




The young side of  
**LYMPHOMA**

gli under 40 a confronto

Milano, 14-15 aprile 2023

Linfoma della zona marginale: dalla definizione dei fattori prognostici al  
trattamento

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## Disclosures of Maria Elena Nizzoli

<b>Company name</b>	<b>Research support</b>	<b>Employee</b>	<b>Consultant</b>	<b>Stockholder</b>	<b>Speakers bureau</b>	<b>Advisory board</b>	<b>Other</b>
<b>No disclosure to declare</b>							

## Clinical case

- Man, **75 years** old. November 2021: swollen legs and mild abdominal pain. No B symptoms.
- **CT scan:** supradiaphragmatic and abdominal adenopathies (supraclavicular 5x3 cm, abdominal mass 10x14x16 cm, externa iliac 6x3 cm). No spleen enlargement.
- Mild anemia (12.2 g/dl), LDH elevation (315 mU/ml n.v <240)
- **18-FGD PET scan:** multiple adenopathies; abdominal mass SUV max: 6.8, supraclavicular SUV max 4.6.
- **Excisional LN biopsy:** presence of nodular infiltrate of small to medium size cells CD20+, CD5-, CD10-, bcl6-, bcl2+, CD23+, SOX11-, cyclin D1-, CD3-. Ki67 30%. Residual lymphoid follicles. Scattered large cells.
- **Bone marrow biopsy:** interstitial lymphoid infiltrate 40% CD20+, CD5-, CD23+, cyclin D1-, CD3-

### **NMZL, stage IV, FLIPI 4 (high)**

- **Comorbidities:** uncontrolled hypertension, hypertensive cardiomyopathy, ascending aortic aneurism (4.8 cm)



## Systemic treatment of symptomatic MZL : current scenario

### 1<sup>st</sup> line treatment

EMZL → **R-C1b** (IELSG 19), mainly **R-bendamustine** (Salar A. Blood 2017)

NMZL → **FL-like R-cht**, frequently R-bendamustine

SMZL → **Rituximab** single agent

**ORR 80-95%, CR 55-80%, 5y PFS 70-87%**

- **Obinutuzumab?** Not superior to rituximab-based therapies (GALLIUM study)
- **Maintenance?** Improved PFS but not OS (IELSG38 in EMZL, MAINTAIN study in SMZL, NMZL)

## Clinical case

- **R-Bendamustine 90 mg/m<sup>2</sup>**
- **April 2022 - Intermediate CT scan after 4 cycles:** reduction of both supradiaphragmatic and abdominal adenopathies (supraclavicular 2.5x1.4 cm vs 5x3 cm, abdominal mass 8x4.5x16 cm vs 10x14x16 cm, externa iliac 4x1.8 vs 6x3 cm). No more lower lib oedema ->**PR**
- **June-July 2022 - Final restaging after 6 cycles: PD**  
swollen legs, abdominal pain  
CT scan: supraclavicular 5.3x3 cm vs 2.5x1.4 cm, abdominal mass 12x10x16cm vs 8x4.5x16 cm, externa iliac 7x3 vs 4x1.8 cm  
PET scan: DS 5 (SUV max 5-10)
- **BM:** MZL infiltrate 25-30%
- **Excisional biopsy:** MZL, ki67 40%



## Systemic treatment of symptomatic MZL : current scenario

### R/R disease

- No standard treatments
- Individualized approach based on prior treatments, duration of remission, comorbidities
- Refractory disease and early relapse, a challenging setting
- Debatable role of autologous stem cell transplantation

### → New therapies

- Few approved drugs
- Available data mainly from phase 2 studies in indolent NHL

## New therapies

- BTK inhibitors
- Rituximab-lenalidomide
- PI3K ~~in~~hibitors
- moAbs
- biAbs
- CAR-T

## BTK inhibitors in r/r MZL

Drug	Trial	Setting	Pts n°	ORR	CR	mPFS	AEs	Ref.
<b>IBRUTINIB</b> 560 mg/d <span style="border: 1px solid red; padding: 2px;">648</span>	Phase 2 PCYC-1121	1+ prior tp	63	58%	10%	15.7m	Gr. ≥3: 71%	Noy A Blood adv 2020
<b>ACALABRUTINIB</b> 100 mg BID	Phase 2 ACE-LY-003	1+ prior tp	43	53%	13%	27.4m	Gr. ≥3: 40%	Strati P. BJH 2022
<b>ZANUBRUTINIB</b> 160 mg BID <span style="border: 1px solid red; padding: 2px;">EMA approved</span>	Phase 2 MAGNOLIA	1+ prior tp	68	68.2%	25.8%	NR (24mPFS 45%)	Gr. ≥3: 48%	Opat S. ASH 2022



## Rituximab-lenalidomide (R2) in r/r MZL

**FDA approved**

Subgroup analysis of two main studies:

- AUGMENT (R2 vs R-placebo, fixed duration 12m)
- MAGNIFY (R2 fixed duration 12m followed by 1:1 randomization R vs R2 maintenance for 18m)

**ORR 65-68%, CR 29-38%, no improvement in PFS**

## Clinical case

- **R-Gemox**
- **Oct-Nov 2022 PD** during R-Gemox: CT scan progression, abdominal pain + **AIHA** followed by **SARS-COV2** infection.
- **VCR bolus + PDN 1 mg/kg/d**
- **December 2022: Ibrutinib 560 mg/d** and PDN decalage
- **March 2023** CT scan: **PR**, blood tests: Hb 13.5 g/dl, mild thrombocytopenia, normal Wbc count.



## Antigen targeting agents in MZL

### Monoclonal Ab

- TAFASITAMAB (CD19, ADCC, ADCP)
- LONCASTUXIMAB (CD19, ADC)

