FONDAZIONE ITALIANA LINFOMI

I "LINFOMI INDOLENTI"

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Definire la prognosi nel linfoma follicolare

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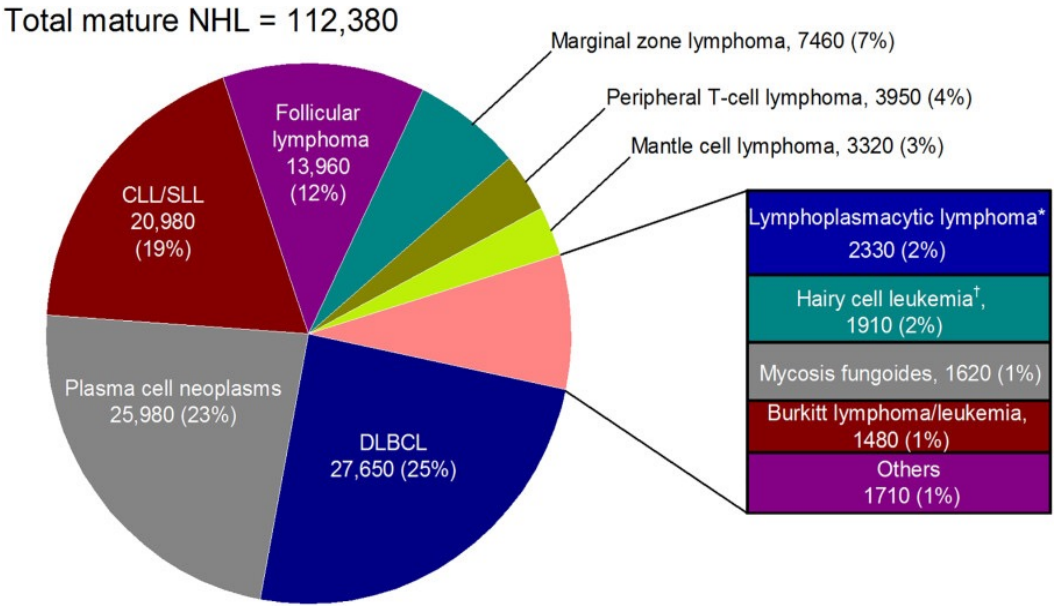
Disclosures of Rita Tavarozzi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie					x		
Sobi					x		
Lilly					x		
Roche							x

