# Critical assessment and new development of prognostic scoring systems

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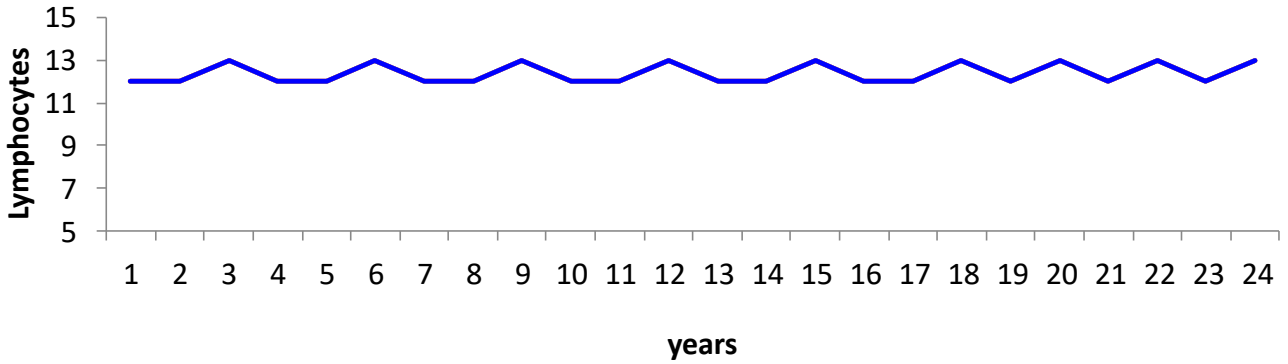
# DISCLOSURES OF COMMERCIAL SUPPORT

| Name of Company | Research support | Employee | Consultant | Stockholder | Speaker's Bureau | Scientific Advisory Board | Other |
|---|---|---|---|---|---|---|---|
| AbbVie | X | | | | | X | |
| AstraZeneca | X | | | | | X | |
| BeiGene | X | | | | | X | |
| BMS | | | | | | X | |
| Janssen | X | | | | | X | |

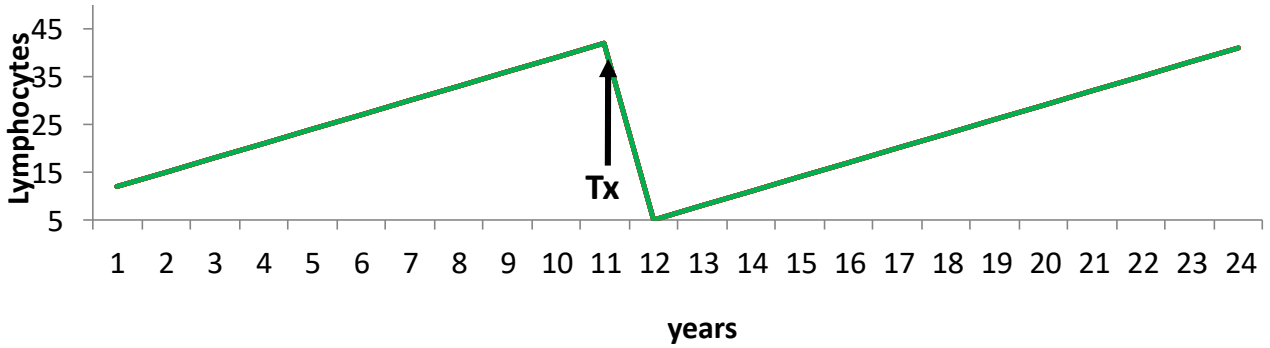
# Time to first treatment

# Heterogeneous course of early stage CLL

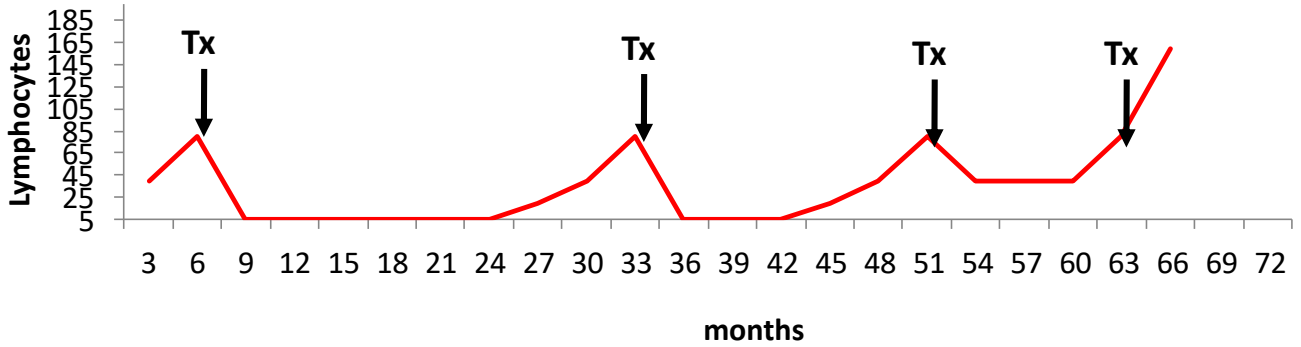
**Highly stable**
**1/3**




**Slowly progressive**
**1/3**




**Rapidly progressive**
**1/3**



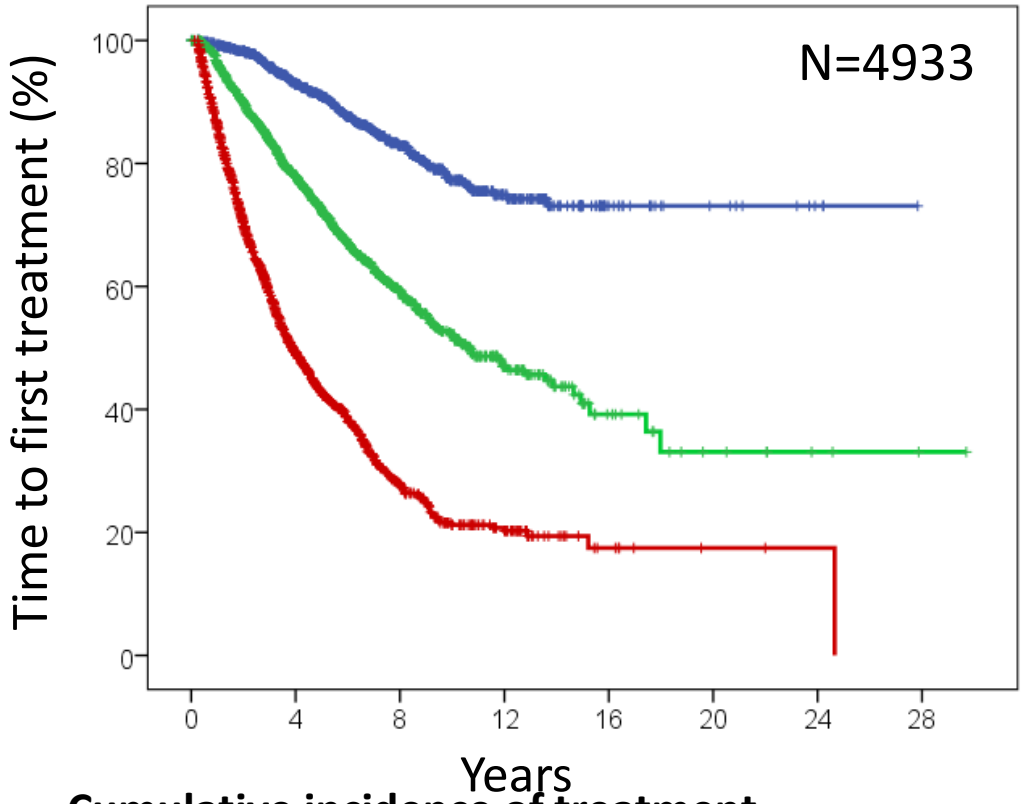
# IPS-E captures the three main patterns of time to first therapy

