

2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 13-14, 2021

Starhotels Majestic

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How I treat high risk Follicular Lymphoma

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Disclosures

Research Support from

- Roche
- Janssen
- Bayer

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Follicular Lymphoma – Current Treatment Strategies

**Stage I/II
(15–20 %)**

- **Radio-Therapy (involved field)
(plus Rituximab)
Intention: Cure**

**Stage III/V
(80–85 %)**

- **Low tumor burden
„watch and wait“**
- **High tumor burden
Immuno- Chemotherapy
Intention: Palliation**

GELF Criteria for High Tumor Burden

Any site >7 cm

Three or more sites greater than 3 cm

B symptoms

Spleen below umbilical line

Compressive symptoms

Pleural or peritoneal effusions

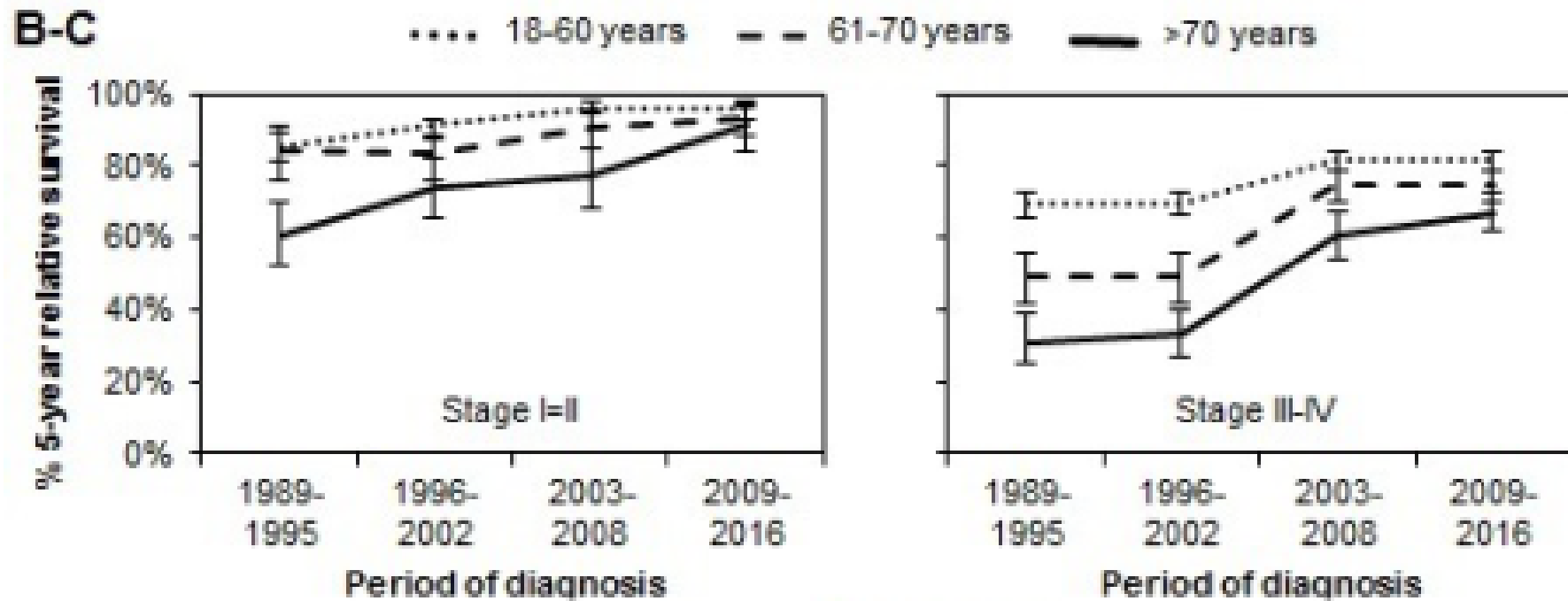
5000 tumor cells/mm³

Absolute neutrophil count <1000/mm³

Platelet count <100 000/mm³

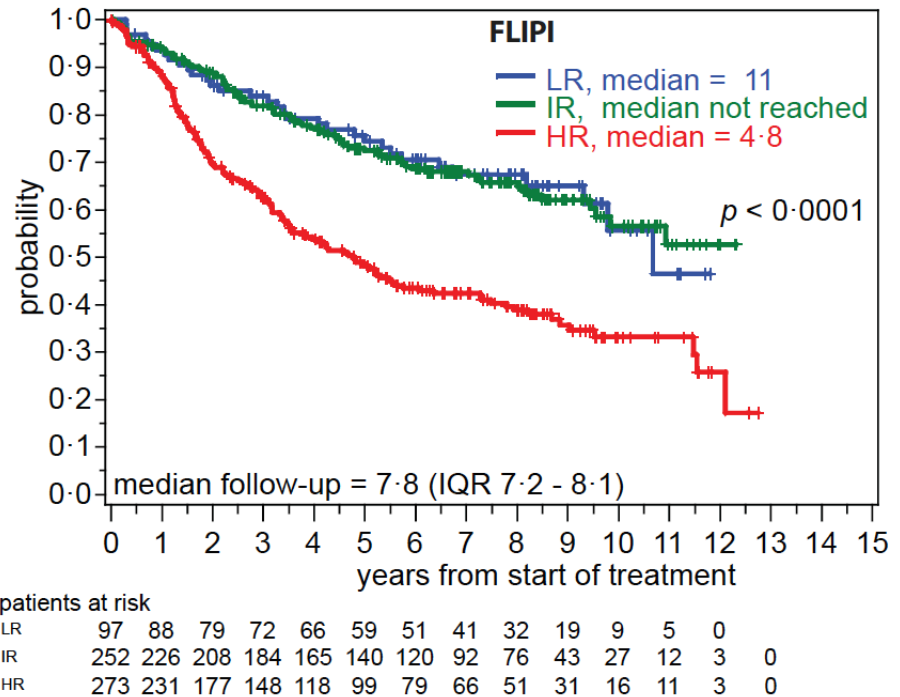
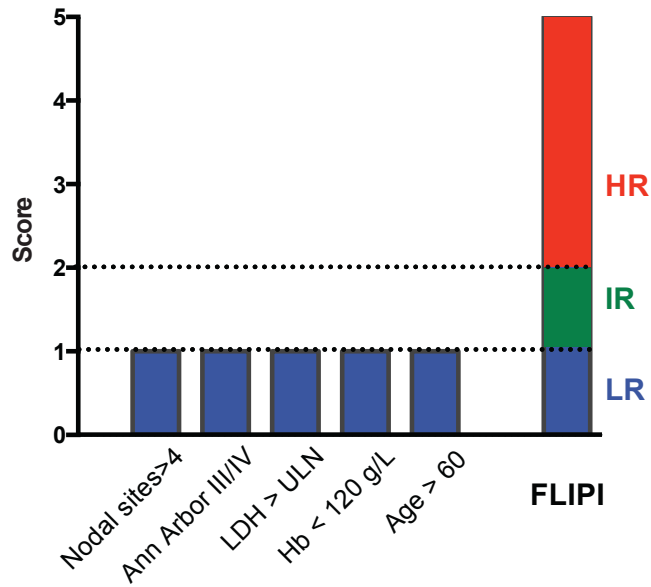
Brice P, Bastion Y, Lepage E, et al. J Clin Oncol. 1997; 15: 1110- 1117