Features of Follicular Lymphoma

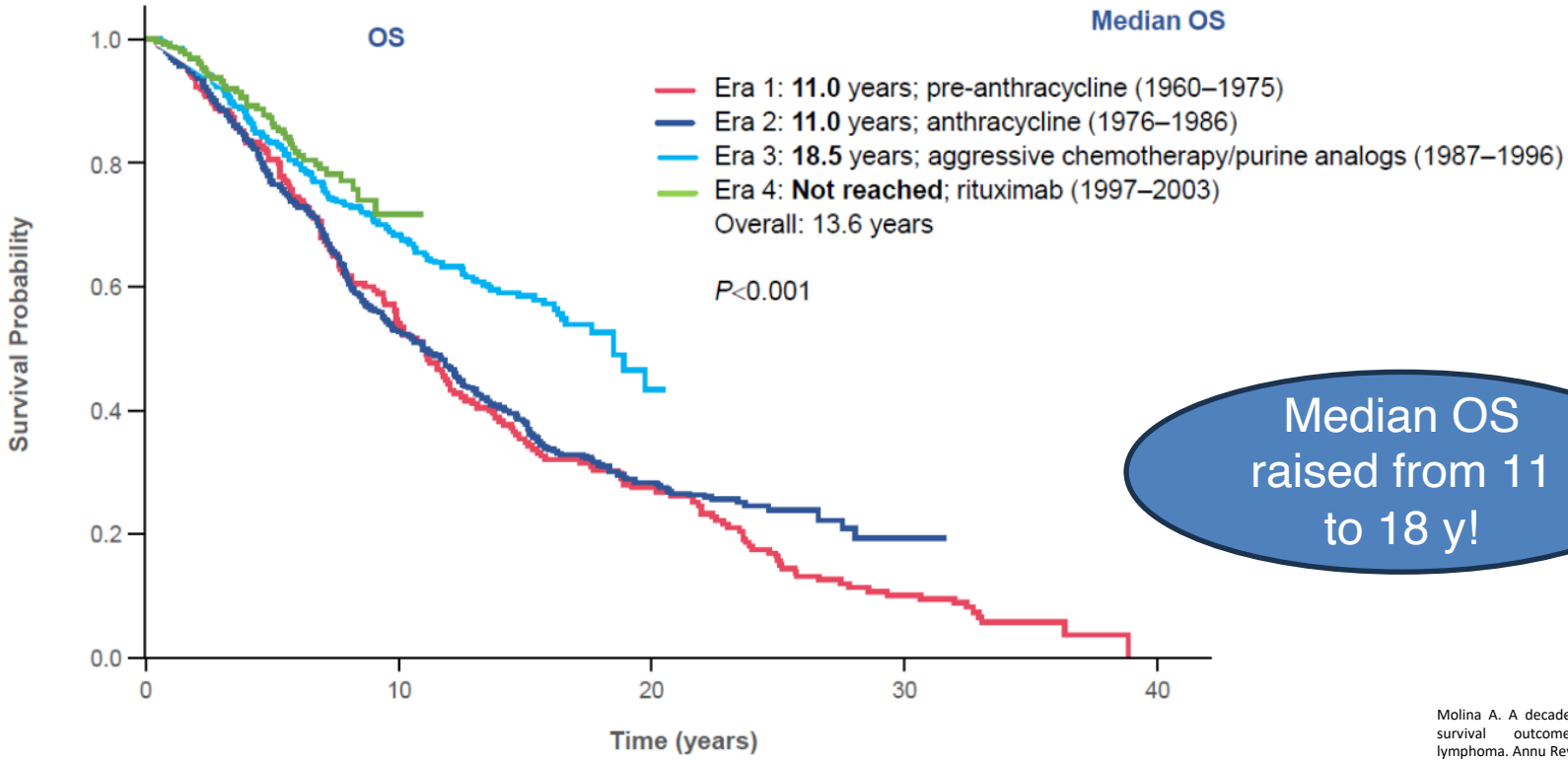


- Relapsing-remitting course with progression over several years (1)
- Low impact on life expectancy with exceptions (2)
- Can transform into more aggressive lymphomas (2%-3% per year) (3)

Teras LR, et al. CA Cancer J Clin. 2016;66(6):443-459

1. Link BK, et al. Br J Haematol. 2019;184(4):660-663. 2. Maurer MJ, et al. Am J Hematol. 2016;91(11):1096-1101. 3. Link BK, et al. J Clin Oncol. 2013;31(26):3272-3278.

Improving Survival in Patients With Follicular NHL



Median OS raised from 11 to 18 y!

Molina A. A decade of rituximab: improving survival outcomes in non-Hodgkin's lymphoma. Annu Rev Med. 2008;59:237-50.

FREE ACCESS | ORIGINAL REPORTS | November 27, 2018

Cause of Death in Follicular Lymphoma in the First Decade of the Rituximab Era: A Pooled Analysis of French and US Cohorts

Authors: Clémentine Sarkozy, MD, Matthew J. Maurer, MS, Brian K. Link, MD, Hervé Ghesquieres, MD, PhD, Emmanuelle Nicolas, MD, Carrie A. Thompson, MD, Alexandra Traverse-Glehen, ... SHOW ALL ... , and Gilles Salles, MD, PhD AUTHORS INFO & AFFILIATIONS

J Clin Oncol **37**, 144-152(2019) • Volume 37, Number 2 • DOI: 10.1200/JCO.18.00400

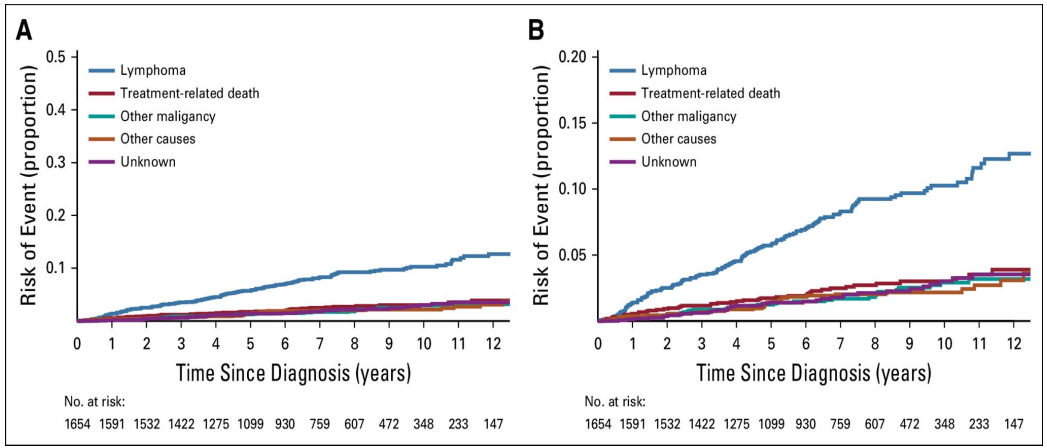


TABLE 2. Causes of Death

Cause	Cohort		
	French (n = 113)	US (n = 170)	Pooled (N = 283)
Lymphoma	70 (65.4)	70 (49.6)	140 (56.5)
Transformed	42	35	77
Treatment related	17 (15.9)	25 (17.7)	42 (16.9)
MDS/AML	6	6	12
Therapy, infection	6	14	20
Therapy, cardiac	2	4	6
Therapy, other	3	1	4
Other cancer	13 (12.1)	20 (14.2)	33 (13.3)
Other causes*	7 (6.5)	26 (18.4)	33 (13.3)
Missing†	6	29	35

NOTE. Data are given as No. (%) unless otherwise indicated.

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

*Other causes listed in Appendix Table A1.

†Missing category is not included in the percentages.