Condoluci A, Blood. 2020

| Variable | Points |
|---|---|
| IGHV unmutated | 1 |
| Lymphocytes >15x10$^9$/L | 1 |
| Nodal involvement | 1 |

| Risk group | Score |
|---|---|
| Low risk | 0 |
| Intermediate risk | 1 |
| High risk | 2-3 |

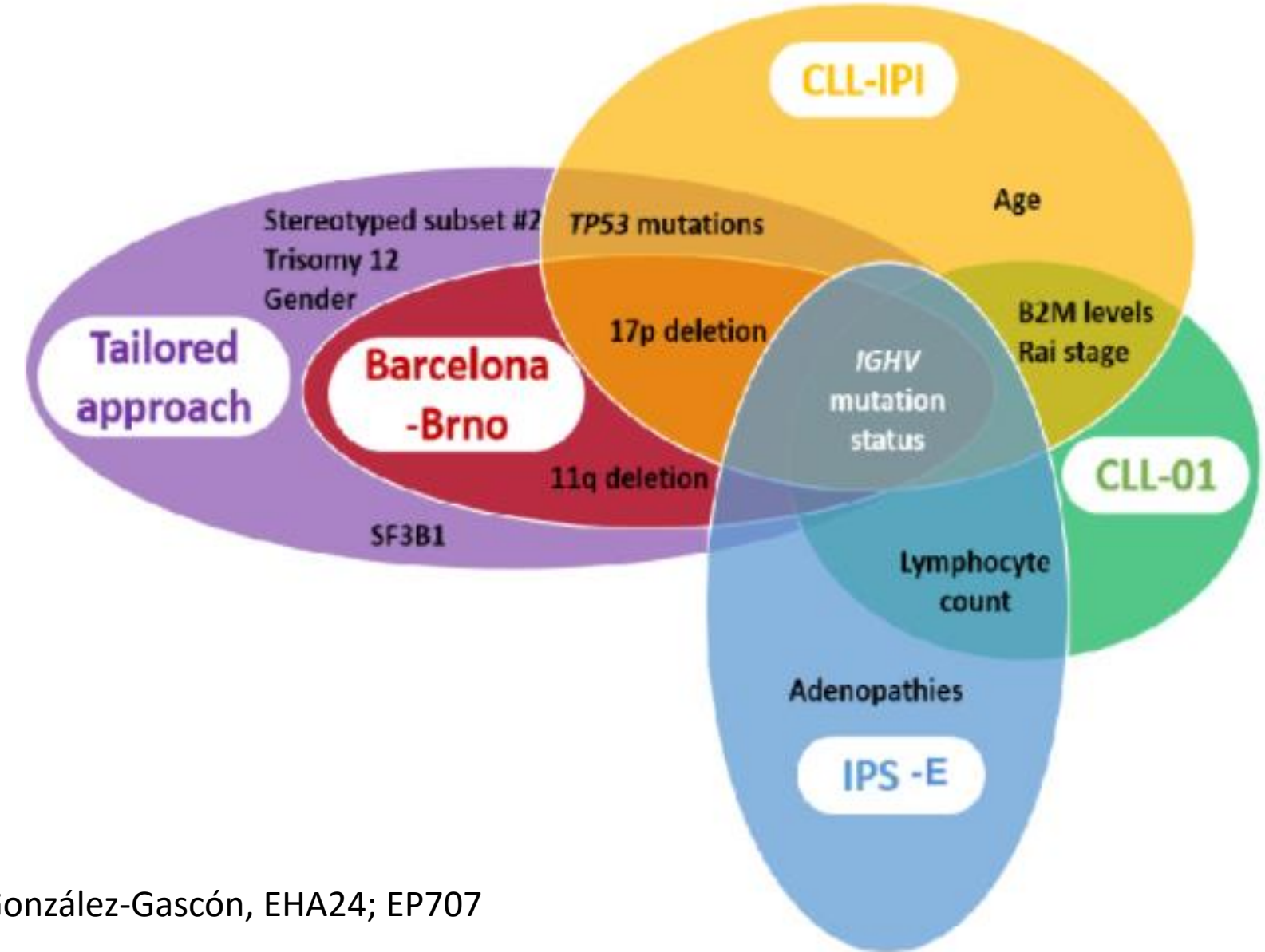
**Validation**
Smolej L, Br J Haematol. 2020
Morabito F, et al. Eur J Haematol. 2021
González-Gascón, EHA24; EP707




**Cumulative incidence of treatment**

| | 1 year | 5 years |
|---|---|---|
| Low risk | <1% | 8% |
| Intermediate risk | 3% | 28% |
| High risk | 14% | 61% |