Follicular Lymphoma – Overall Survival



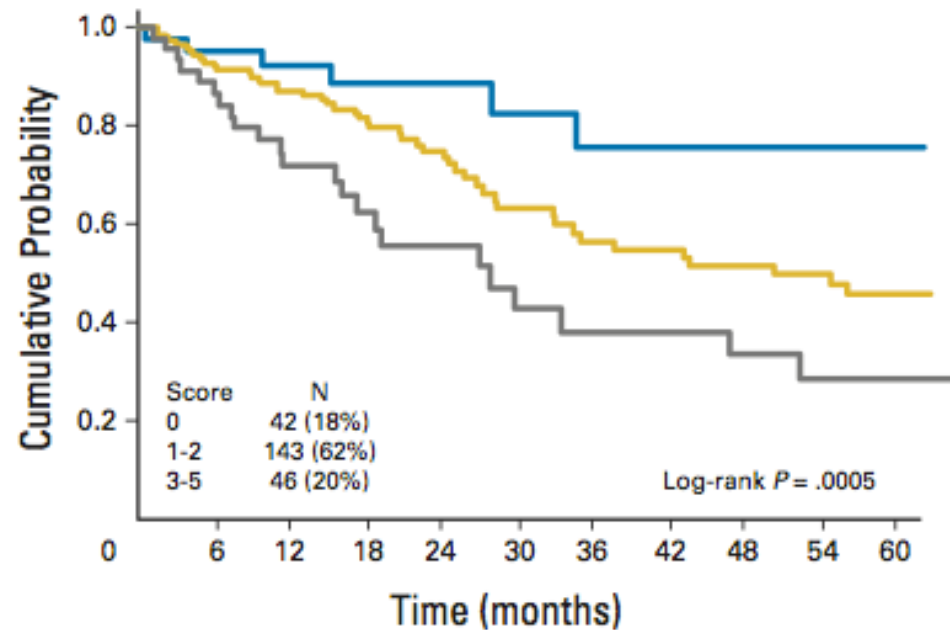
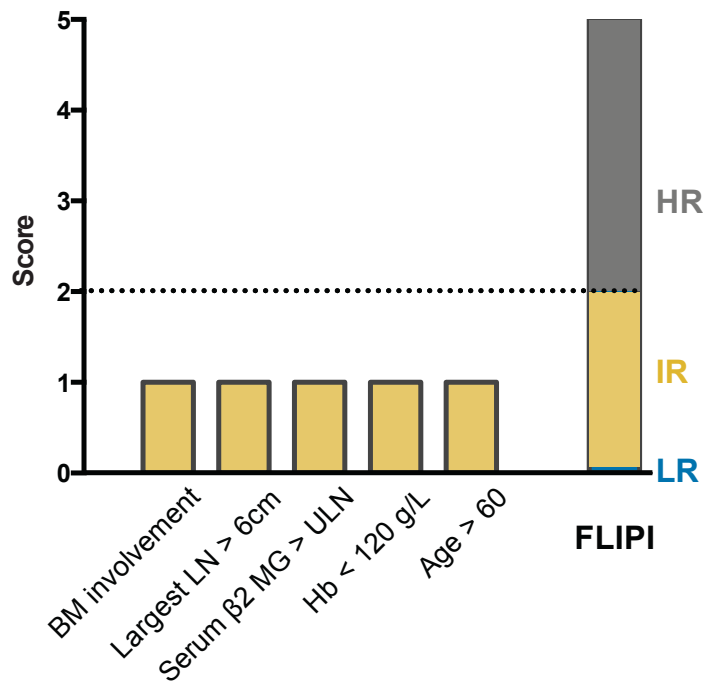
Manette Dinnessen et al. EHA 2019 (PS 1250)

Follicular Lymphoma International Prognostic Index (FLIPI)



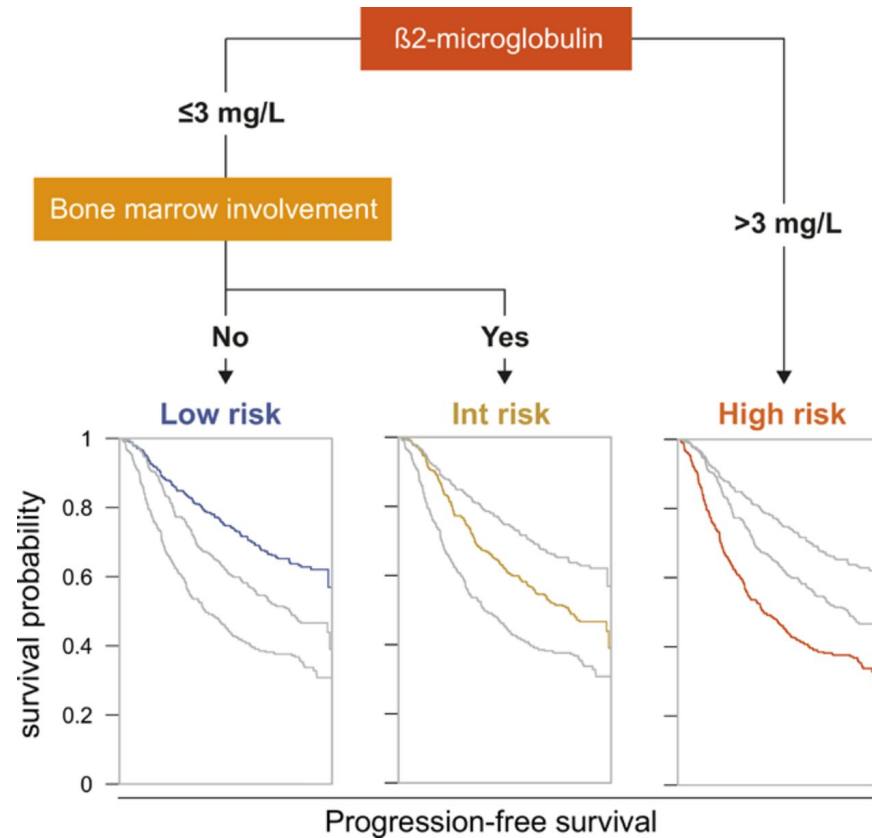
Solal-Céligny et al., Blood, 2004; Buske et al., Blood 2006; Pastore et al., Lancet Oncol 2015