### Bispecific Ab(CD3-CD20)

- EPCORITAMAB
- MOSUNETUZUMAB
- ODRONEXTAMAB

- Few preliminary data in phase 1-2 studies
- Towards combination therapies

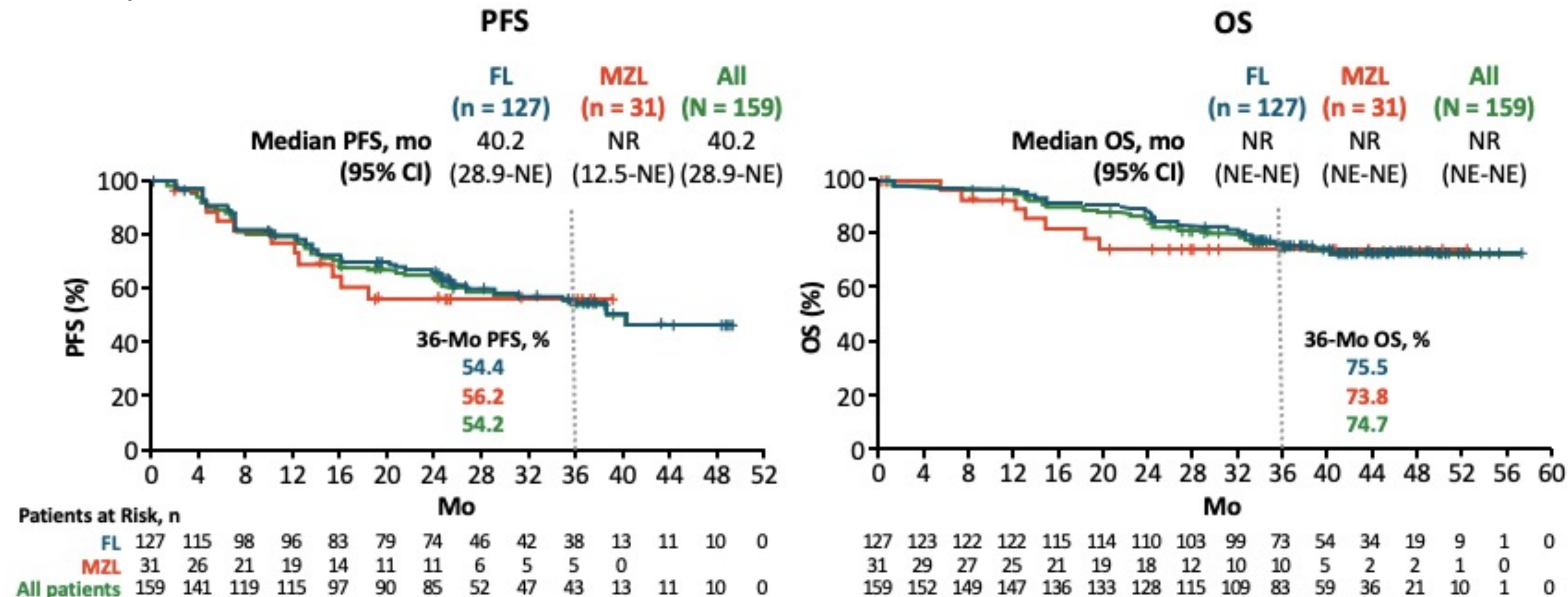
## Antigen targeting agents in MZL

### CAR-T: Axi-cel (ZUMA 5 trial)

Phase 2 trial, Axi-cel in r/r FL/MZL after  $\geq 2$  prior tp

24 r/r MZL, 3 median prior therapies, mFU 40.5 months.

**ORR 83%, CR 63%, mDOR and mPFS not reached**



Jacobson CA. Lancet 2022, Neelapu SS ASH 2022



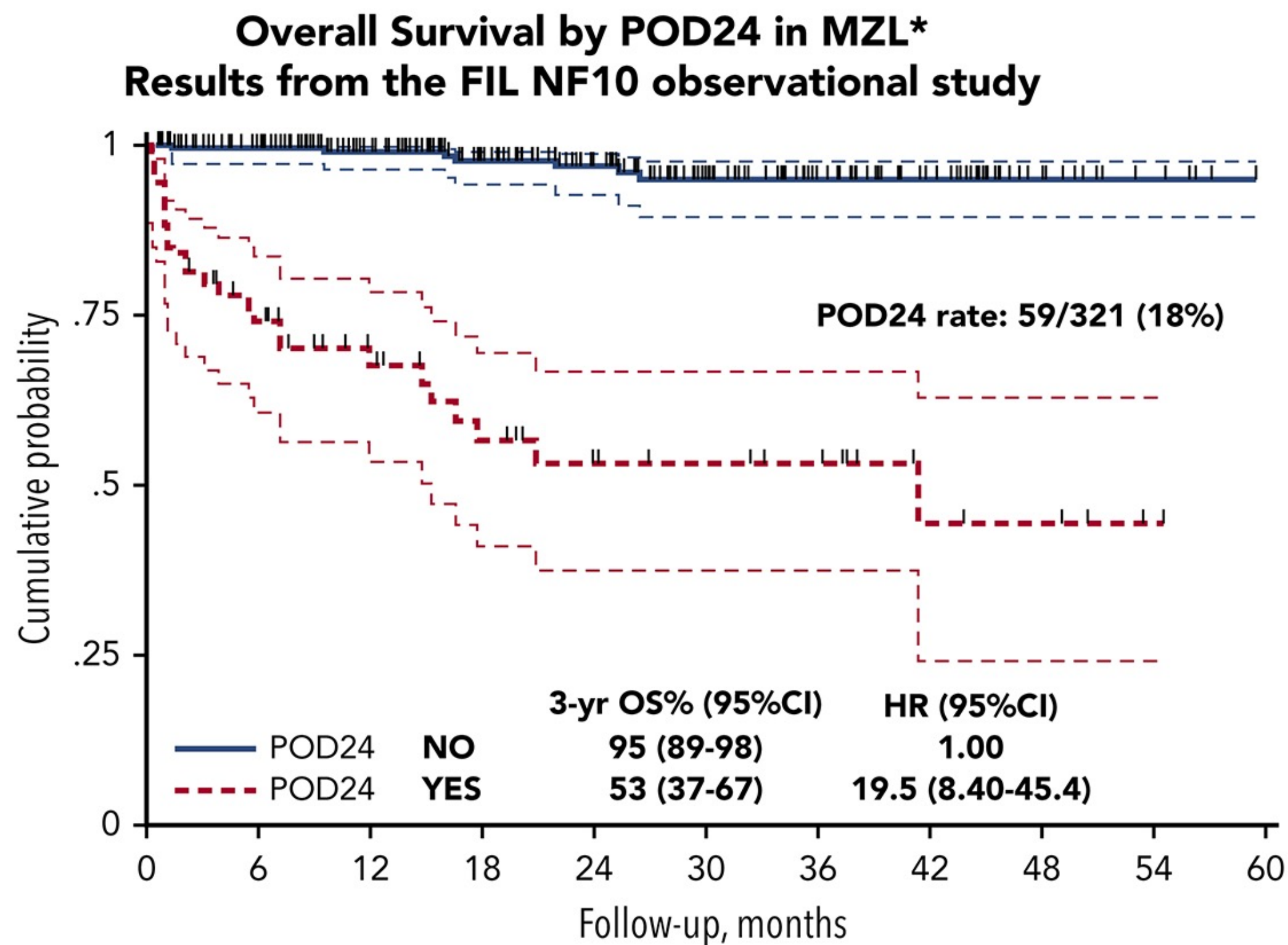
## Possible future scenario

- Several available options with different efficacy and safety profile
- Heterogeneous needs: toxicity concerns in low-risk long-term survivors  
efficacy concerns in high-risk patients

Need for proper identification of high-risk patients



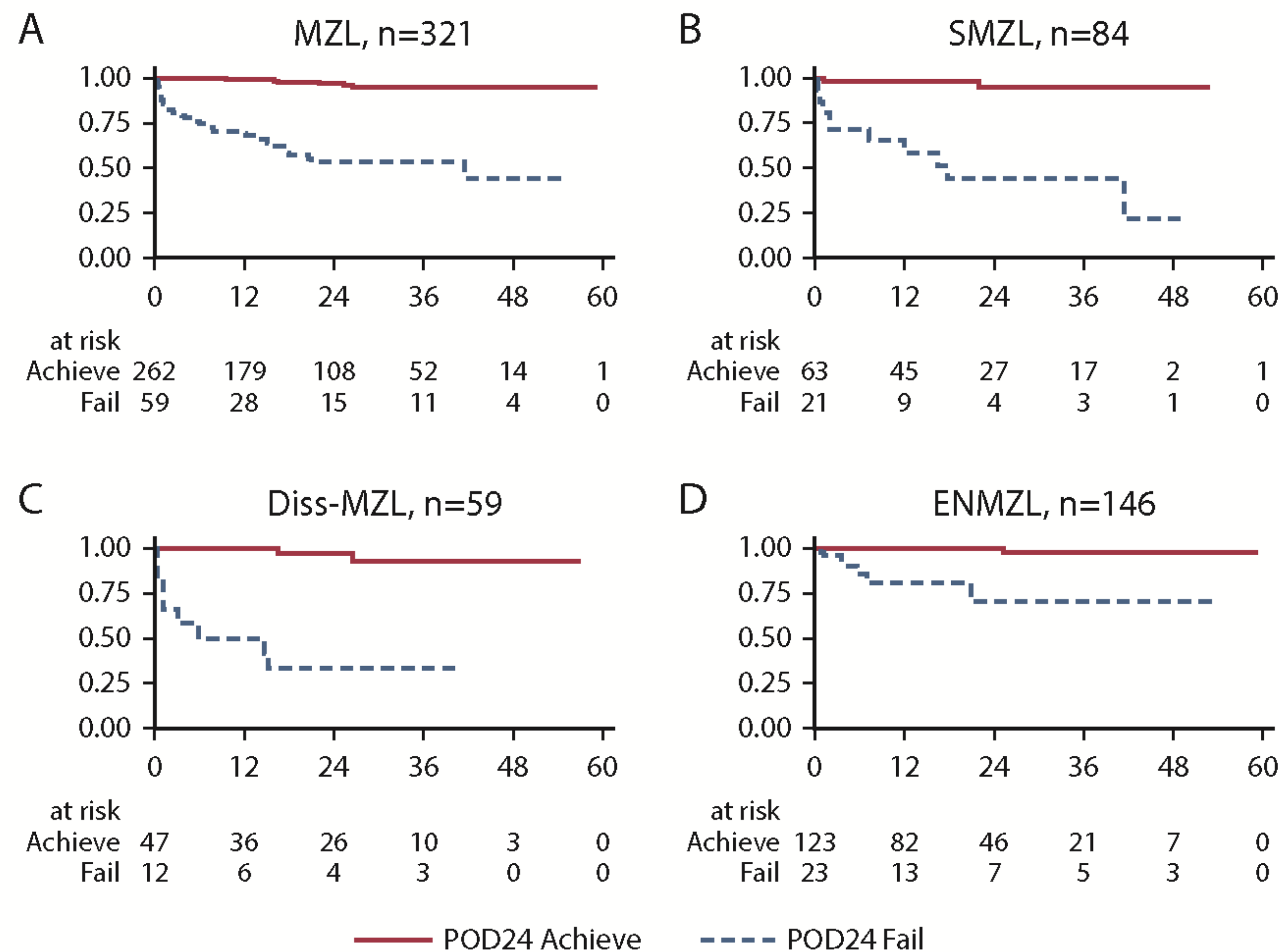
## Inferior outcome of early progressors: POD24 in FIL-NF10