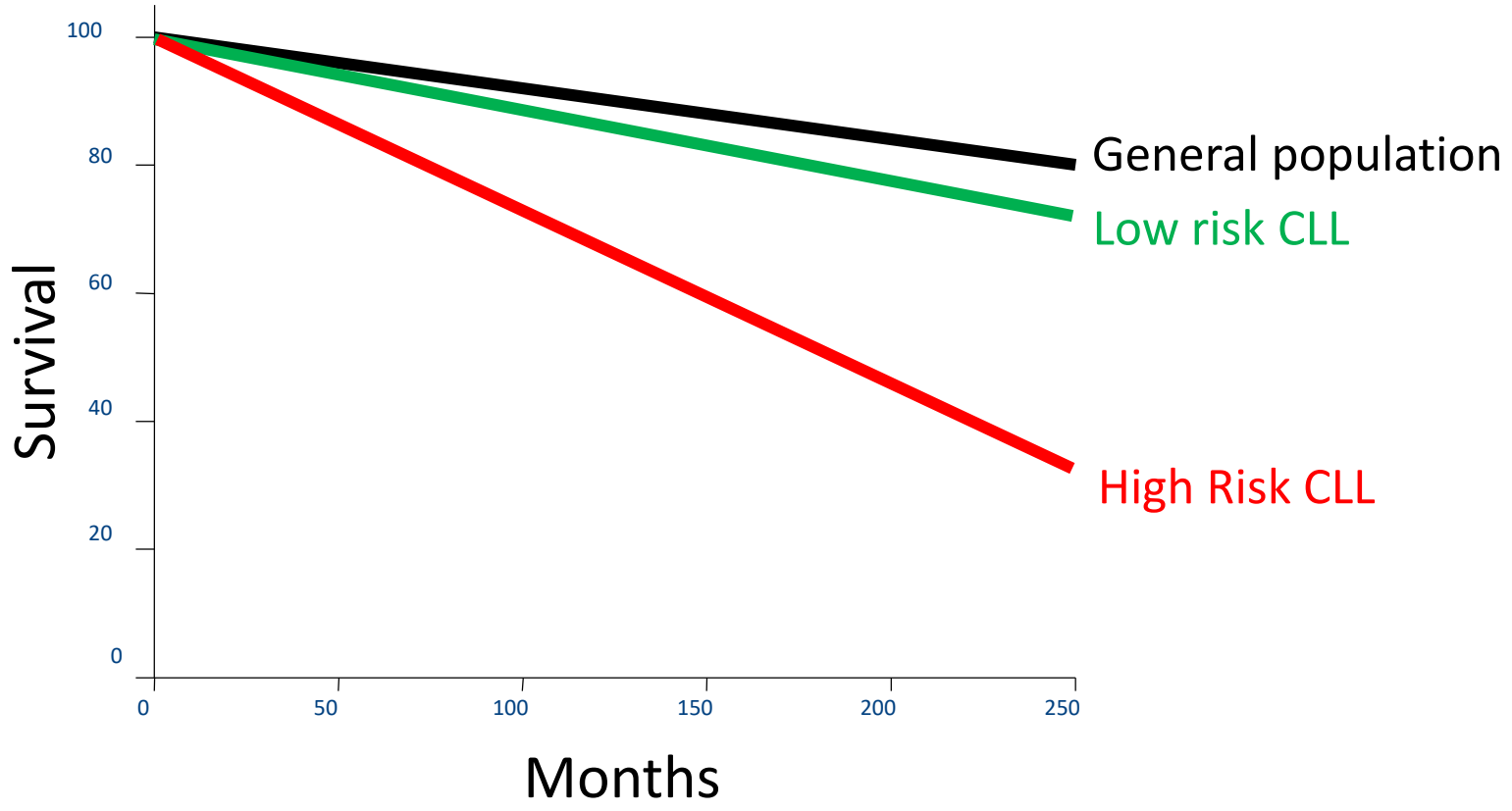
# What is the most robust biomarker?




González-Gascón, EHA24; EP707

# Overall survival

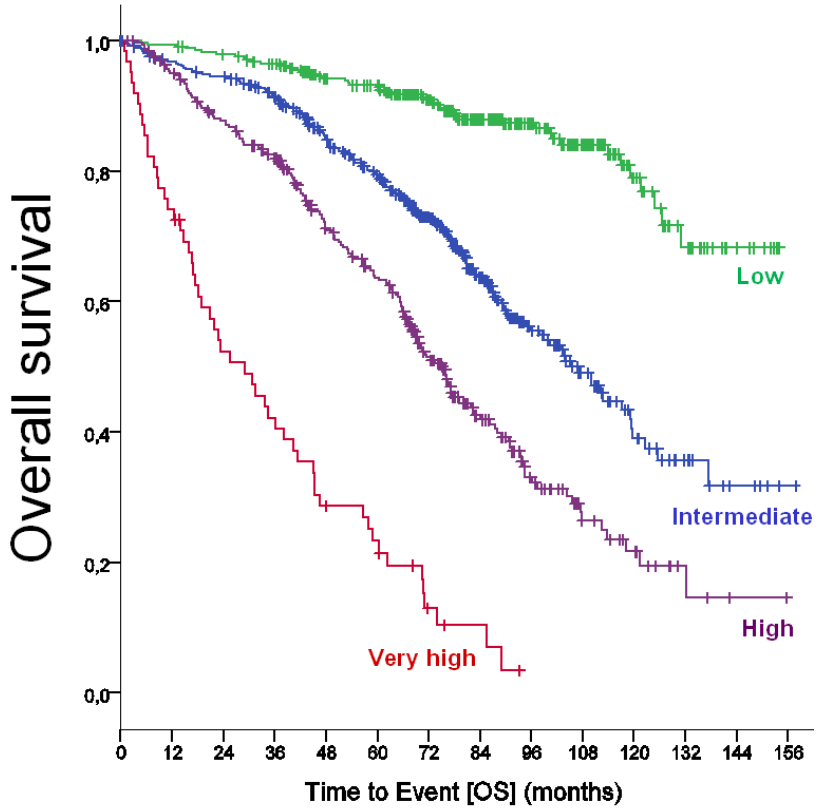
# Life expectancy (relative survival)



# Prognostication of survival of unselected CLL

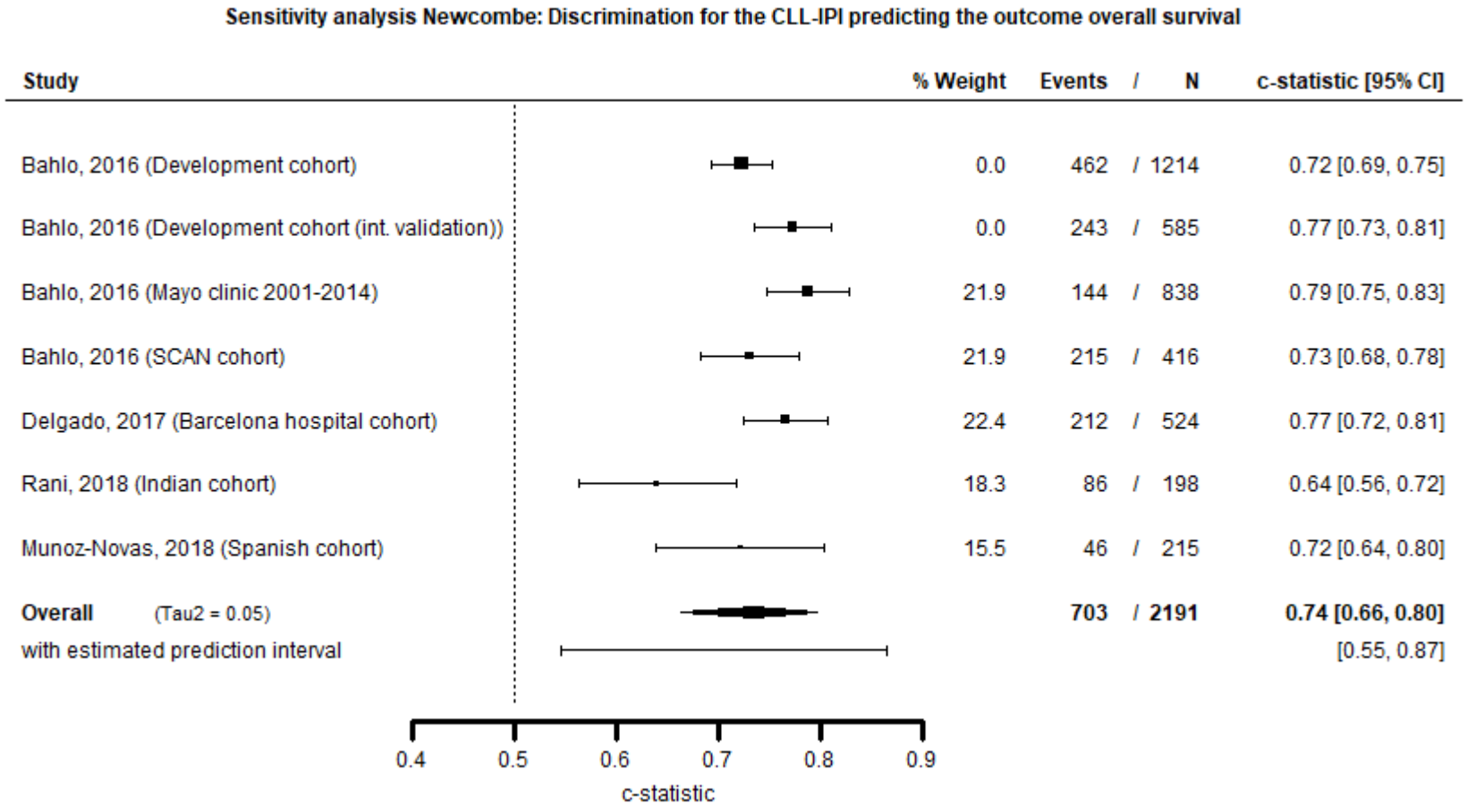
| Variable | Adverse factor | Coeff. | HR | Grading |
|---|---|---|---|---|
| *TP53* (17p) | deleted and/or mutated | 1.442 | 4.2 | 4 |
| *IGHV* status | Unmutated | 0.941 | 2.6 | 2 |
| B2M, mg/L | > 3.5 | 0.665 | 2.0 | 2 |
| Clinical stage | Binet B/C or Rai I-IV | 0.499 | 1.6 | 1 |
| Age | > 65 years | 0.555 | 1.7 | 1 |
| Prognostic Score | | | | 0 – 10 |