Follicular Lymphoma International Prognostic Index 2 (FLIPI 2)



Federico et al., JCO 2009

Follicular Lymphoma – PRIMA Prognostic Index



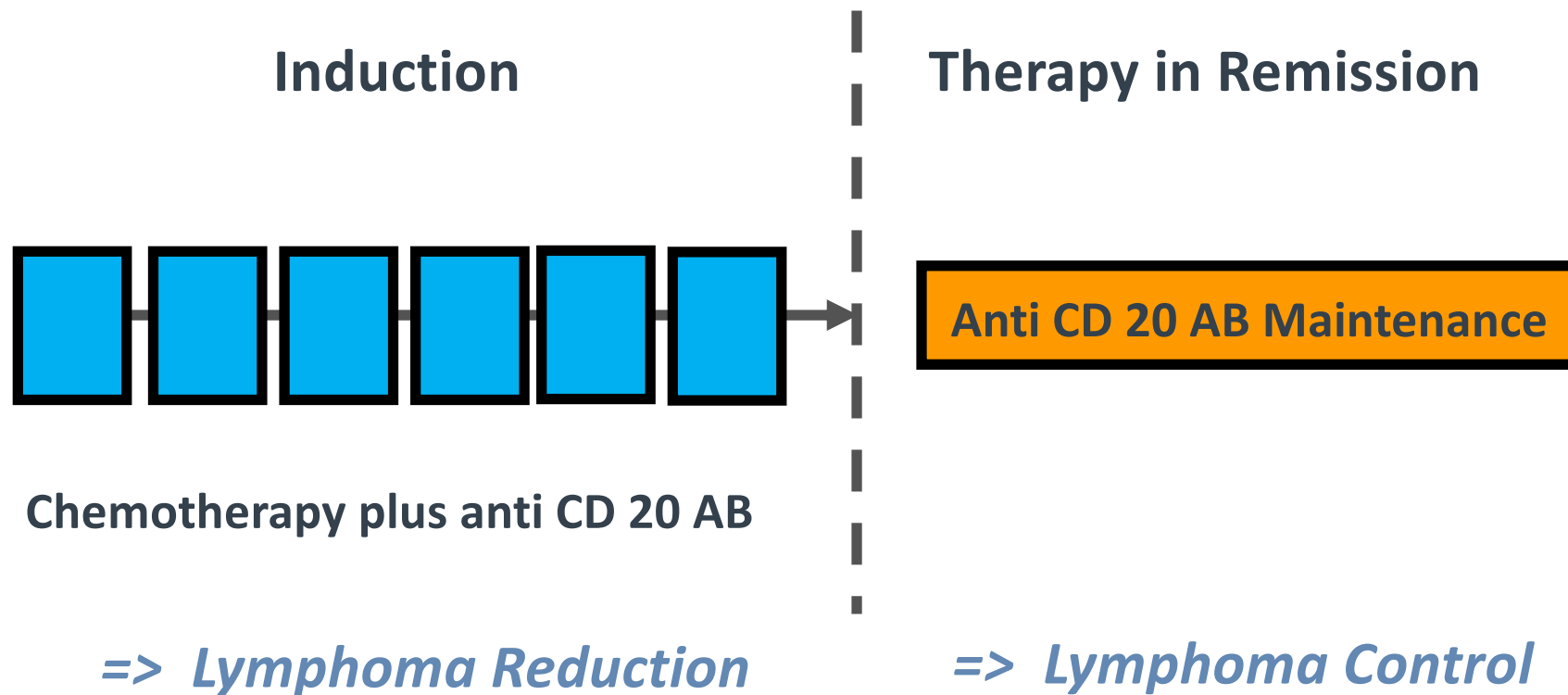
Bachy E et al. Blood 2018

Definition of High Risk Follicular Lymphoma

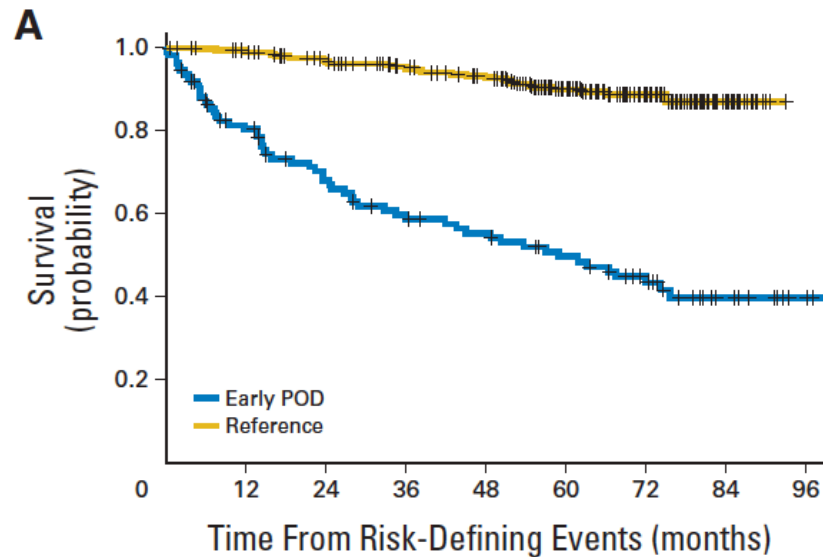
Current Prognostic Indices:

- are primarily based on clinical factors
- are not specific enough for individual treatment decisions
- are rarely used in clinical practice