Patients at risk

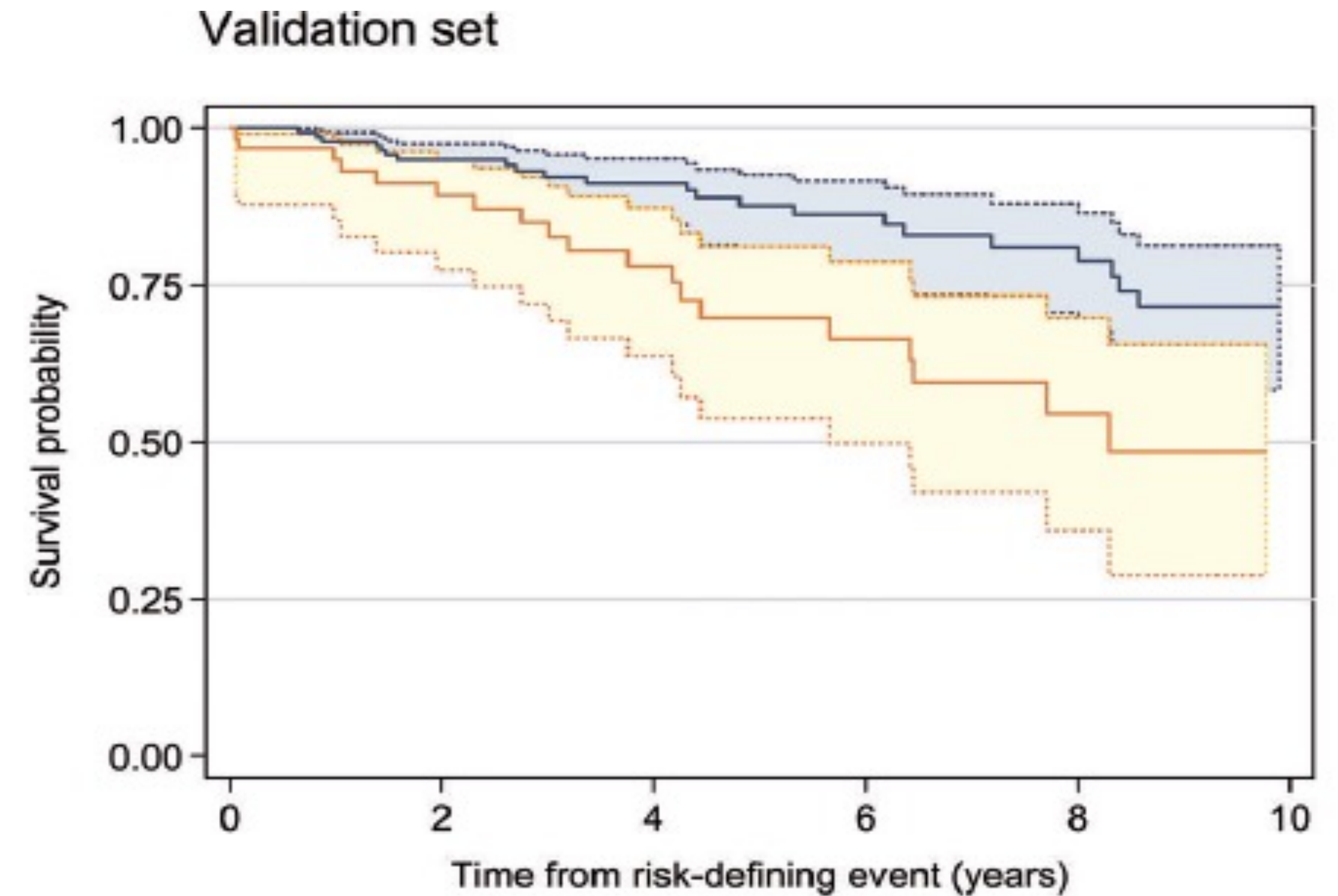
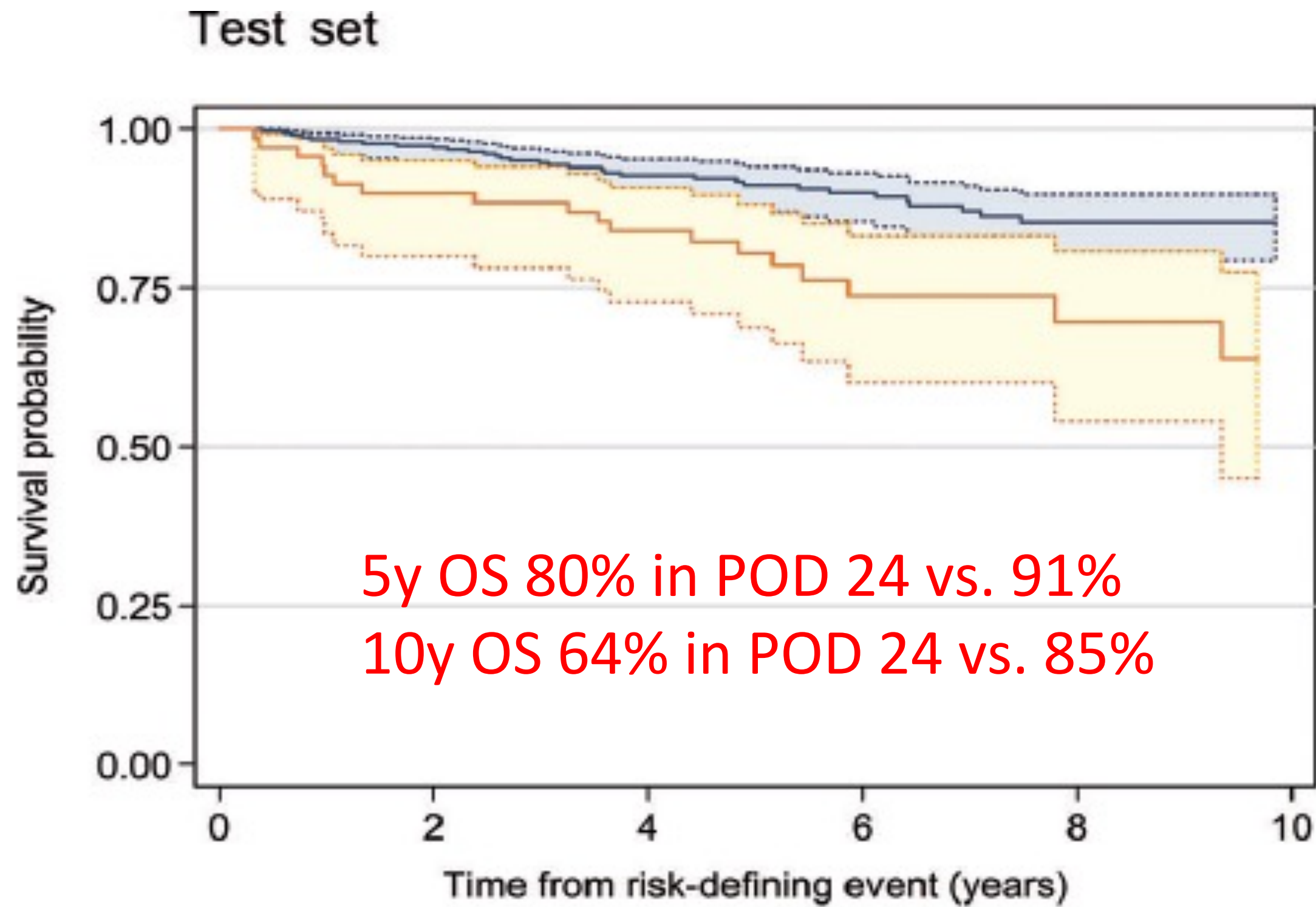
	0	6	12	18	24	30	36	42	48	54	60
POD24 No	262	224	179	138	108	74	52	33	14	7	1
POD24 Yes	59	40	28	20	15	13	11	5	4	1	0