| Risk group | Score | Patients N (%) | 5-year OS, % |
|---|---|---|---|
| Low | 0 – 1 | 340 (29) | 93.2 |
| Intermediate | 2 – 3 | 464 (39) | 79.4 |
| High | 4 – 6 | 326 (27) | 63.6 |
| Very High | 7 – 10 | 62 (5) | 23.3 |



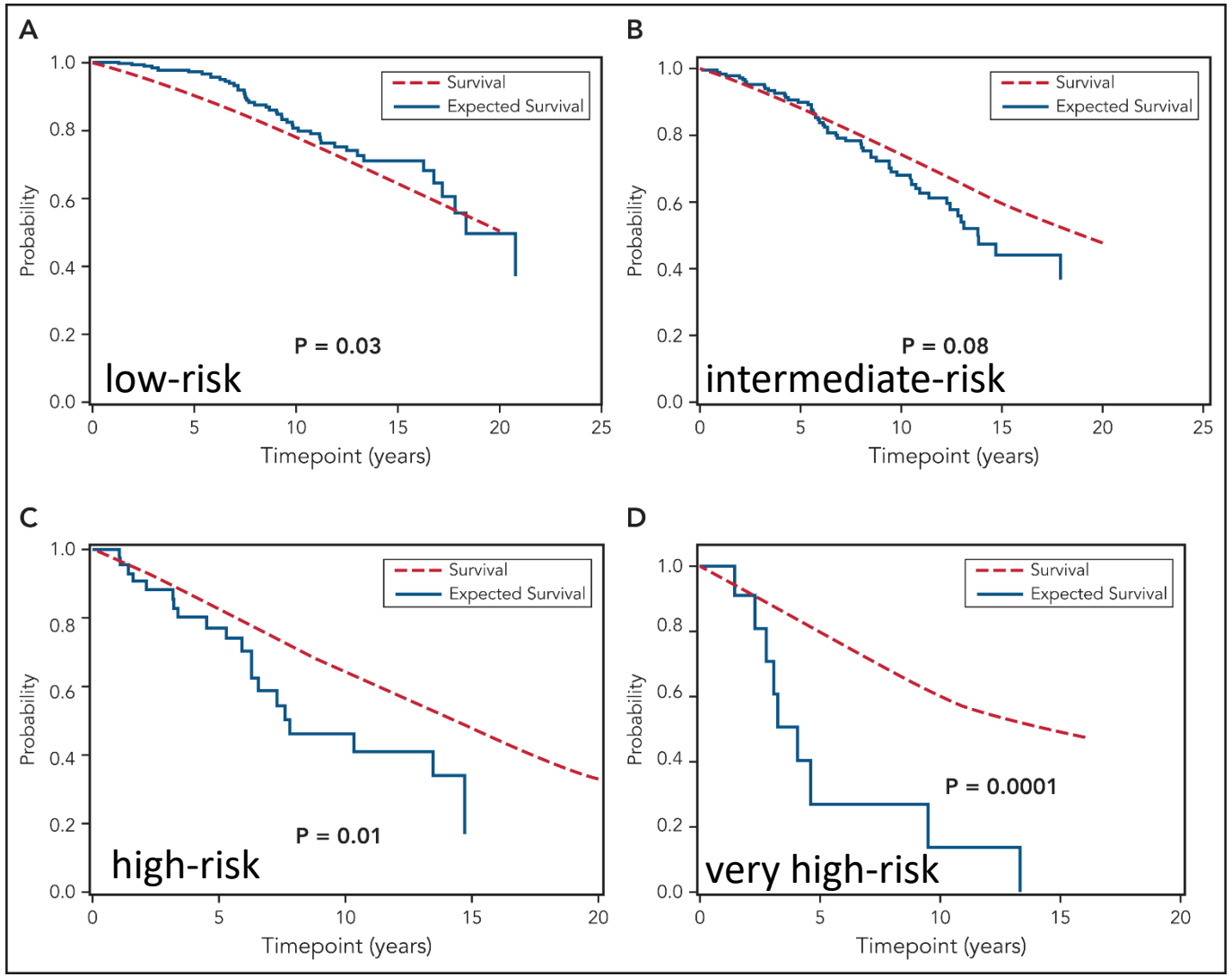

International CLL-IPI working group. Lancet Oncol 2016

# CLL-IPI is strongly validated at a ca. 70% accuracy




Kreuzberger N, Cochrane Database Syst Rev. 20200%

# Survival of Rai 0 CLL patients, according to the CLL-IPI risk score, relative to the general population



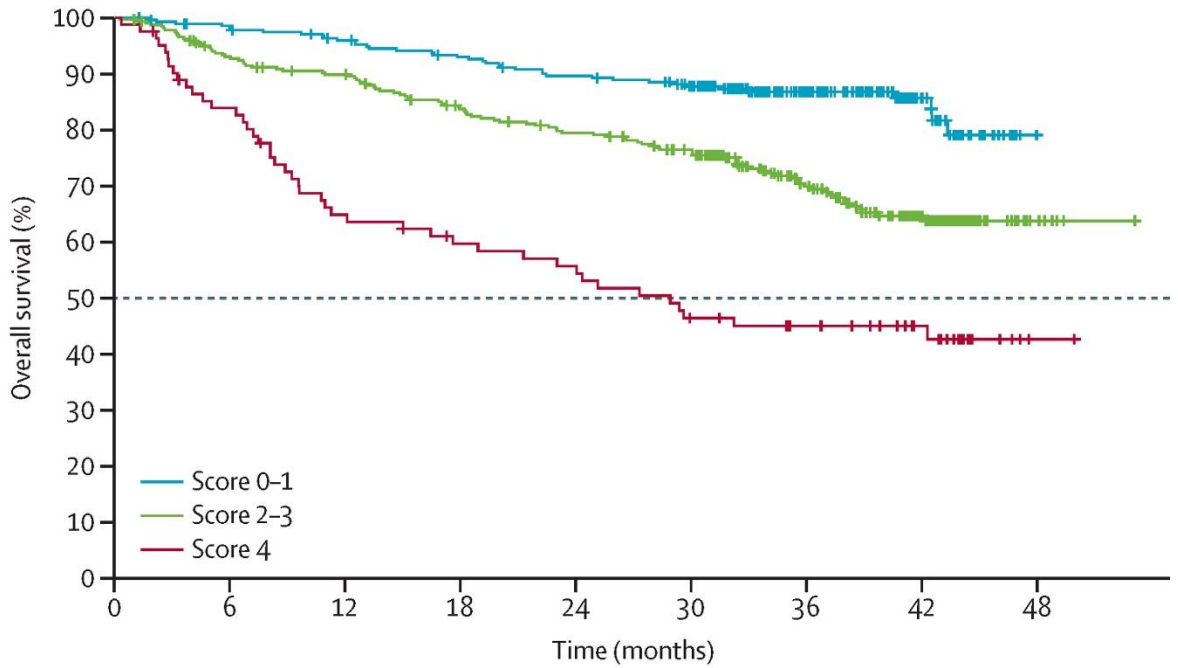

Parikh SA, Blood. 2021

# Prognostic scores adapted to the new treatment context

# Prognostication of survival after treatment ibrutinib: BALL score

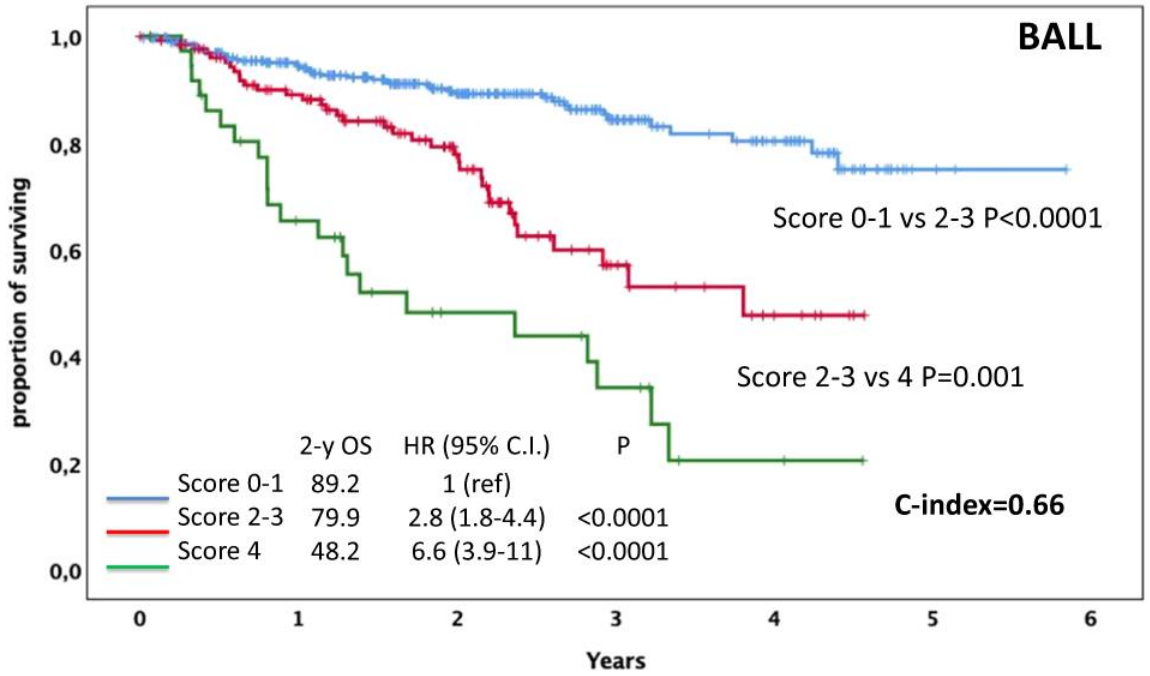
| Variable | Points |
|---|---|
| Hb <12 g/dl (M) or <11 g/dl (F) | 1 |
| B2M ≥5 mg/l | 1 |
| LDH >ULN | 1 |
| Time from last therapy <24 months | 1 |

| Risk group | Score |
|---|---|
| Low risk | 0-1 |
| Intermediate risk | 2-3 |
| High risk | 4 |