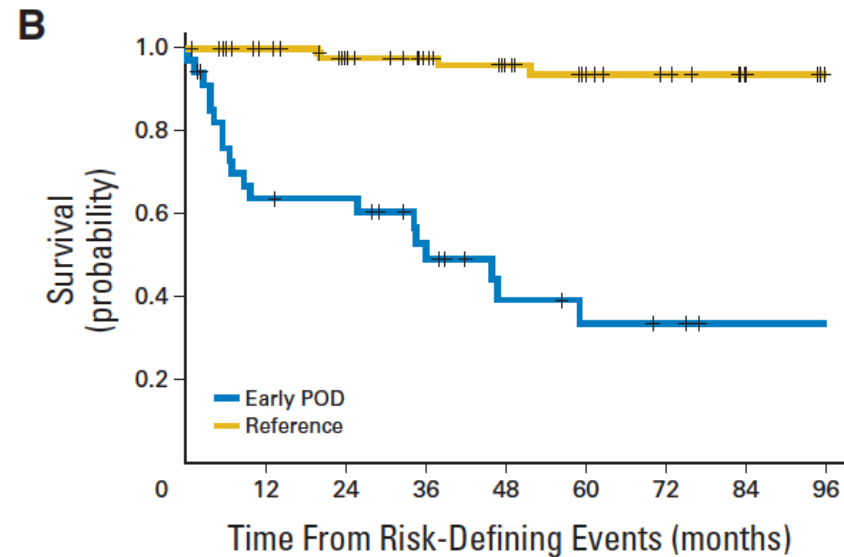
High Risk Follicular Lymphoma Current Standard of Therapy



Early Progression of Disease (POD 24)



No. at risk	0	12	24	36	48	60	72	84	96
Early POD	110	82	66	56	50	42	32	14	3
Reference	420	408	387	363	344	253	145	34	0



Casulo C et al., J Clin Oncol 33:2516-22, 2015
 Jurinovic V et al., Blood 20216

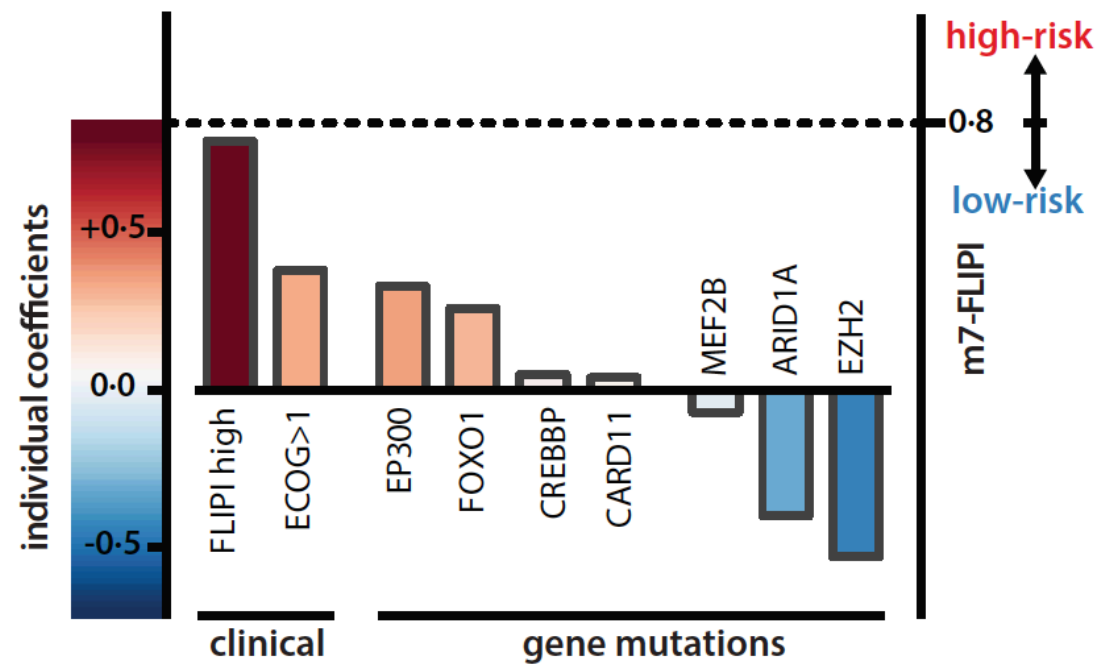
Early Progression of Disease (POD 24)

- Can we identify these patients upfront?
- Can we prevent POD 24?
- How to treat patients with POD 24?

Early Progression of Disease (POD 24)

- **Can we identify these patients upfront?**
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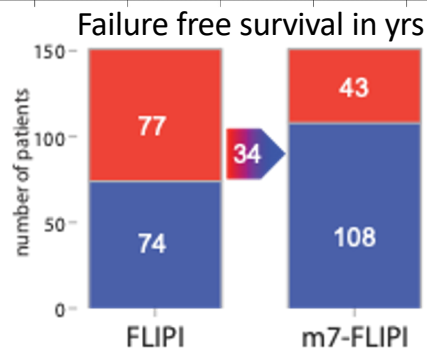
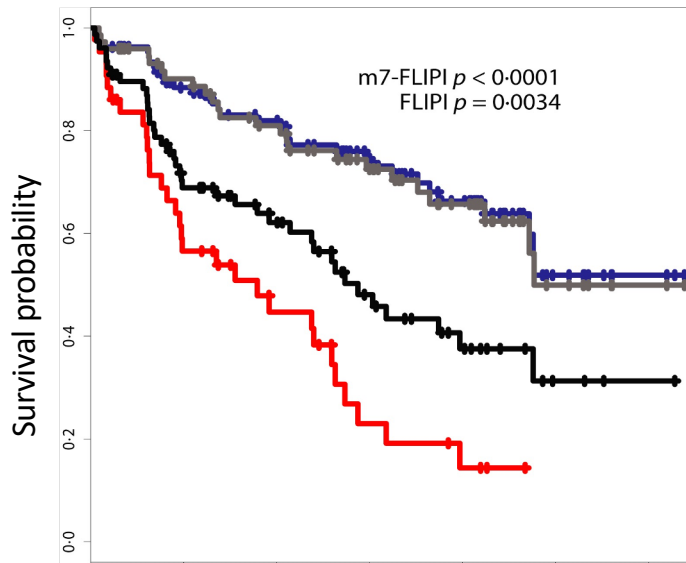
Clinico-Genetic Risk Model – m7 FLIPI