\*Only patients who received systemic therapy within three months from diagnosis were included  
POD24; progressive disease within 24 months from diagnosis. MZL, Marginal Zone Lymphoma





## Inferior outcome of early progressors: POD24 in IELSG-19



Number at risk

— No early POD	315	298	211	142	64	1
— Early POD	69	62	54	26	17	8

Number at risk

— No early POD	160	121	84	55	36	25
— Early POD	64	44	31	20	9	6

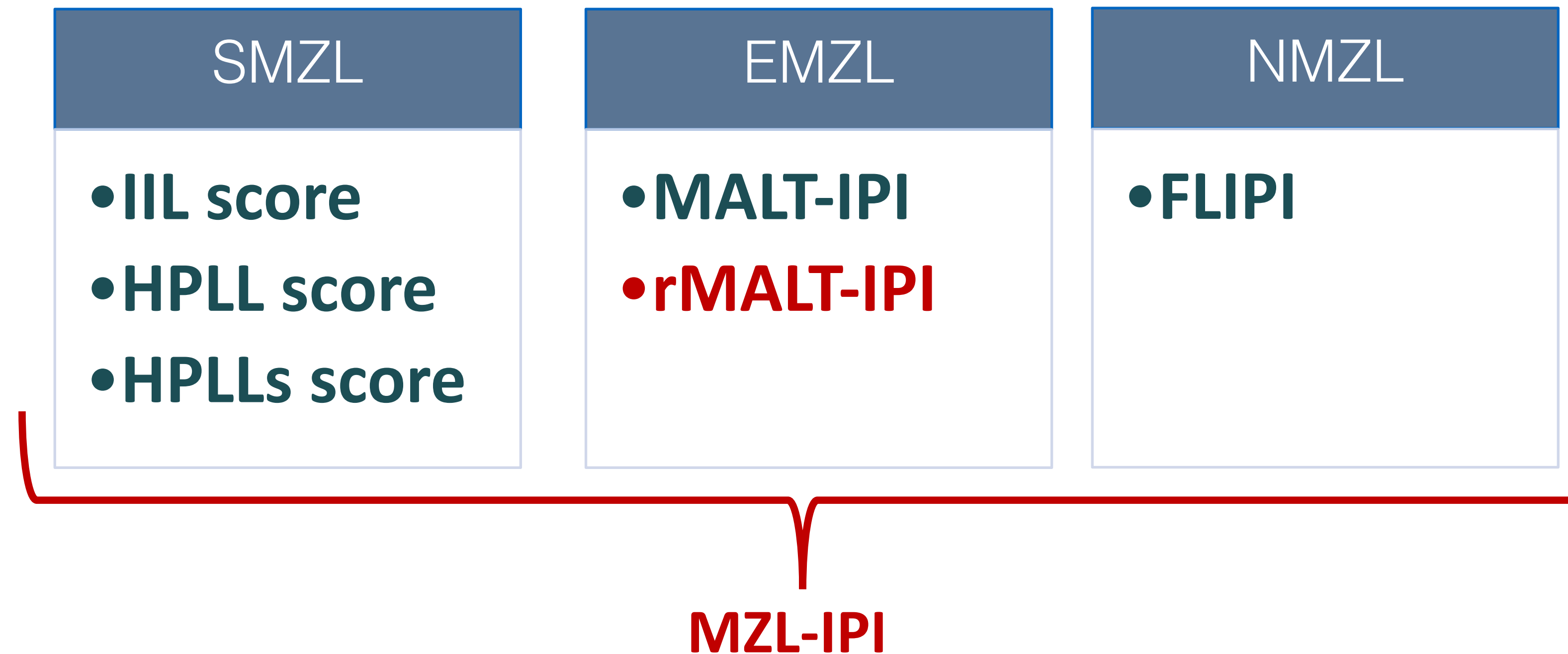
## Prognostic scores in MZL

SMZL	EMZL	NMZL
<ul style="list-style-type: none"><li>• IIL score</li><li>• HPLL score</li><li>• HPLLs score</li></ul>	<ul style="list-style-type: none"><li>• MALT-IPI</li></ul>	<ul style="list-style-type: none"><li>• FLIPI</li></ul>

1. MZL subtype specificity
2. Clinical variables (e.g Age, Hb, plt, LDH elevation)
3. Potential loss of predictive power with different induction regimens
4. Difficult use in clinical trials involving all subtypes of MZL