Why prognosis matters in Follicular Lymphoma

- Indolent disease
- Heterogeneous outcomes
- Risk of histologic transformation
- Long survival – quality of life impact
- Prognosis as guide to timing and intensity of therapy
- Predictable course

- At diagnosis – defining risk and disease biology before treatment initiation
  - *Clinical Prognostic Scores*
  - *Biological predictors*
  - *PET-based prognostic factors*
- Beyond diagnosis - monitoring disease during and after treatment:
  - *Response-adapted prognostic factors*
- Conclusions

- At diagnosis – defining risk and disease biology before treatment initiation
  - *Clinical Prognostic Scores*
  - *Biological predictors*
  - *PET-based prognostic factors*

How can I assess prognosis in Follicular Lymphoma?

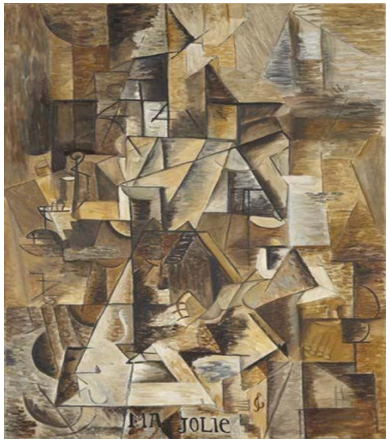
At diagnosis

Pablo Picasso - Science and Charity (1897)

CLINICAL SCORES

Biological predictors

PET-based prognosticators



Pablo Picasso – Ma Jolie (1911–1912)

INNOVATIVE SCORES

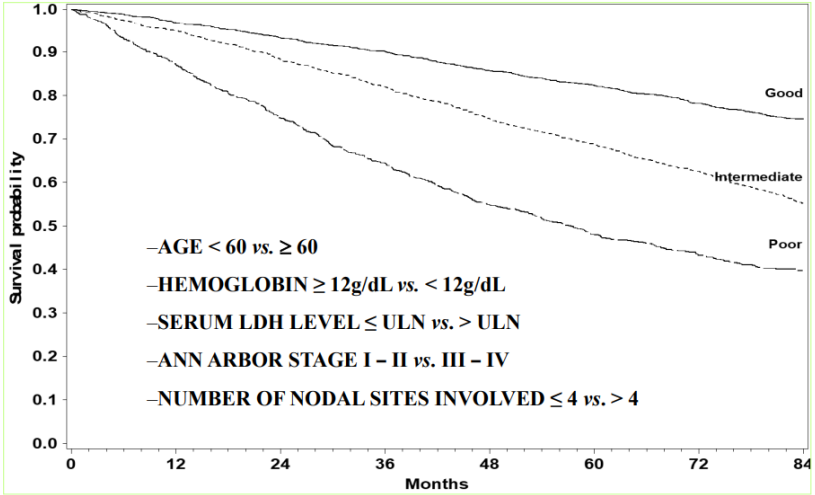
Clinical Prognostic Scores

- ✓ *Purpose: population risk stratification*
- ✓ *Simple, widely available tools*
- ✓ *Still relevant in daily practice*
- ✓ *Limitations in individual patient prediction*

Feature	FLIPI[17]	FLIPI-2[7]	PRIMA-PI[18]	FLIPI24
Developed in	Early 2000s	2009	2018 (from PRIMA trial)	2025
Factors included	1. Age >60 yrs 2. Stage III–IV 3. Hb <12 g/dL 4. >4 nodal sites 5. Elevated LDH	1. β2-microglobulin ↑ 2. LN >6 cm 3. BM involvement 4. Hb <12 g/dL 5. Age >60	1. β2-microglobulin ↑ 2. BM involvement	1. hemoglobin 2. lactate dehydrogenase 3. beta-2 microglobulin 4. WBC count
Risk categories	- Low (0–1) - Int. (2) - High (≥3)	- Low (0–1) - Int. (2) - High (≥3)	- Low (0) - Int. (1) - High (2)	- Low (0) - Int. (1) - High (2)

FLIPI: The Historical Cornerstone

- ✓ *Three risk categories*
- ✓ *Developed for overall survival*
- ✓ *Developed in the **pre-rituximab era***



0-1 factor

2 factors

3-5 factors

Solal-Celigny, Blood 2004

ORIGINAL ARTICLES | HEMATOLOGIC MALIGNANCIES · Volume 24, Issue 2, P441-448, February 2013 · Open Archive