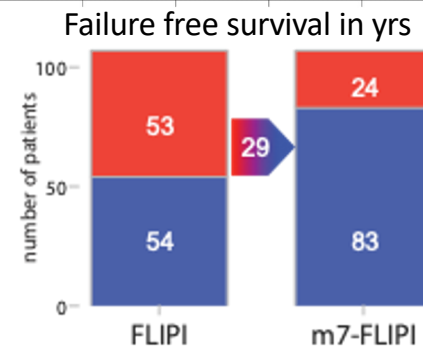
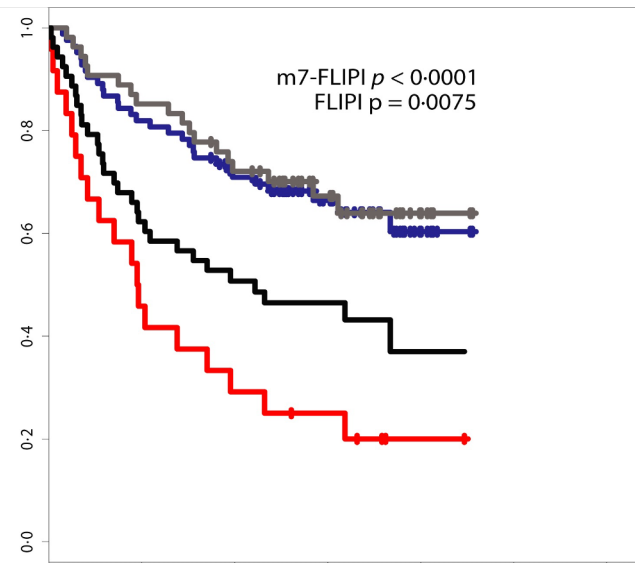
Pastore et al., Lancet Oncol 2015

M7 FLIPI – Failure Free Survival

GLSG training cohort

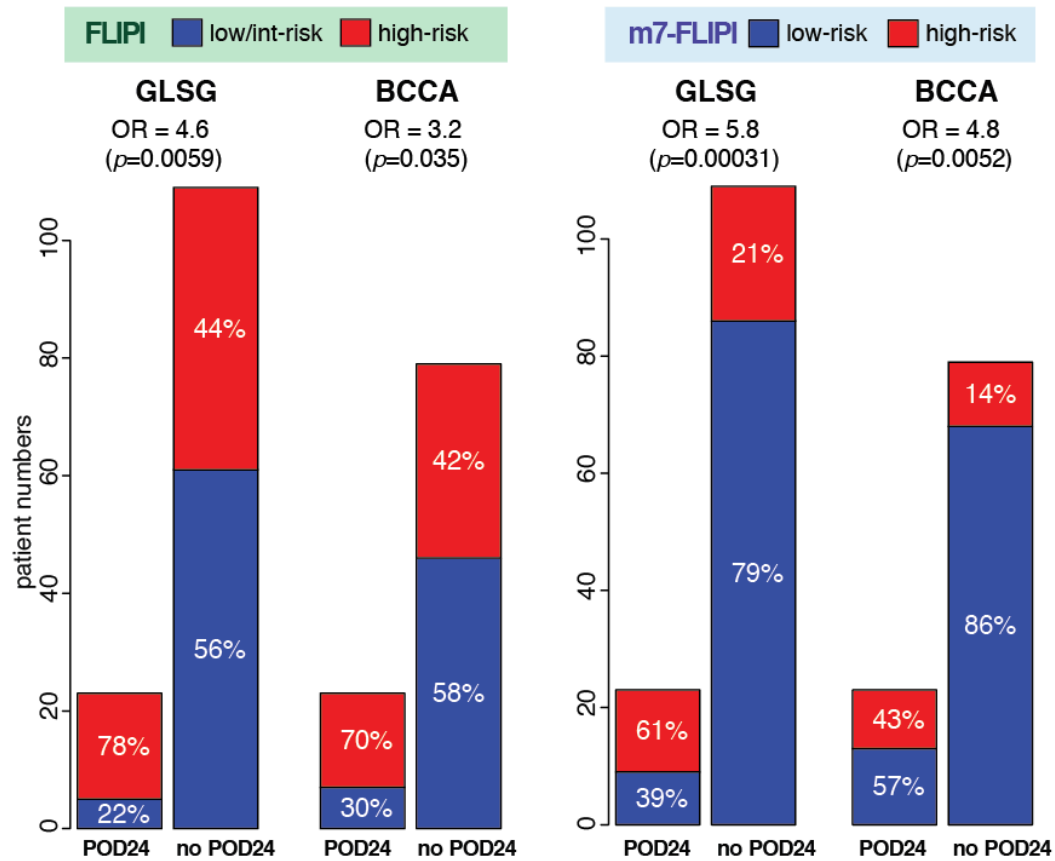


BCCA validation cohort



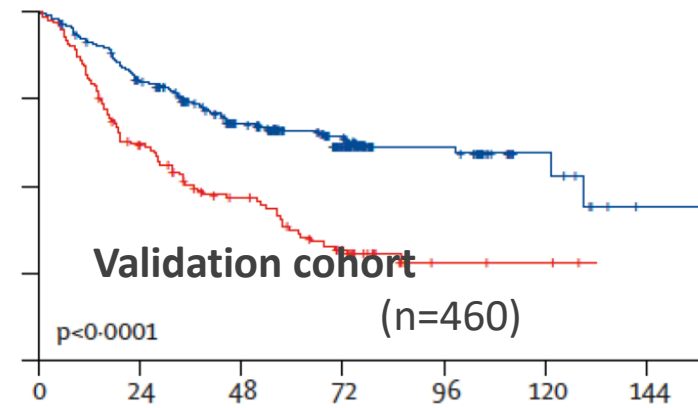
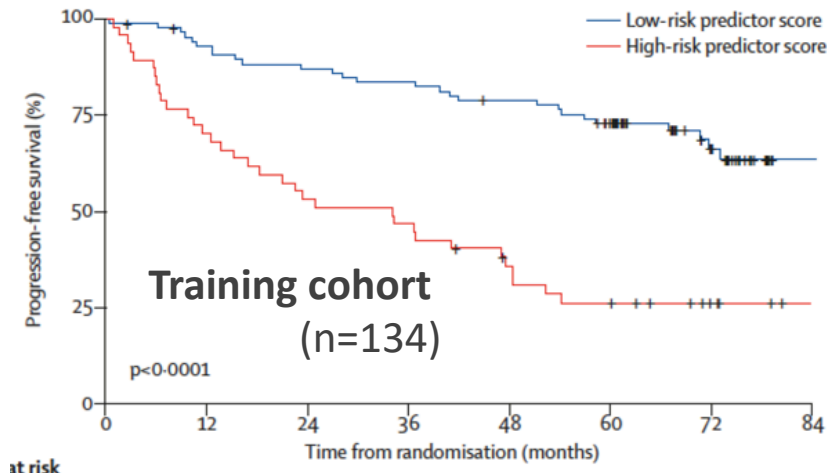
Pastore et al., Lancet Oncol 2015