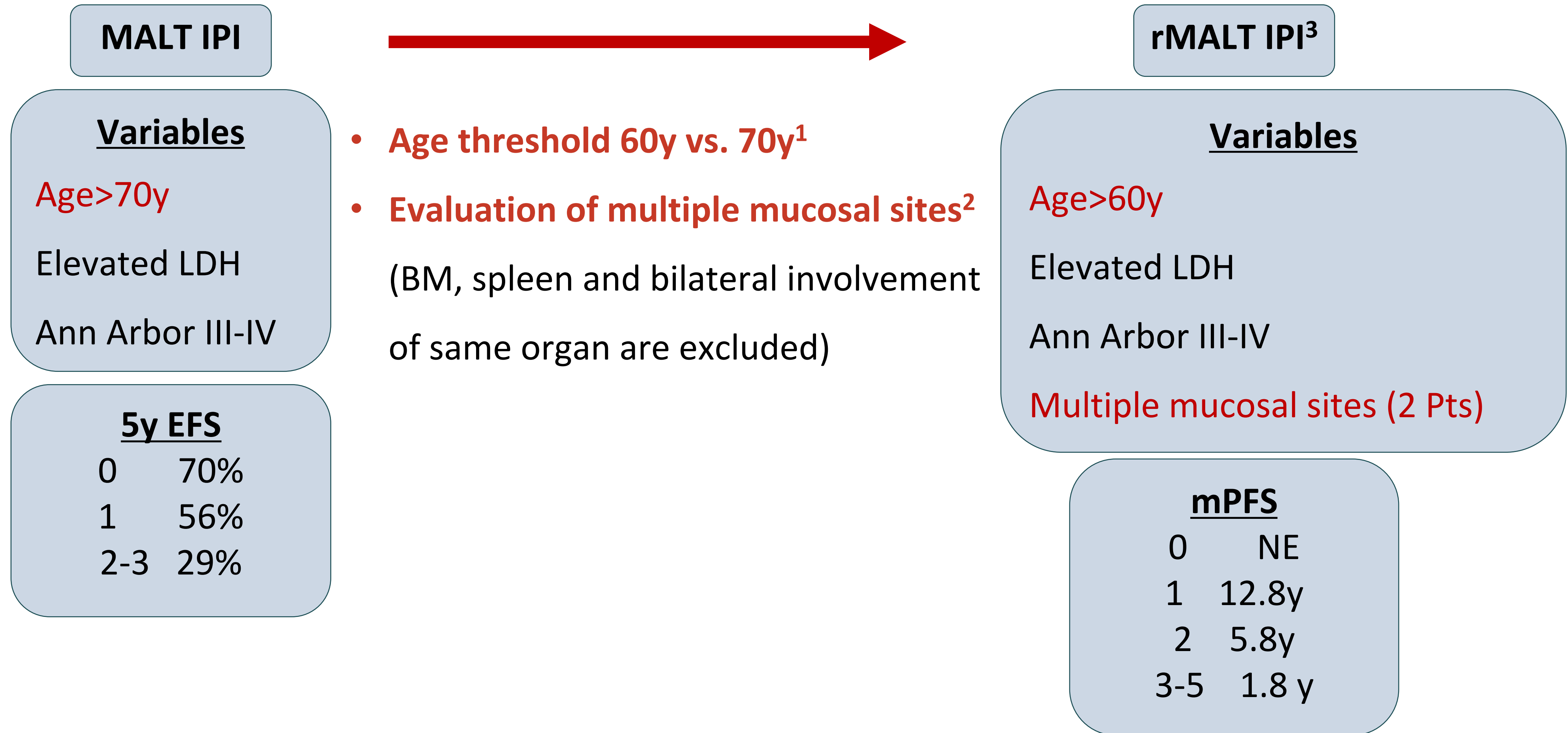


## Prognostic scores in MZL



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## Refined identification of high risk EMZL patients: from MALT-IPI to rMALT-IPI



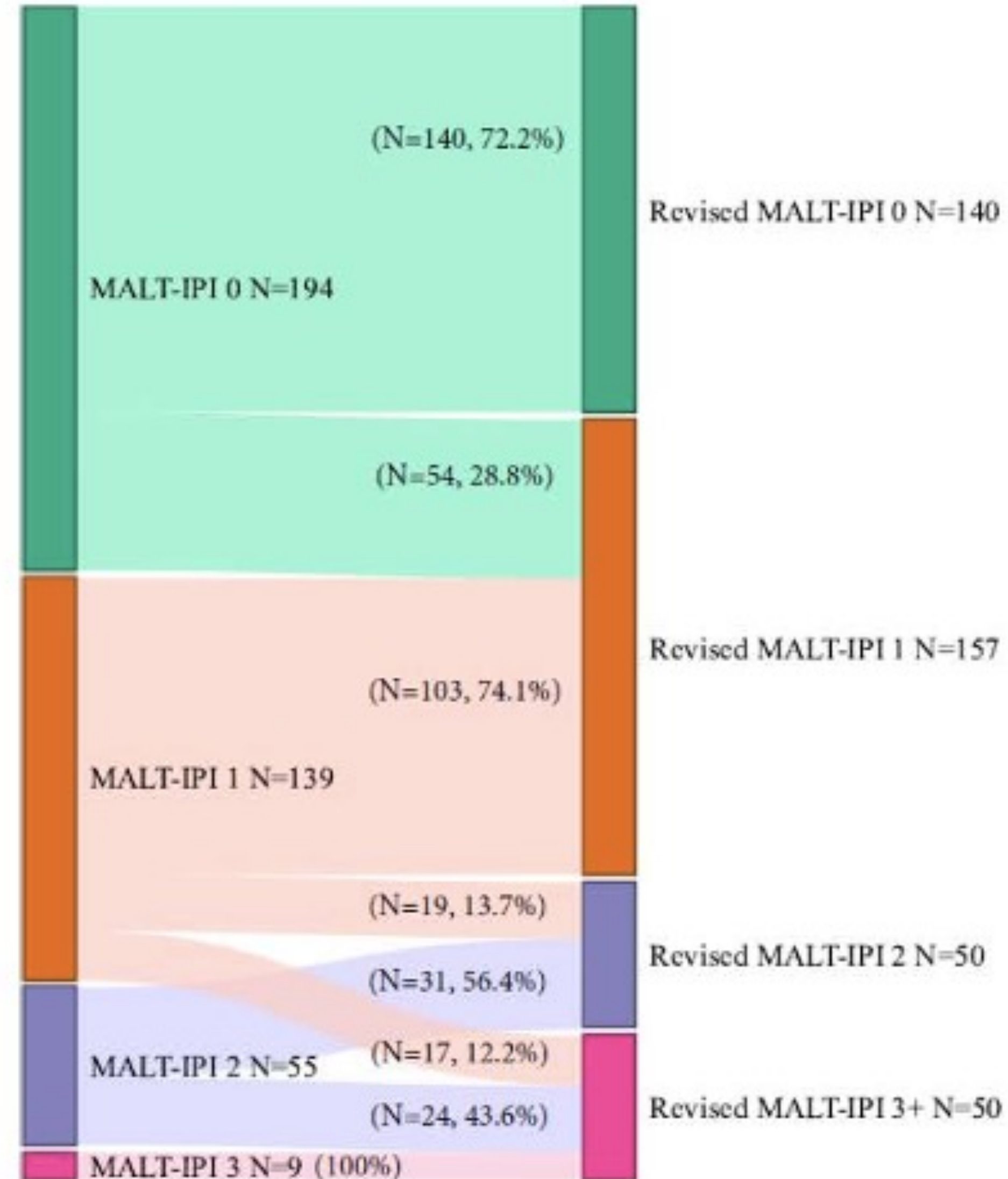
1. Alderuccio JP Cancers 2021; 2. Alderuccio JP BHJ 2019 3. Alderuccio JPAJH 2022