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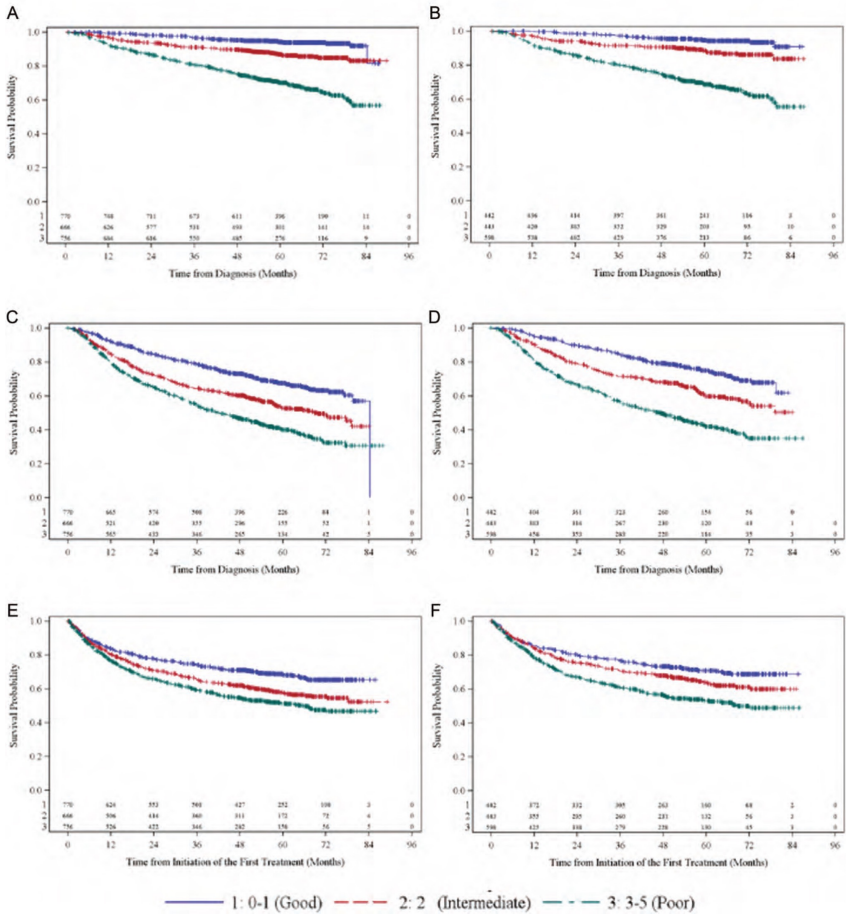
Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices

A.K. Nooka [1] · C. Nabhan [2] · X. Zhou [3] · ... · K. Dawson [4] · J.H. Hirata [4] · C.R. Flowers [1] ... Show more

Treatment modality	FLIPI risk group			Total *N* (%)
	Good *N* (%)	Intermediate *N* (%)	Poor *N* (%)	
	770 (100)	666 (100)	756 (100)	2192 (100)
Watch and wait	170 (22.1)	129 (19.4)	74 (9.8)	373 (17.0)
R/R-containing regimen				
R-Mono	95 (12.3)	88 (13.2)	113 (14.9)	296 (13.5)
R-Chemo	304 (39.5)	348 (52.3)	480 (63.5)	1132 (51.6)
Combined modality–XRT	42 (5.5)	7 (1.1)	4 (0.5)	53 (2.4)
Combined modality–BMT	1 (0.1)		1 (0.1)	2 (0.1)
Any of the above	442 (57.4)	443 (66.5)	598 (79.1)	1483 (67.7)
Non-R-containing regimens				
Chemo	18 (2.3)	21 (3.2)	23 (3.0)	62 (2.8)
XRT	99 (12.9)	9 (1.4)	6 (0.8)	114 (5.2)
Combined modality–XRT	2 (0.3)			2 (0.1)
Investigational	31 (4.0)	61 (9.2)	52 (6.9)	144 (6.6)
Other	8 (1.0)	3 (0.5)	3 (0.4)	14 (0.6)
Any of the above	158 (20.5)	94 (14.1)	84 (11.1)	336 (15.3)



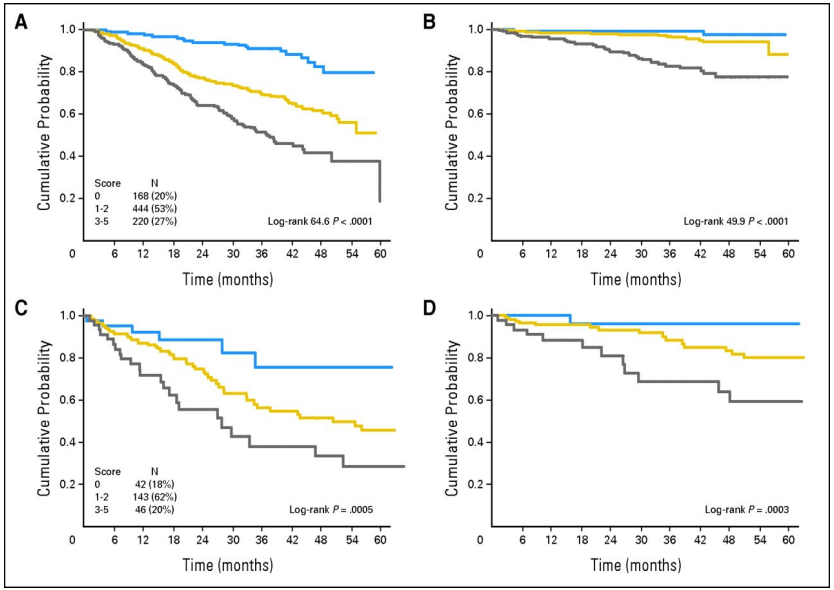
Kaplan–Meier (K–M) survival functions for OS, PFS, and time to next treatment (TTNT) by the FLIPI risk group. (A) Overall survival (OS) by the FL international prognostic index (FLIPI) risk groups for all treatments. (B) OS by FLIPI risk groups for R-containing regimens. (C) Progression-free survival by FLIPI risk groups for all treatments. (D) Progression-free survival by FLIPI risk groups for R-containing regimens. (E) Time to next treatment by FLIPI risk groups for all treatments. (F) Time to next treatment by FLIPI risk groups for R-containing regimens.