Early Progression of Disease (POD 24) Comparison of FLIPI and m7 FLIPI



Jurinovic et al., Blood 2016

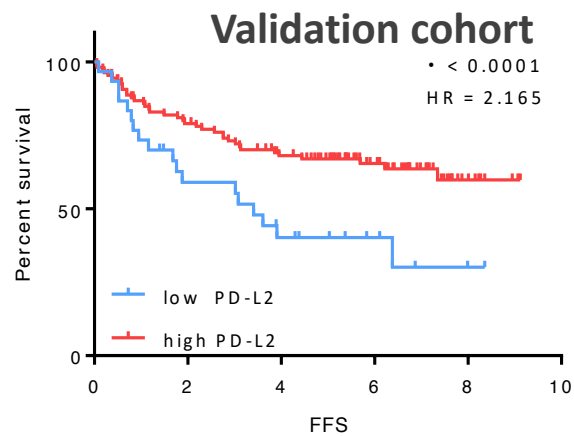
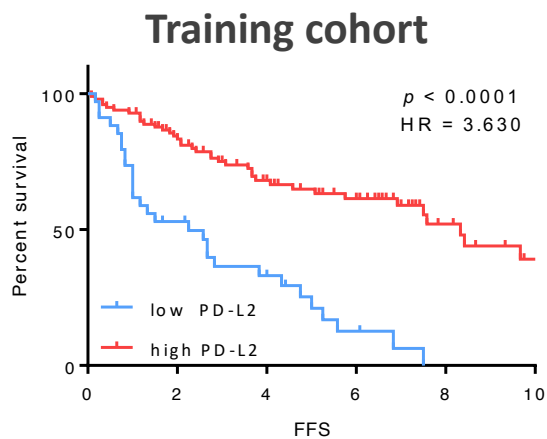
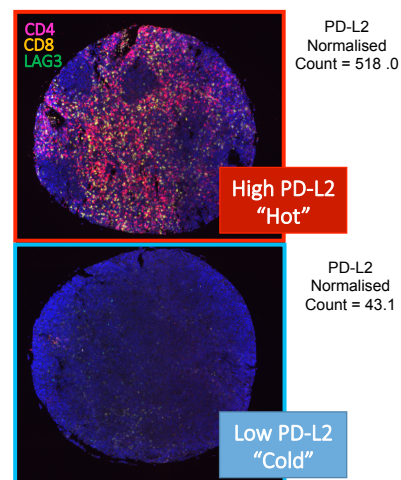
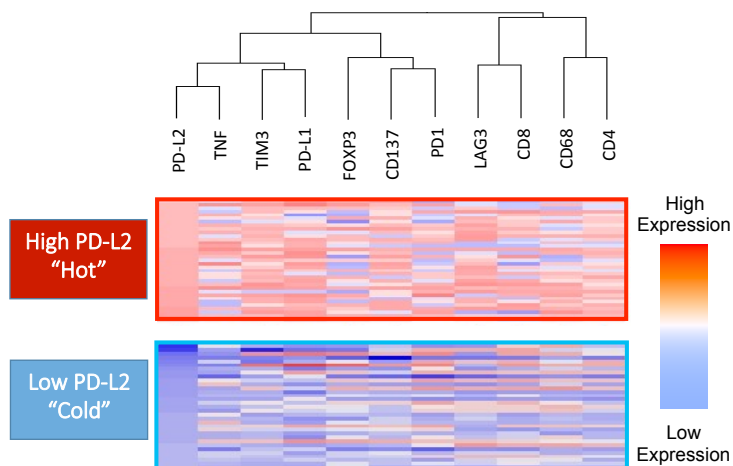
23 Gene Expression Score



	23-Gene Expression Score	m7-FLIPI
High-risk [% of patients]	21 - 34%	22 - 28%
HR for PFS	2.1 - 2.6	2.02 - 3.58
5-yr PFS [high- vs low-risk]	34-42% vs 62-70%	25-38% vs 68-77%
POD24 [% in high- vs low risk]	38% vs 19%	43-61% vs 14-21%
Predictive of OS	no	yes

Huët et al, Lancet Oncology 2018

Intratumoral Immune Infiltration



Tobin et al, JCO 2019

Early Progression of Disease (POD 24)

- Can we identify these patients upfront?
 - **Can we prevent POD 24?**
- How to treat patients with POD 24?

Early Progression of Disease (POD 24) in the GALLIUM Study

	n	Deaths	Crude death rates per 100 patient–years (95% CI)	Median follow-up (y)	Patient–years at risk*
POD24	155	56	19.4 (14.9–25.2)	1.88	289
No POD24	1202	39	1.0 (0.8–1.4)	3.32	3772