## Revised MALT-IPI

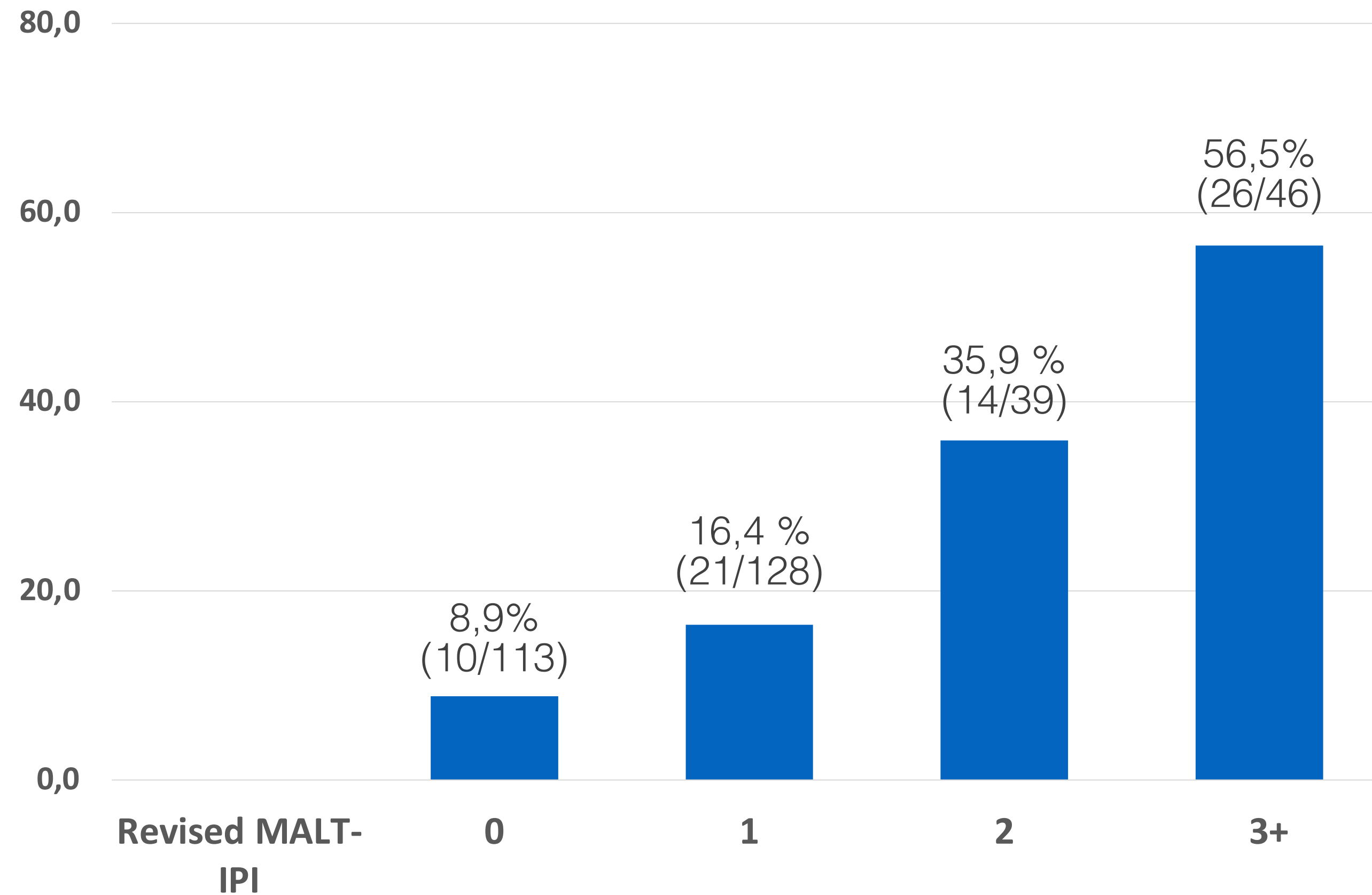
- Enriched high-risk group
- MALT IPI high risk: **17%**
- rMALT-IPI high risk (medium-high + high): **26%**

**90% experienced POD24** →



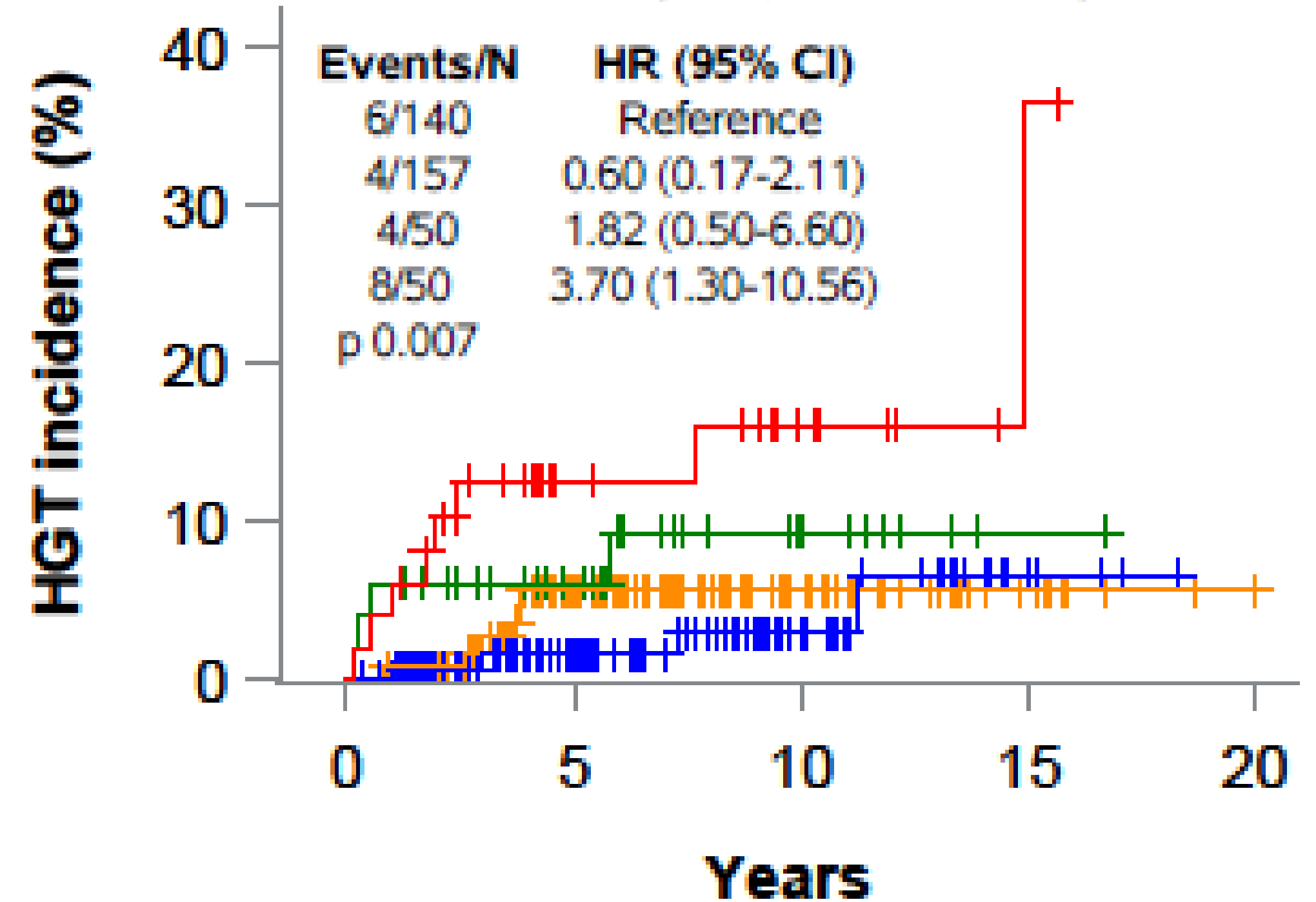
## Revised MALT-IPI

### Prediction of POD24



### Prediction of transformation

#### A. Revised MALT-IPI (UM, 22 events)



Alderuccio JP et al AJH 2022





## MZL-IPI

- Prognostic score for the entire spectrum of MZL
- Originated from FFL retrospective study NF10 and externally validated
- Variables: elevated LDH, cytopenias, M> subtype (NMZL or dissMZL)

## Take home message

1. Prognostic stratification does not currently influence treatment choice
2. New prognostic scores need to be validated according to new therapeutic approaches and may be enriched with genetic/radiomic biomarkers
3. Reliable risk stratification tools are awaited both in trial design and in clinical practice