- ✓ *Improved applicability in the modern era*
- ✓ *Designed for progression-free survival*
- ✓ *Ease of use vs prognostic precision*

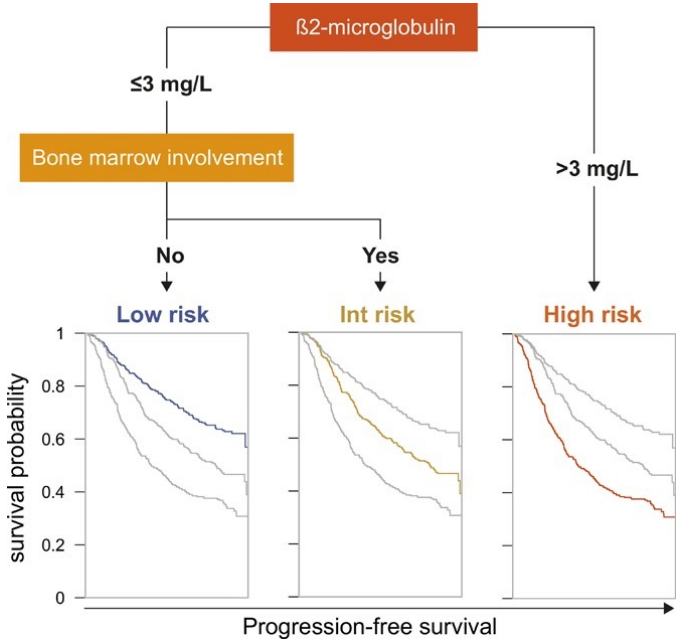
FLIPI-2

(50% rituximab)

1. β2-microglobulin ↑
2. LN >6 cm
3. BM involvement
4. Hb <12 g/dL
5. Age >60



PRIMA-PI

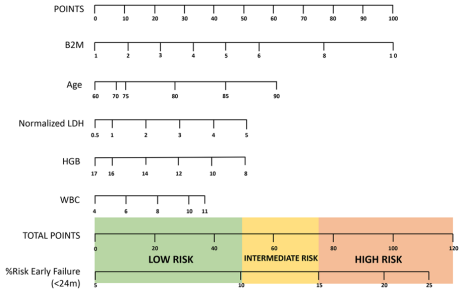


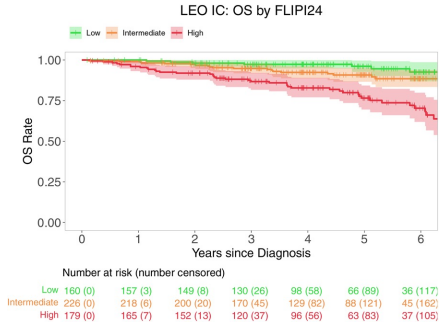
Federico et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol. 2009 Sep 20;27(27):4555-62.

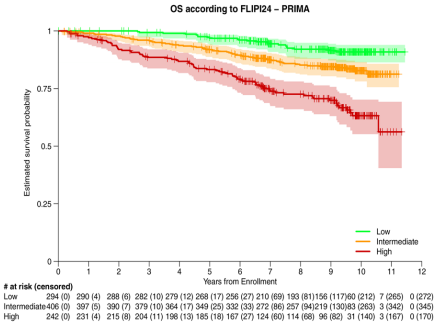
Bachy E, et al. A simplified scoring system in de novo follicular lymphoma treated initially with immunochemotherapy. Blood. 2018 Jul 5;132(1):49-58.

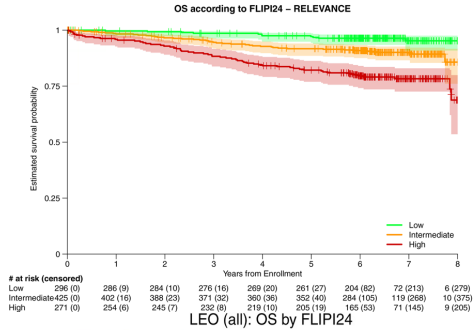
FLIPI-24

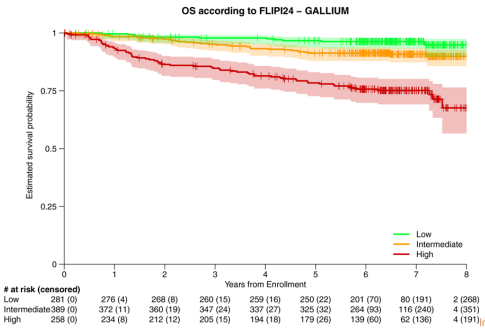
- ✓ *The FLIPI24 model robustly stratifies patients at increased risk of lymphoma-related death*