Soumerai JD, Lancet Haematol. 2019

# Validation of the BALL score in a RW cohort

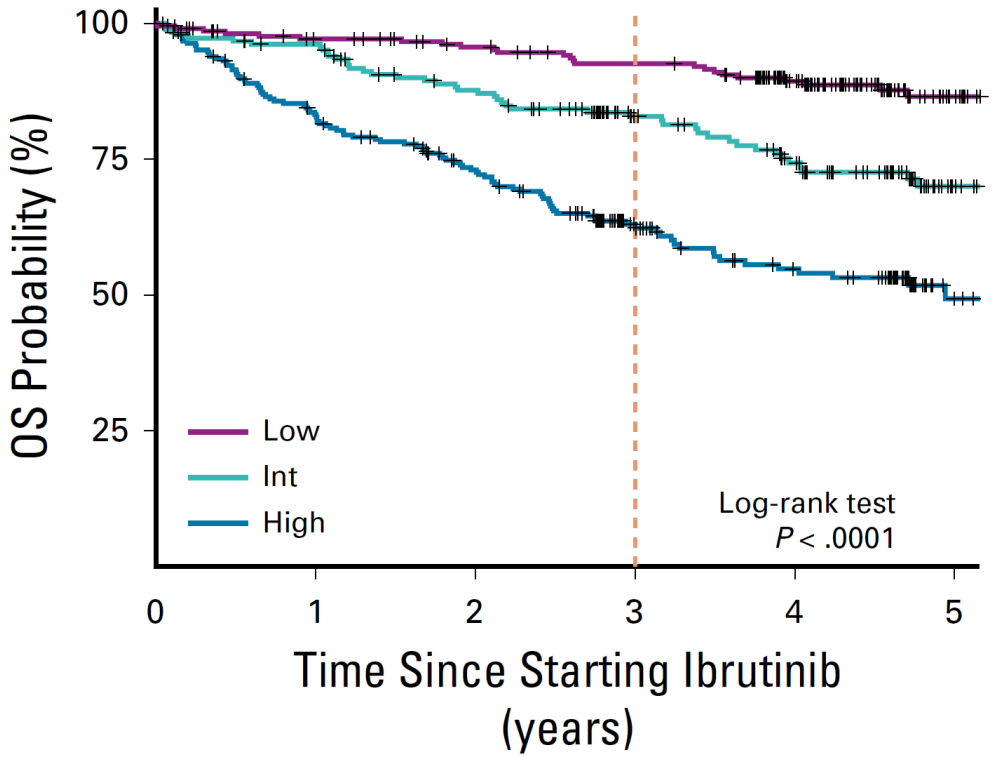



Gentile M, Leukemia. 2021

# Prognostication of survival after treatment ibrutinib: the 4-factor score

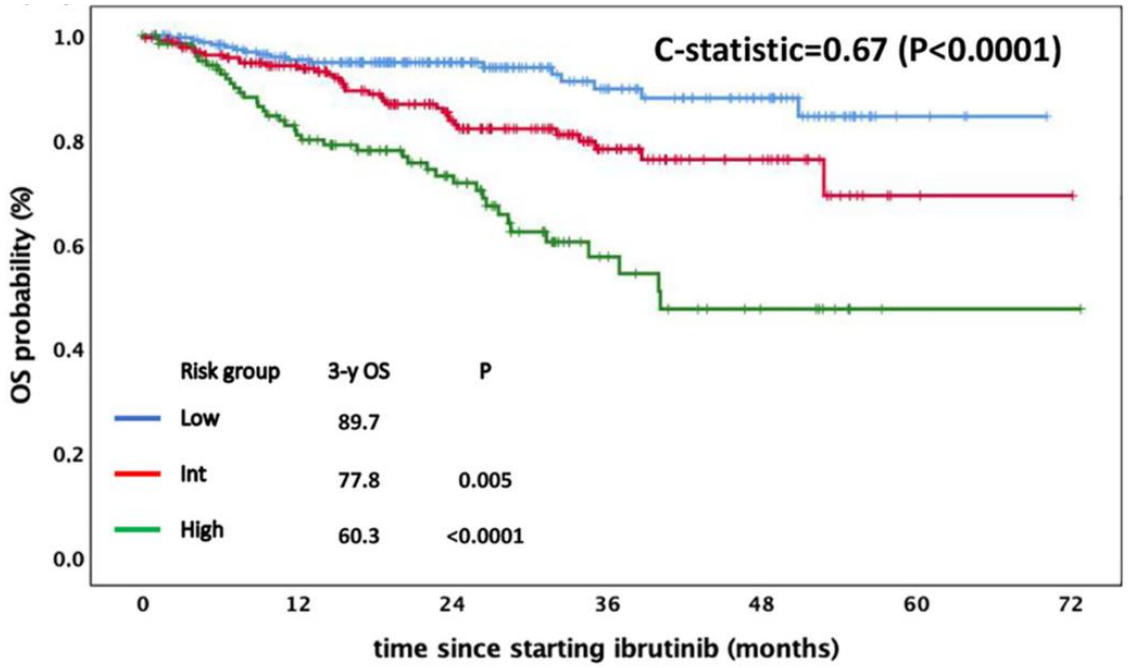
| Variable | Points |
|---|---|
| TP53 aberration | 1 |
| Prior treatment | 1 |
| B2M ≥5 mg/l | 1 |
| LDH ≥250 U/l | 1 |

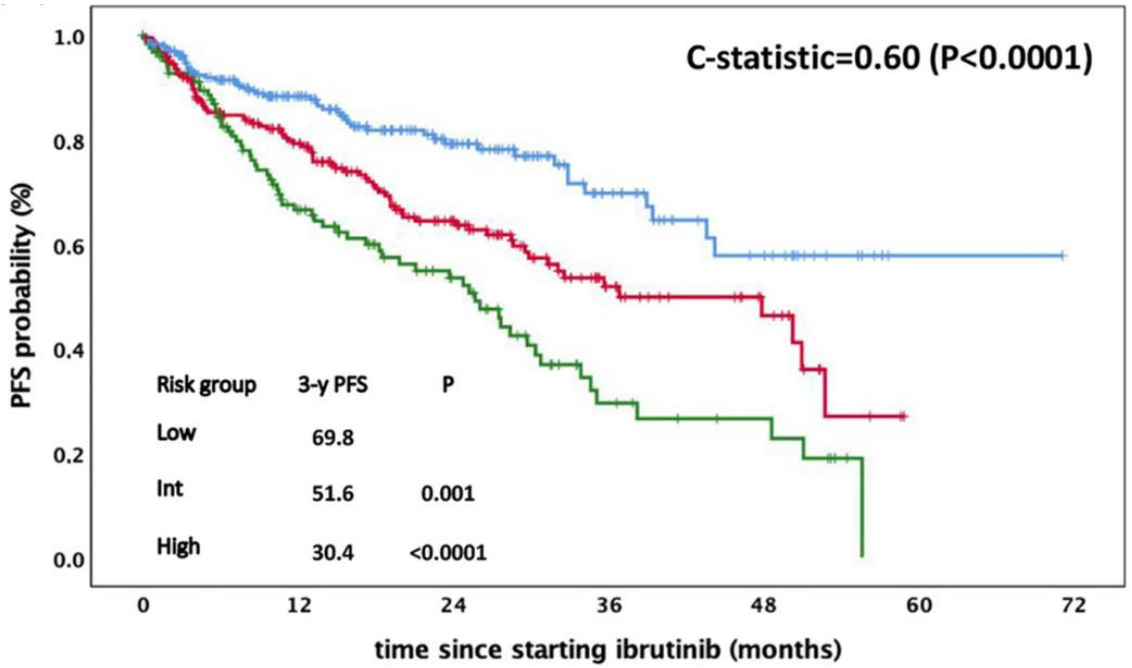
| Risk group | Score |
|---|---|
| Low risk | 0-1 |
| Intermediate risk | 2 |
| High risk | 3-4 |