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Slides aggiuntive



## Prognostic scores in SMZL: IIL score

### IIL score

#### Variables

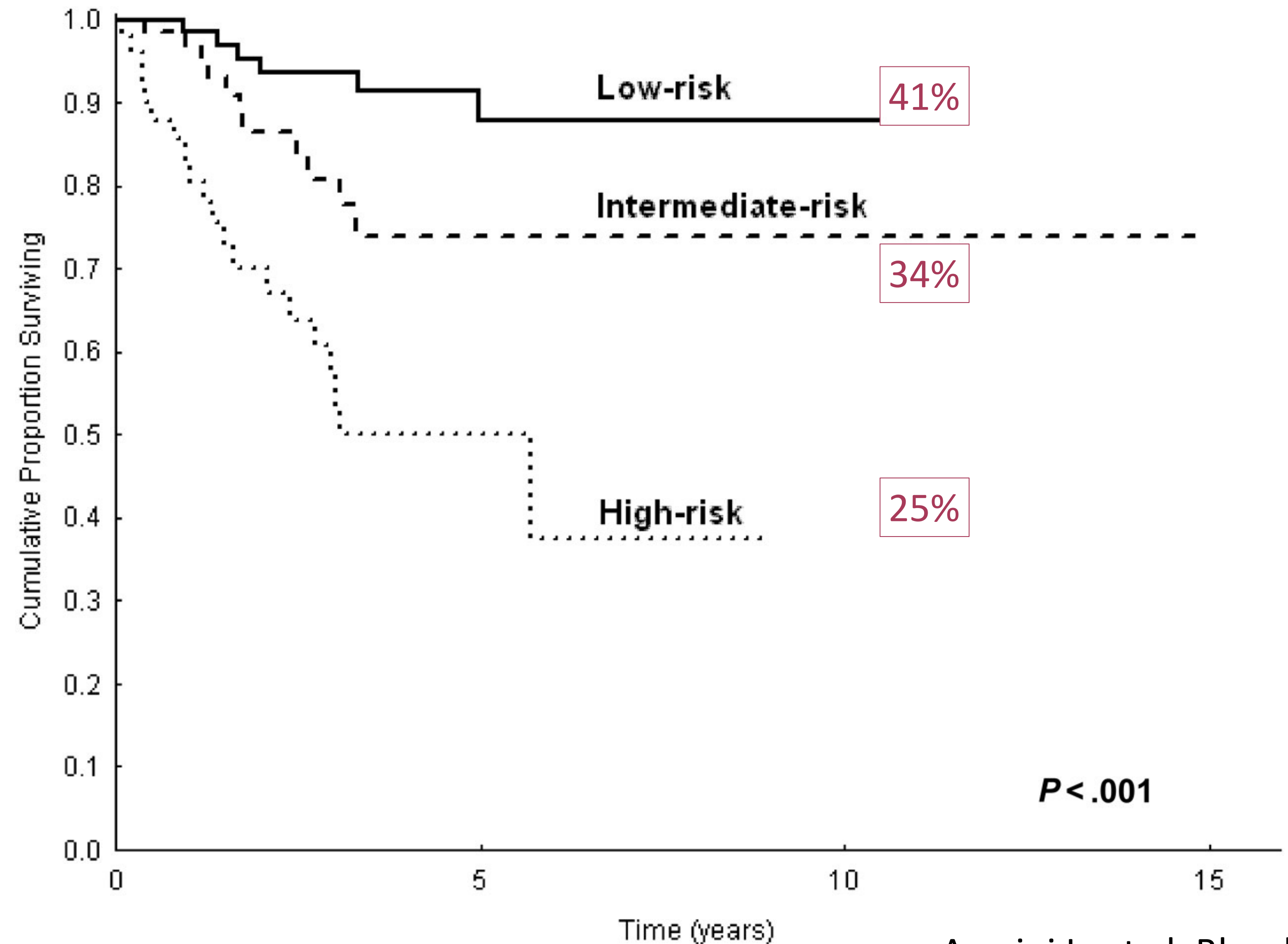
Hb < 12 g/dl  
Elevated LDH  
Albumin < 3.5 g/dl

#### Score

0 low risk  
1 intermediate risk  
2-3 high risk

#### 5y OS

0 83%  
1 72%  
2-3 56%



Arcaini L. et al, Blood 2006

## Prognostic scores in SMZL: HPLLs

### HPLL score<sup>1</sup>

#### Variables

Hb level

Plt count

LDH elevated

Extrahilar Lymphadenopathy

#### 5y LSS

A 94%

B 78%

C 69%

### HPLLs score<sup>2</sup>

#### Variables

Hb <9.5 g/dl

Plt < 80.000/mmc

Elevated LDH

Extrahilar lymphadenopathy

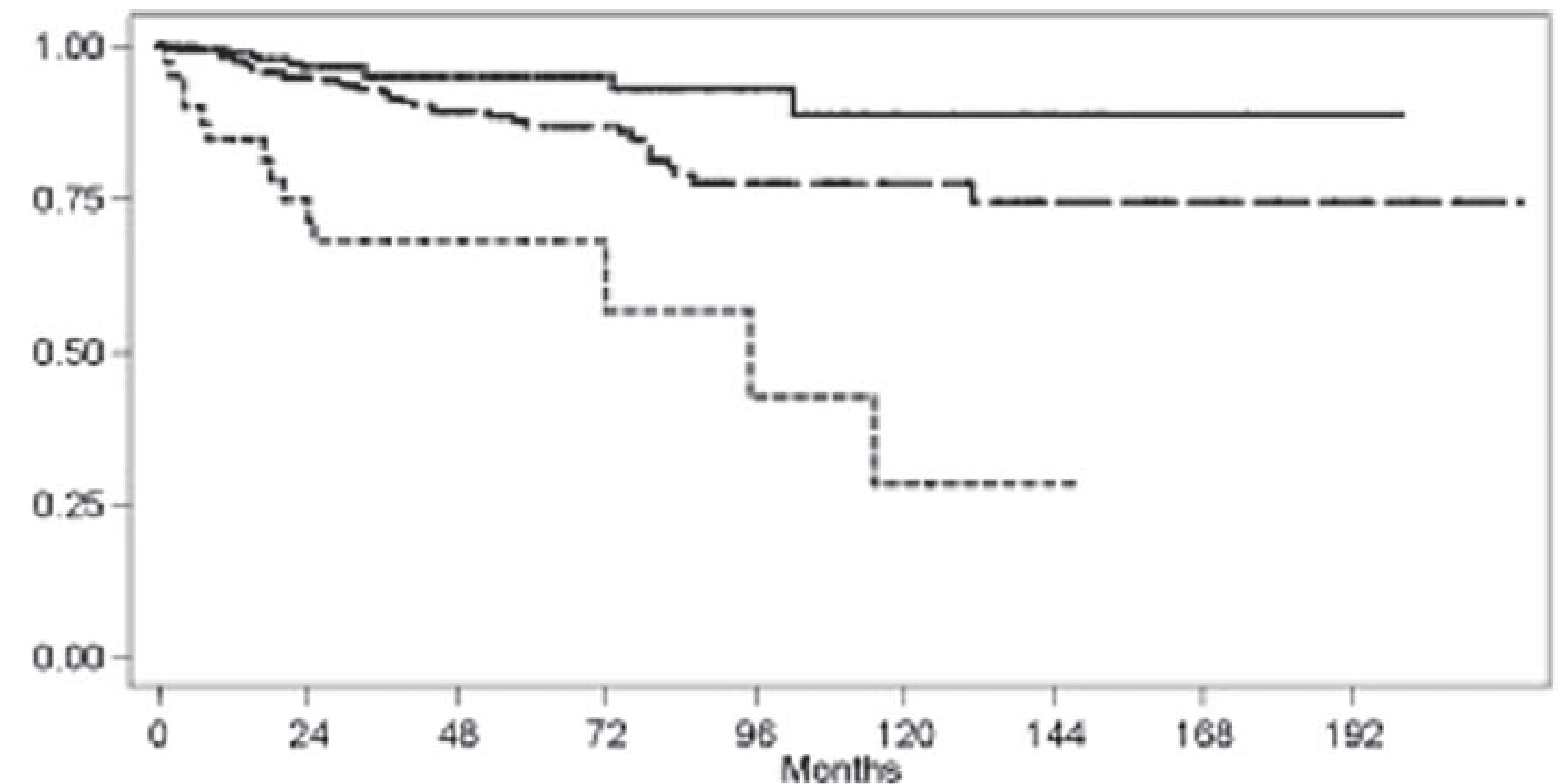
#### 5y LSS

A 95%

B 87%

C 68%

- Derived from retrospective SMZLSG studies
- Tested in a validation set <sup>3</sup>