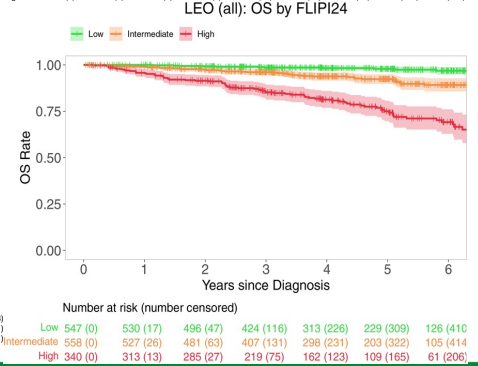












Maurer MJ, Prochazka VK, El-Galaly TC, et al. FLIPI24: A Modern Prognostic Model and Clinical Trial Enrichment Tool for Newly Diagnosed Follicular Lymphoma. J Clin Oncol. 2025 Dec 2:JCO2500892.

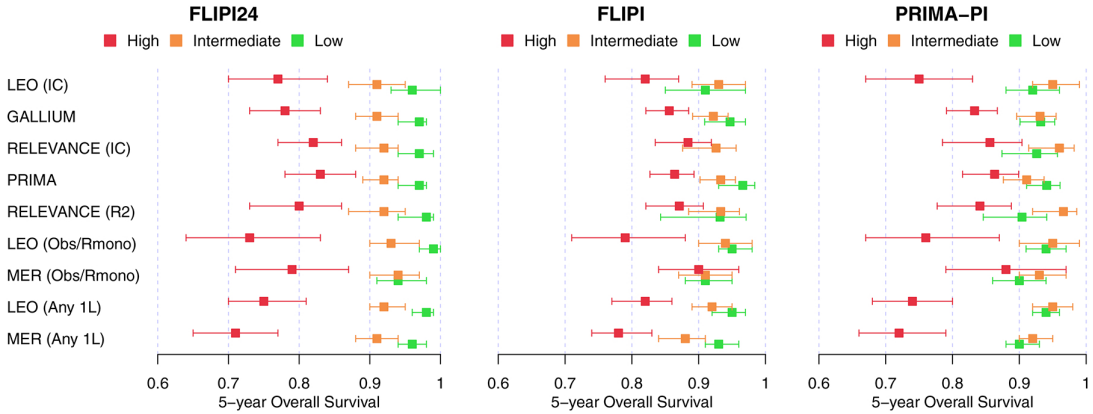
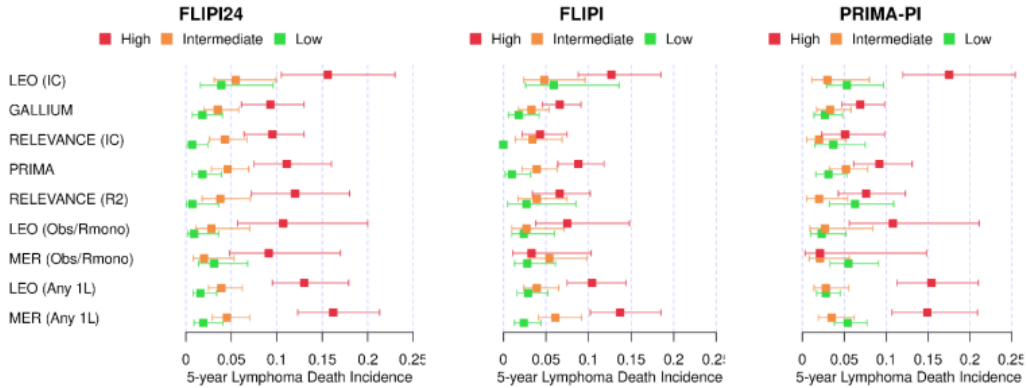


Figure S7. Lymphoma-related death by FLIPI24, FLIPI, and PRIMA-PI in Validation Datasets



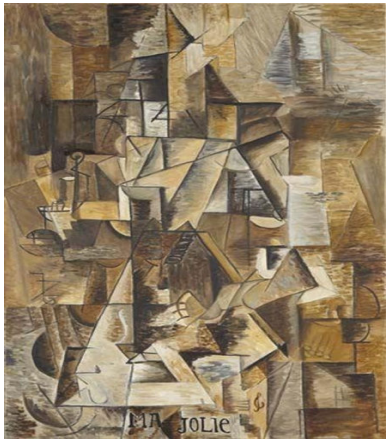
Maurer MJ, Prochazka VK, El-Galaly TC, et al. FLIPI24: A Modern Prognostic Model and Clinical Trial Enrichment Tool for Newly Diagnosed Follicular Lymphoma. J Clin Oncol. 2025 Dec 2:JCO2500892.

- *Do not capture tumor biology*
- *Limited discrimination within intermediate-risk groups*
- *Designed for cohorts, not individuals*
- *Cannot fully inform treatment selection*

How can I assess prognosis in Follicular Lymphoma?