Seymour JF et al. Haematologica 104: 1202 – 1208, 2019

Early Progression of Disease (POD 24) in the GALLIUM Study

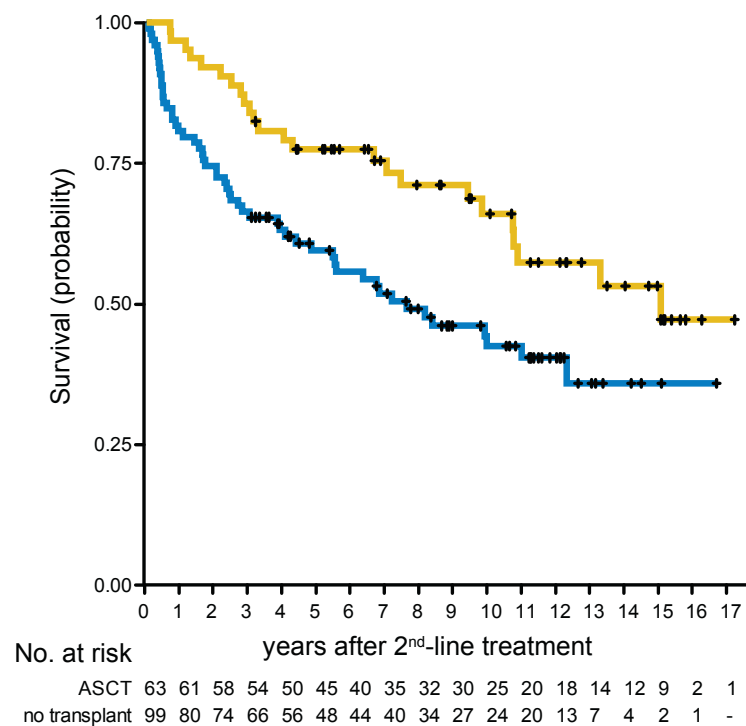
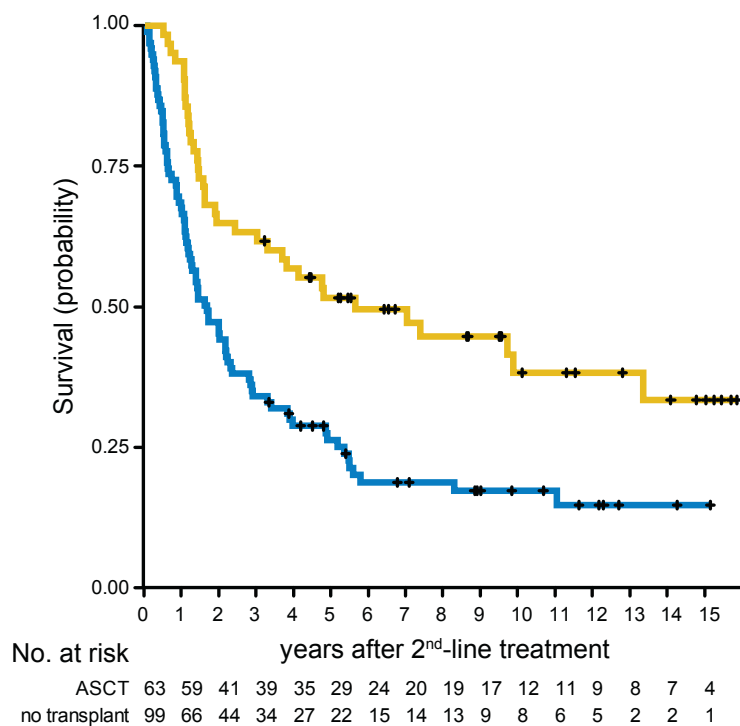
	G-chemo (n=601)	R-chemo (n=601)
Absolute risk of a PFS event before 24 months and 95% CI, %	12.53 (10.06–15.55)	18.94 (15.94–22.42)
PFS events at 24 months		
All	71	107
POD24 events (PD or death due to PD)	57	98
noPOD24 events (death not due to PD)*	14	9
2-year cumulative incidence of POD24 events (95% CI)	0.10 (0.08–0.12)	0.17 (0.14–0.20)
Difference in incidence, % (p value, Gray's Test for Equality of Cumulative Incidence Functions†)	-41.5 (p=0.0004)	

Seymour JF et al. Haematologica 104: 1202 – 1208, 2019

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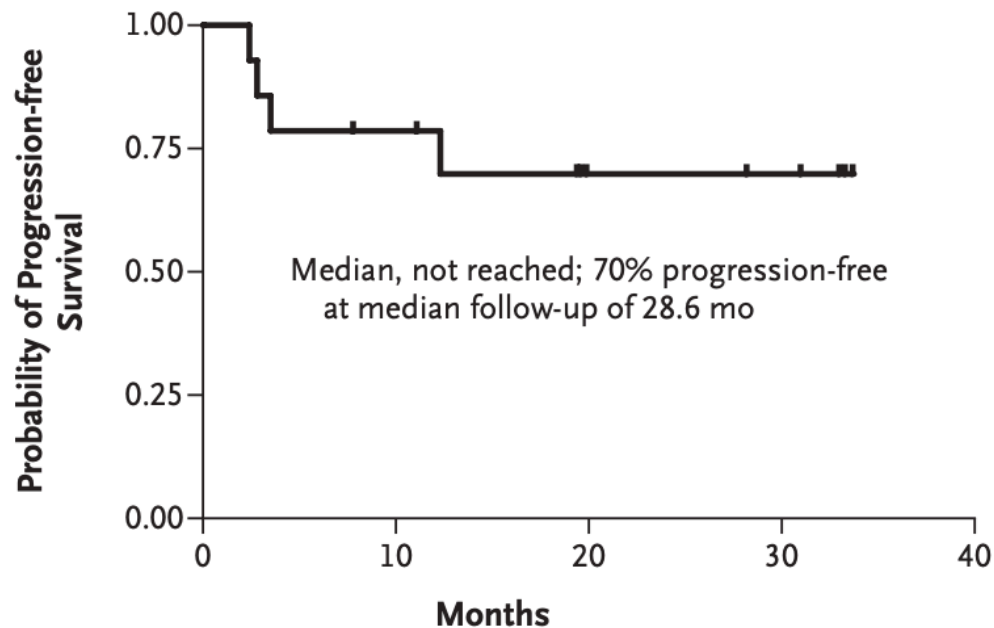
Early Progression of Disease (POD 24) Autologous Transplantation