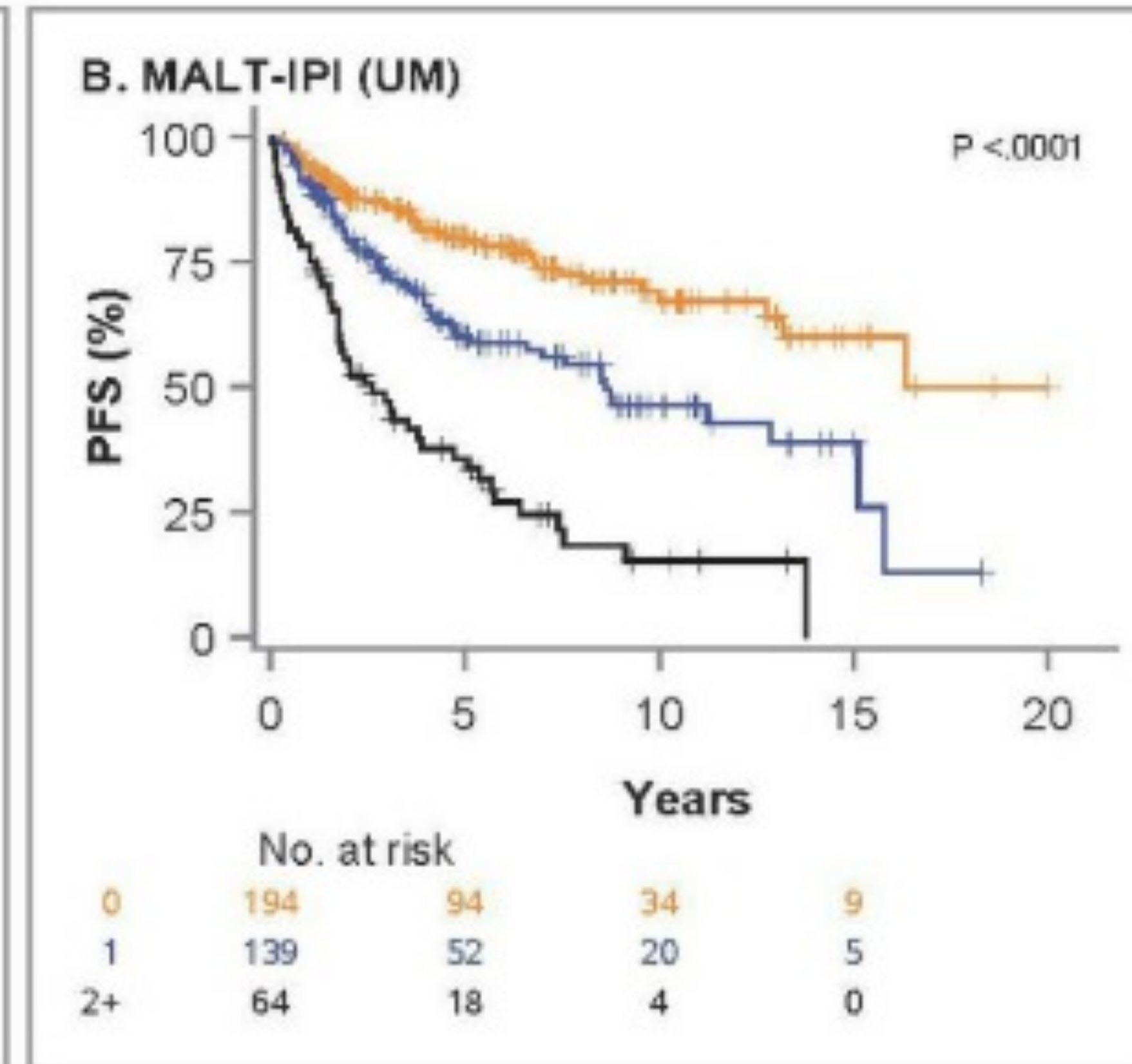
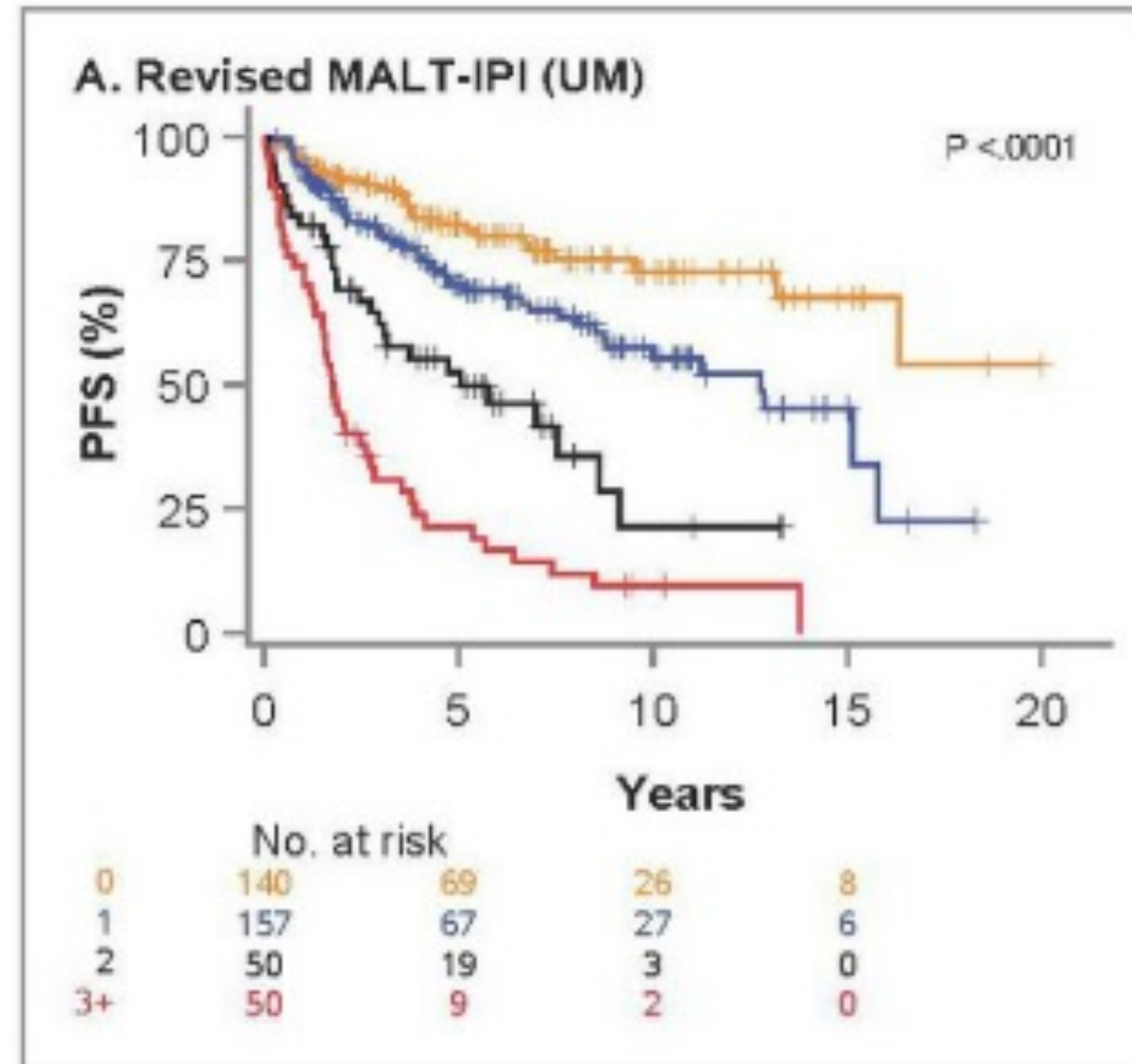


1. Montalban C BJH 2012; 2. Montalban C Leukemia 2014; 3. Kalpadakis C. Leukemia 2014



## Revised MALT-IPI

- Better PFS prediction (no difference in OS prediction)



## Upcoming data on chemo-free approaches

### Untreated MZL

- R-ibrutinib (IELSG47-MALIBU trial)
- Mosunetuzumab-lenalidomide (BrUOG-401 trial)

### R/R MZL

- Tafasitamab-acalabrutinib after 1<sup>st</sup> line (IELSG49)
- Tafasitamab-R2 after 1<sup>st</sup> line (InMIND)
- Lisocabtagene maraleucel after 2<sup>nd</sup> line (TRANSCEND-FL)