PET-based prognosticators

Biological predictors



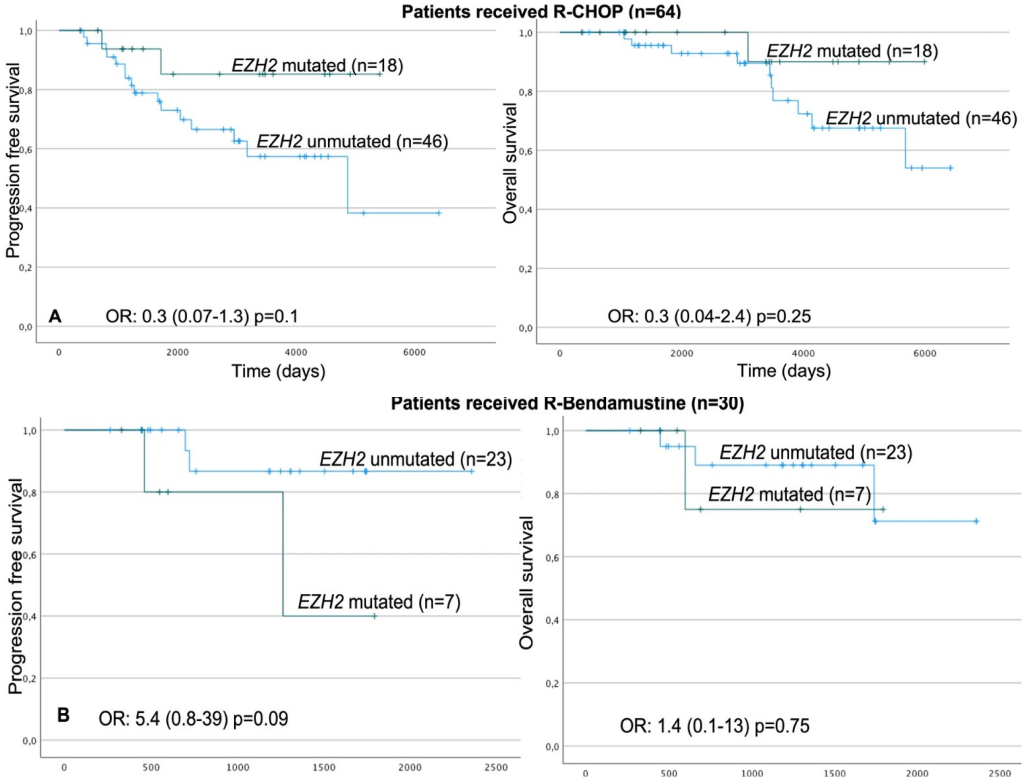
Pablo Picasso – Ma Jolie (1911–1912)

INNOVATIVE SCORES

Biological Predictors

- ✓ *Genetic landscape of follicular lymphoma*
- ✓ *Key alterations: EZH2, CREBBP, EP300, etc.*
- ✓ *Role of the tumor microenvironment*
- ✓ *Prognosis as a biological phenotype*

EZH2 mutations at diagnosis in follicular lymphoma: a promising biomarker to guide frontline treatment

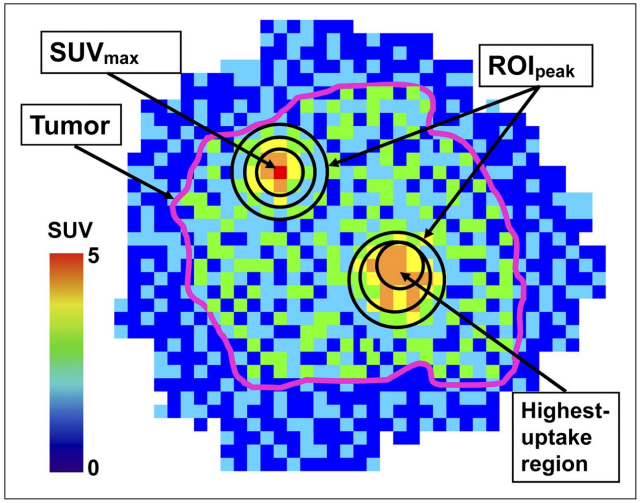


Martínez-Laperche, C., et al. EZH2 mutations at diagnosis in follicular lymphoma: a promising biomarker to guide frontline treatment. BMC Cancer 22, 982 (2022).

PET-based prognostic factors

- ✓ *Baseline FDG-PET/CT*
- ✓ *SUVmax – not standardized cut-off value*
- ✓ *Metabolic tumor burden (TMTV)*

Is hotter more aggressive? Baseline SUVmax in follicular lymphoma



Impact of the Definition of Peak Standardized Uptake Value on Quantification of Treatment Response.
Matt Vanderhoek, Scott B. Perlman and Robert Jeraj
Journal of Nuclear Medicine January 2012, 53 (1) 4-11