Jurinovic et al., BBMT 2018

Early Progression of Disease (POD 24) CART Cell Therapy

B Follicular Lymphoma, Progression-free Survival

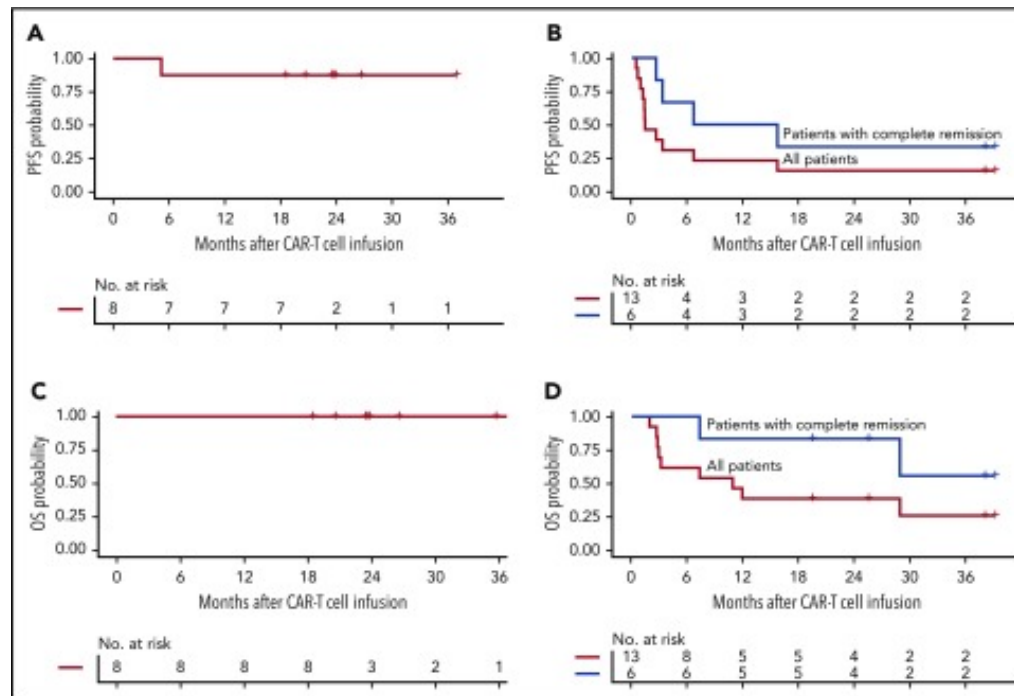


No. at Risk 14 10 5 4 0

- „double refractory“: 57% of all patients, previous auto-HSCT: 21%
- N = 14, Median OS = N.R.

Schuster et al., NEJM , 2017

Early Progression of Disease (POD 24) CART Cell Therapy

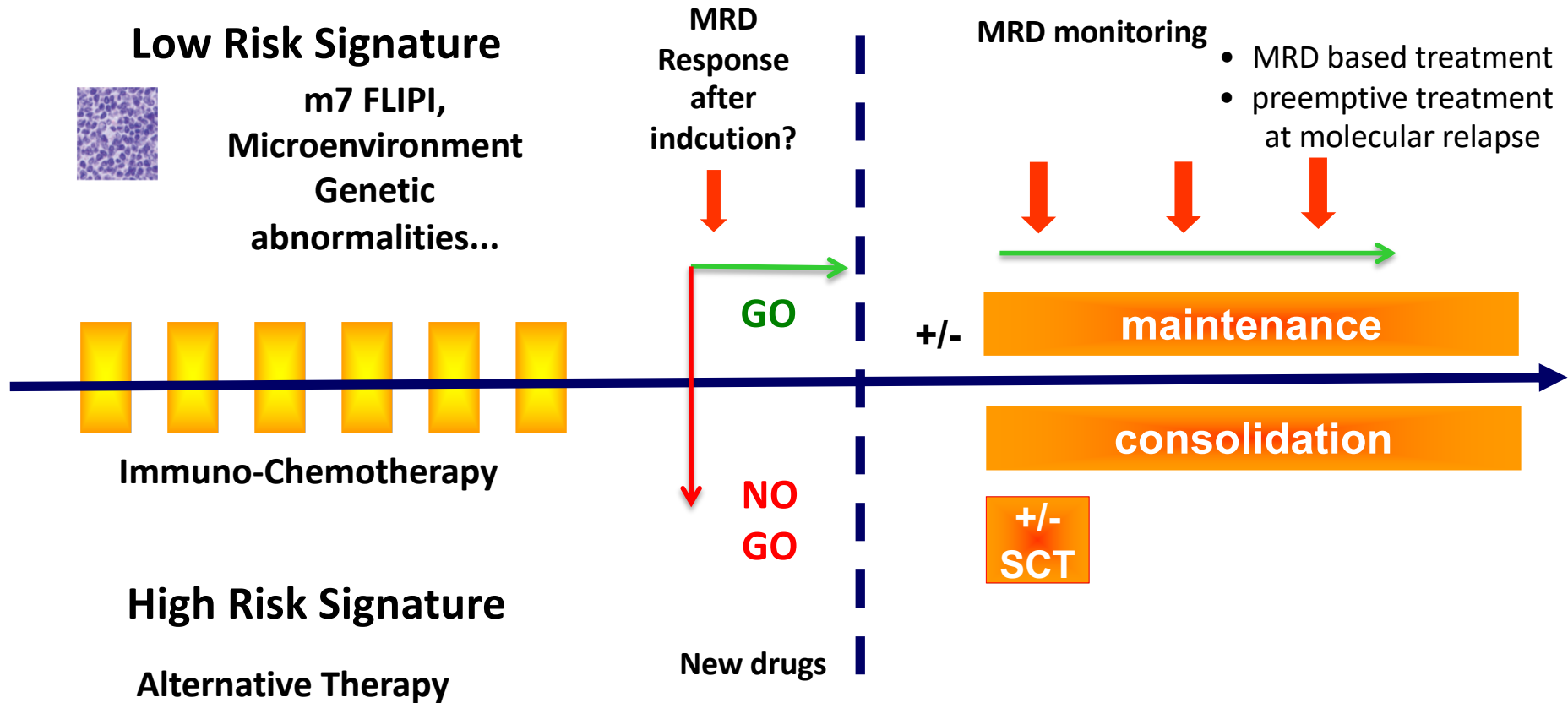


Hirayama AV et al. Blood 2019

How I treat high risk Follicular Lymphoma

- The current approach is Immuno-Chemotherapy
- Definition of High Risk is not satisfactory
- Development of Biology based Risk Scores is urgently needed possibly accompanied by Assessment of Early Response

Risk Adapted Therapy of Follicular Lymphoma



Stratification will be Key for Future Therapies



Different Clinical Priorities:

- distinct treatment goals / study endpoints
- distinct treatment strategies

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How I treat high risk Follicular Lymphoma

What is the treatment of first choice for high-risk follicular lymphoma patients?

- Autologous stem cell transplantation
- Single agent anti-CD 20 antibody therapy
- Immuno-Chemotherapy
- Combination of new agents such as lenalidomide/rituximab

How I treat high risk Follicular Lymphoma

What are the treatment options for patients with POD 24?

- Retreatment with initial therapy
- Change of anti-CD 20 antibody
- Autologous stem cell transplantation
- Palliative care