Ahn IE, J Clin Oncol. 2020

# Validation of the 4-factor score in a RW cohort



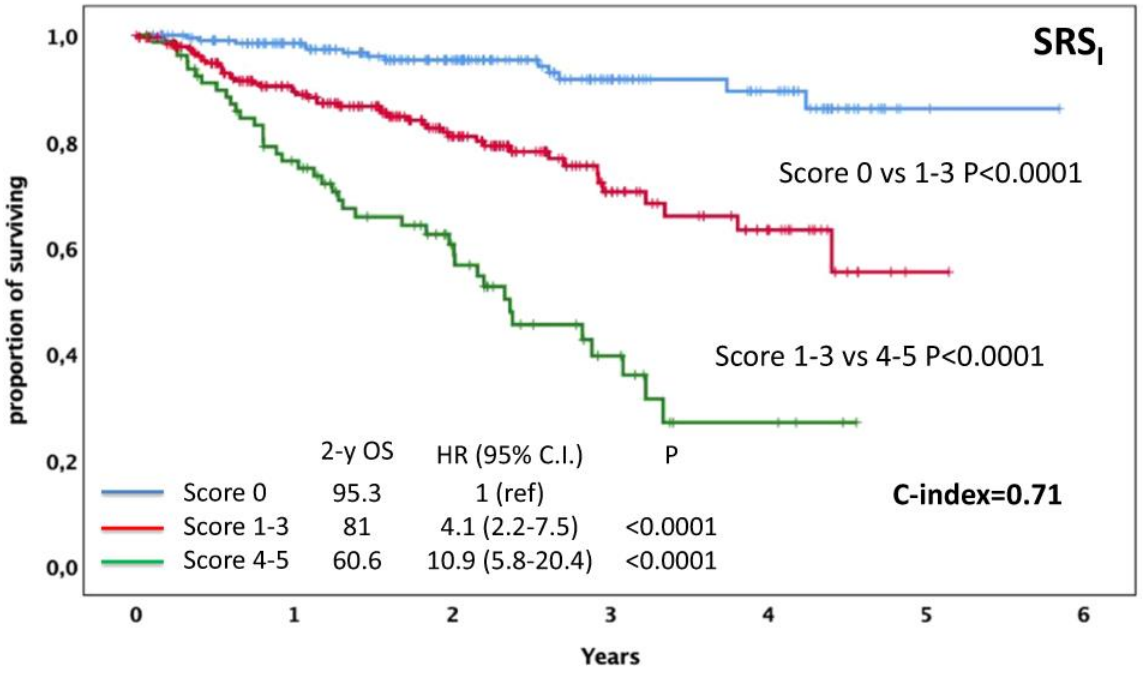




Morabito F, Am J Hematol. 2021

# Prognostication of survival after treatment ibrutinib: SRS score

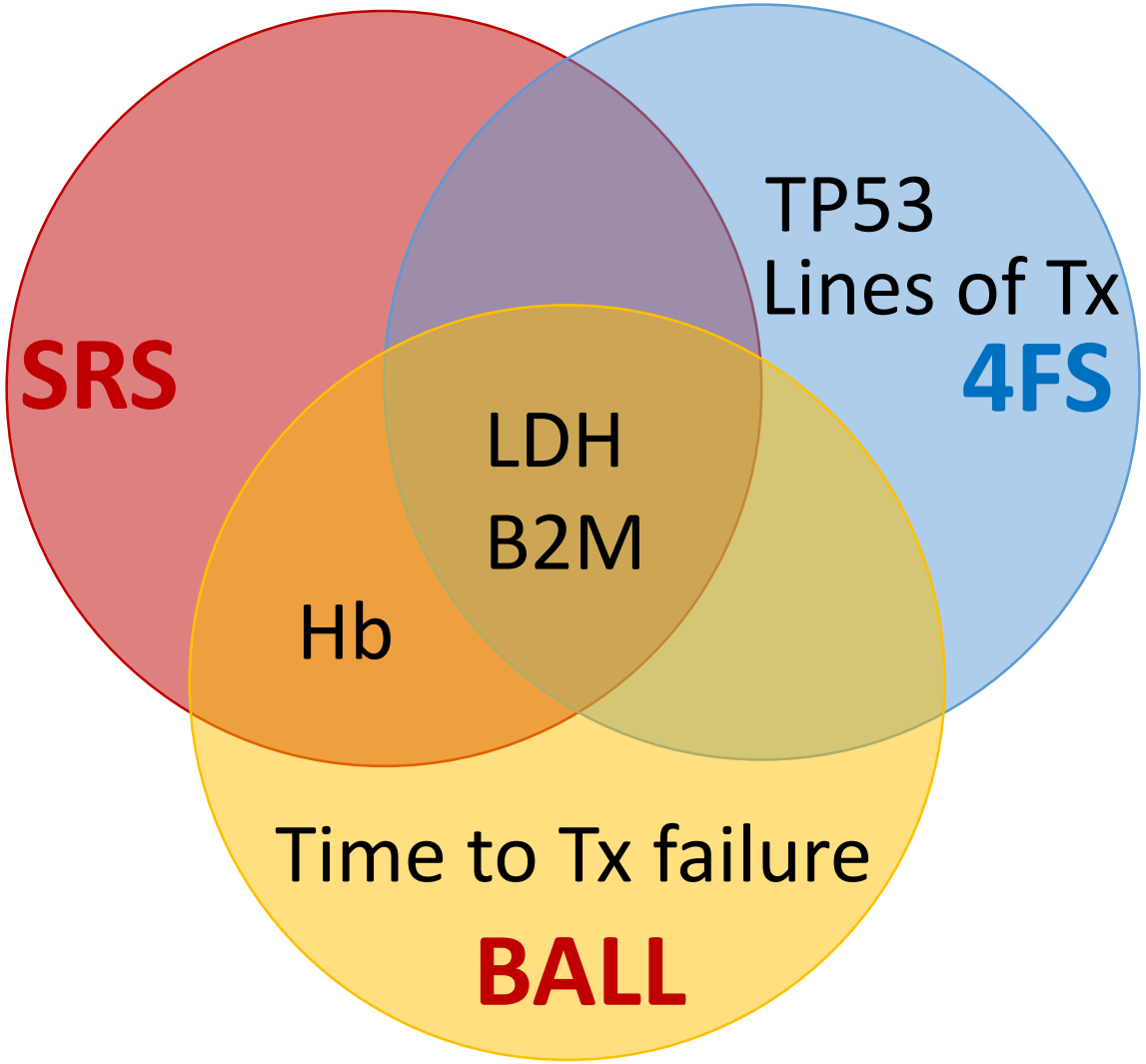
| Variable | Points |
|---|---|
| Hb <12 g/dl (M) or <11 g/dl (F) | 2 |
| B2M ≥5 mg/l | 1 |
| LDH >ULN | 2 |

| Risk group | Score |
|---|---|
| Low risk | 0 |
| Intermediate risk | 1-3 |
| High risk | 4-5 |




