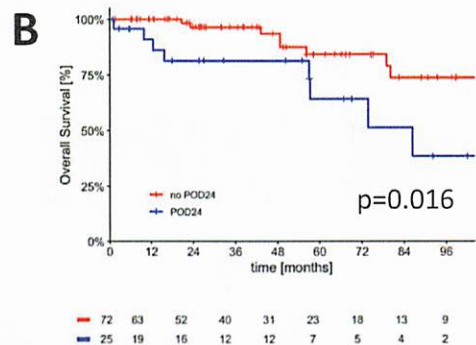
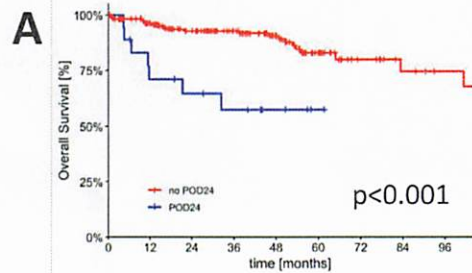
We conducted a multicenter retrospective FIL study including WM patients treated with frontline bendamustine-rituximab (BR, n=244), frontline dexamethasone-rituximab-cyclophosphamide (DRC, n=116), and BTK inhibitors (BTKi) in relapsed disease (n=102: 71 ibrutinib, 31 zanubrutinib). Survival was estimated by Kaplan–Meier and compared by log-rank test. The impact of POD24 on survival outcomes has been evaluated through a landmark analysis considering a 24-months mark. Standardized mortality ratios (SMR) were calculated using matched general population data. Median follow-up was 54, 59, and 44 months for BR, DRC, and BTKi, respectively.

POD24 incidence was 9.4% in the BR cohort, 25.8% in DRC and 16.9% in BTKi. Across all cohorts, POD24 was associated with significantly inferior overall survival (OS) respect to non-POD24: BR (5-year OS 57% vs 83%, HR 4.6 (95% CI: 1.9-11.0), $p<0.001$; figure 1A), DRC (64% vs 84%, HR 3.1 (95% CI: 1.2-8.4), $p=0.016$; figure 1B), and BTKi (0% vs 79%, HR 15.7 (95% CI: 5.0-49.6), $p<0.001$; figure 1C). In the BR cohort, POD24 patients showed increased mortality compared with the general population (SMR 4.8), whereas non-POD24 patients had only a modest excess risk (SMR 2.3). In the DRC cohort, SMR was 5.1 for POD24 versus 1.9 for non-POD24. The most pronounced difference was observed in the BTKi cohort, where POD24 patients had extremely high mortality (SMR 22.2), while non-POD24 patients showed a limited increase (SMR 3.5).

CXCR4 mutations were associated with inferior outcomes, particularly in BTKi-treated patients, whereas MYD88L265P status did not significantly impact OS. Among BTKi patients in the landmark analysis, 13 experienced POD24: 10 treated with ibrutinib and 3 with zanubrutinib. MYD88 was wild-type in 23%, mutated in 61%, and unknown in 15%; CXCR4 was wild-type in 15%, mutated in 23%, and unknown in 61%. Prior therapies included BR (31%), DRC (61%), and other R-chemotherapies (8%).

Considering basal clinical characteristics a solely correlation between age and POD24 was found in BR cohort (OR 1.08; 95% CI: 1.02-1.14; $p=0.009$). No correlation was observed between POD24 and high IPSSWM ($p=0.18$). POD24 appeared to provide stronger prognostic discrimination than IPSSWM in BR-treated patients, whereas IPSSWM retained greater prognostic value in DRC cohort.

In conclusion, POD24 could potentially represent a prognostic marker for WM across distinct treatment settings including relapsed disease treated with BTK inhibitors, given its impact on survival outcomes and as compared to the outcomes of the general population. Main limitations are the retrospective design of the study in addition to the missing data regarding mutational status and the small number of second progressions in the BTKi cohort. These findings might suggest the incorporation of POD24 into risk-adapted strategies and its potential use as early surrogate endpoint in prospective clinical trials.



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