Gentile M, Leukemia. 2021

# What is the most robust biomarker?

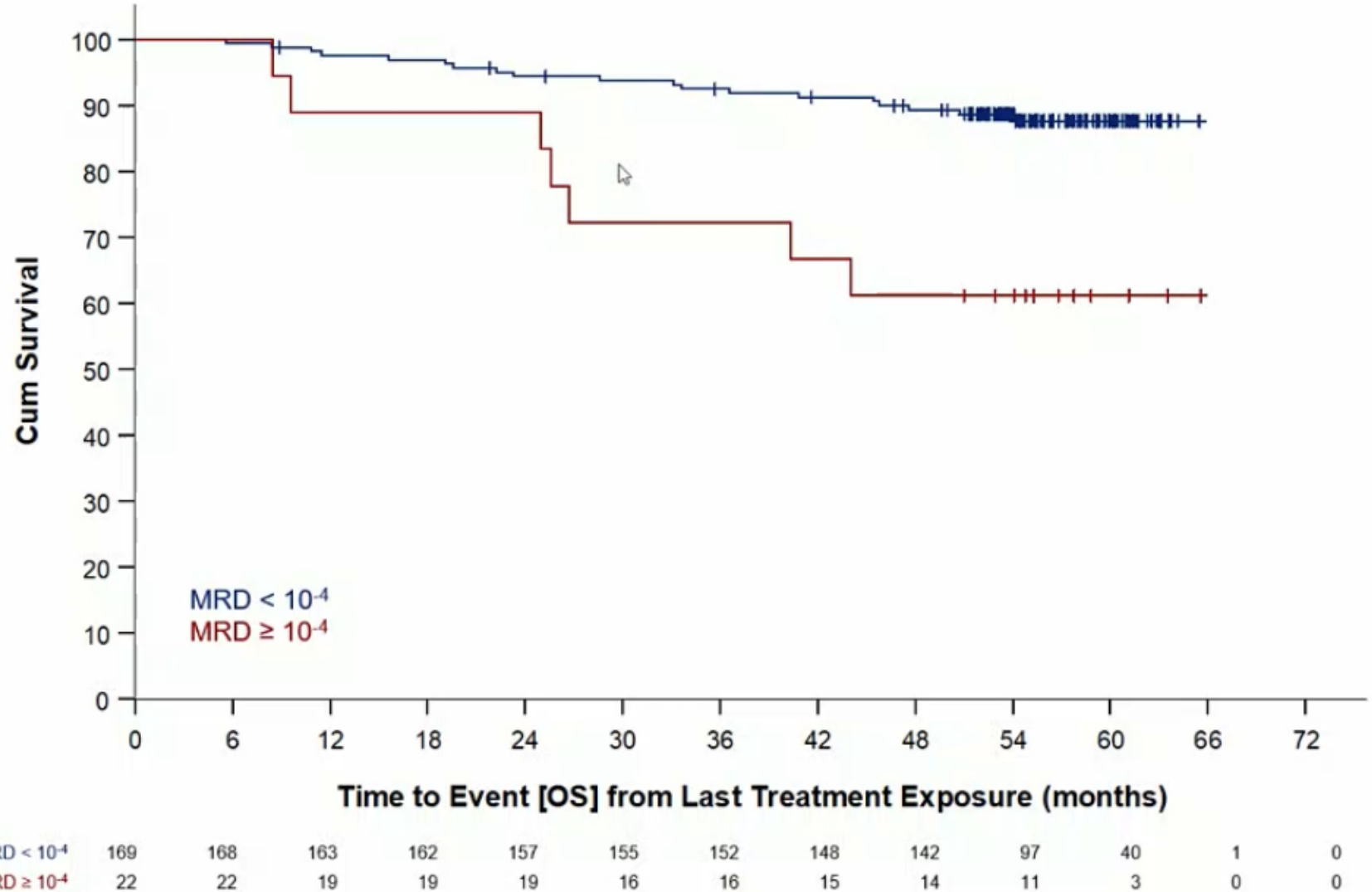



*IGHV* mutation status: not selected as independent variable

# What’s new?

# OS AFTER VEN-OBI ACCORDING TO MRD STATUS

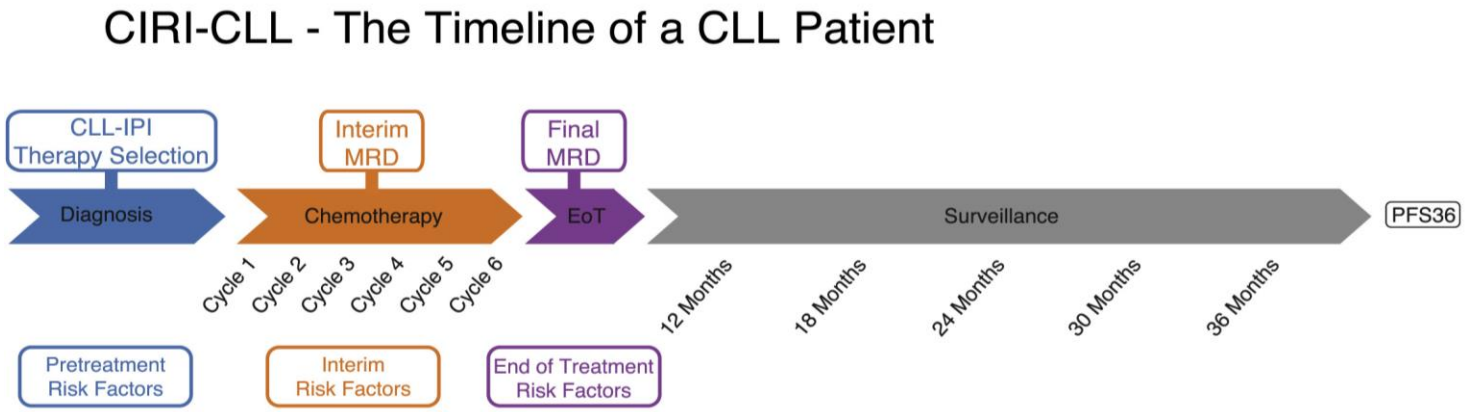
End of treatment MRD status in peripheral blood, by NGS

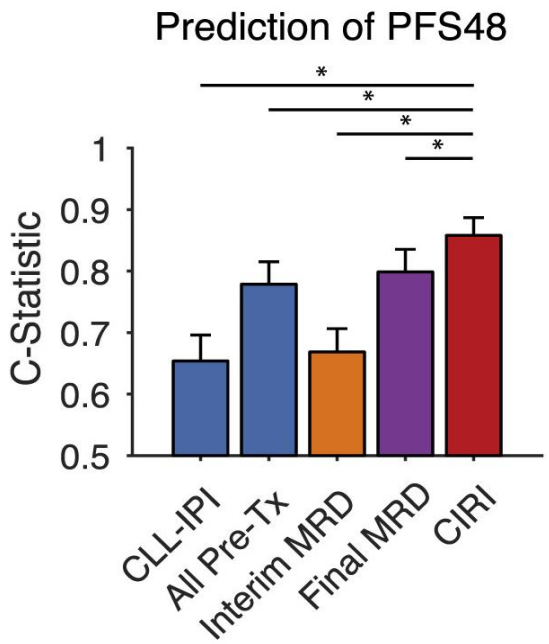


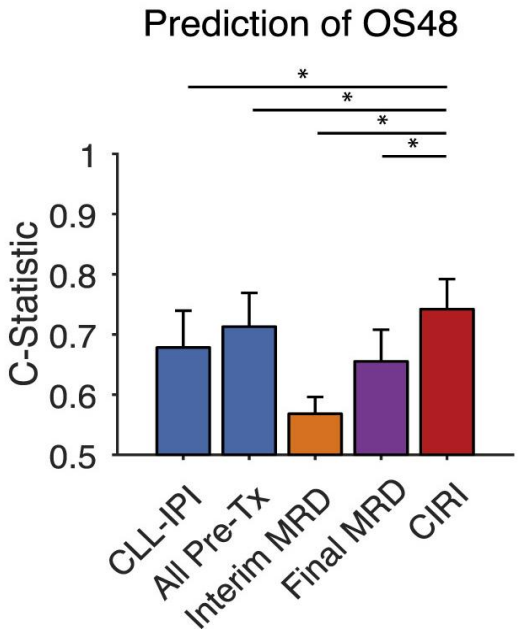

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MRD < $10^{-4}$ | 169 | 168 | 163 | 162 | 157 | 155 | 152 | 148 | 142 | 97 | 40 | 1 | 0 |
| MRD ≥ $10^{-4}$ | 22 | 22 | 19 | 19 | 19 | 16 | 16 | 15 | 14 | 11 | 3 | 0 | 0 |

Patients with MRD ≥$10^{-4}$ after Ven-Obi have **a shorter OS** than patients with MRD <$10^{-4}$, highlighting the need for dedicated MRD-guided approaches.

# Dynamic risk profiling using serial tumor biomarkers for personalized outcome prognostication




Kurtz DM, Cell. 2019

# Summary

- IPS-E for TTFT prognostication in early stage CLL
- CLL-IPI for OS prognostication in early stage CLL
- IGHV and *TP53* are no longer strong biomarkers in a pathway inhibitor Tx setting