Table 1. Key studies relating baseline SUVmax with outcome in FL

Reference	Patients, n	Median baseline SUVmax (range)	HT	PFS
PET in PRIMA (retrospective)[41]	58	11.7 (4.6-35.6)	No patients with HT	No association of bSUVmax with PFS ($P = 0.53$). ROC analysis did not identify an optimal pretreatment SUVmax cutoff with a significant impact on PFS
FOLLCOLL (retrospective)[28]	181	10 (3-35; IQR 7-14). No correlation with histologic grade, $P = 0.66$. Best cutoff on ROC and X-tile analysis SUVmax 9.4	2 patients with HT	SUVmax > 9.4: 5-y PFS 62%, median PFS 78.7 mo. SUVmax <9.4: 5-y PFS 47%, median PFS 48.7 mo. $P = 0.0318$. No difference in OS, 93.7% vs 88.4%; $P = .15$
GALLIUM (prospective)[31]	549	Range, 3-64; median, 12.4 (8.1-28.0) in HT; median 11.8 (3.1-64.4) in non-HT	15 patients (2.7%) with HT at 5 y	No association of bSUVmax with PFS, Q1 vs Q4; HR, 1.14 (95% CI, 0.72-1.81), $P = 0.58$
Strati et al (retrospective)[25]	346	11 (1.5-42) 52 patients (15%) with SUVmax >18	HT excluded from study population	No effect on PFS if treated with R-CHOP or other CIT. Inferior 8-y OS if SUVmax >18 (65% vs. 89%; $P = 0.001$)

Trotman J et al, Blood. 2022 Mar 17;139(11):1631-1641

Pre-treatment maximum standardized uptake value predicts outcome after frontline therapy in patients with advanced stage follicular lymphoma

Paolo Strati, Mohamed Amin Ahmed, Nathan H. Fowler, Loretta J. Nastoupil, Felipe Samaniego, Luis E. Fayad, Fredrick B. Hagemeister, Jorge E. Romaguera, Alma Rodriguez, Michael Wang, Jason R. Westin, Chan Cheah, Mansoor Noorani, Lei Feng, Richard E. Davis, Sattva S. Neelapu

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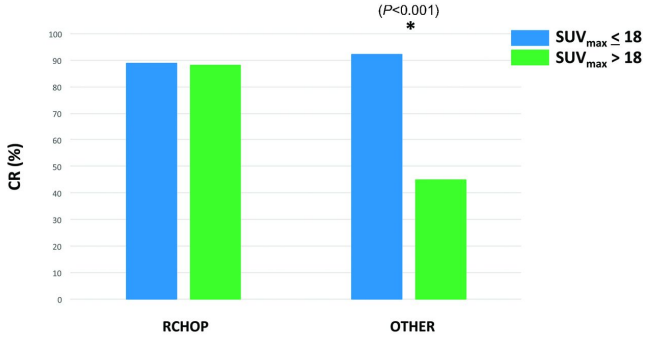
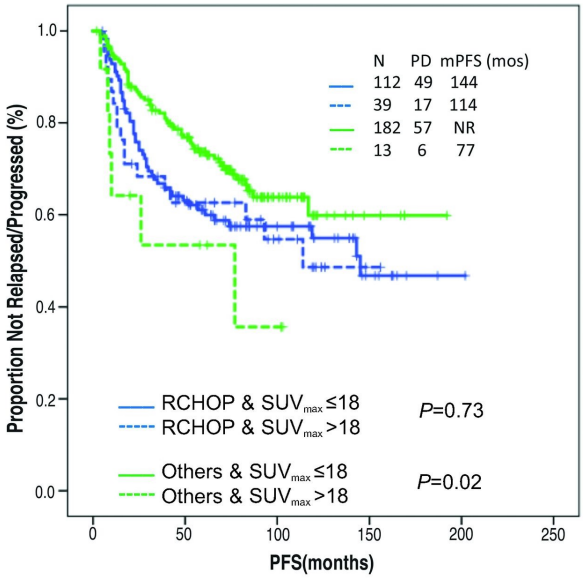
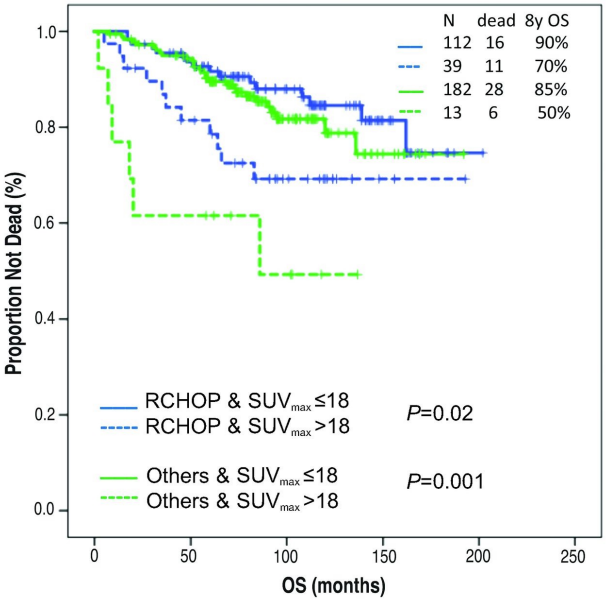
Vol. 105 No. 7 (2020): July, 2020 https://doi.org/10.3324/haematol.2019.230649







Blood. 2020 Jan 21;135(15):1214–1218. doi: 10.1182/blood.2019001091

Baseline SUVmax did not predict histological transformation in follicular lymphoma in the phase 3 GALLIUM study

Farheen Mir [1,✉], Sally F Barrington [2], Helen Brown [3], Tina Nielsen [4], Deniz Sahin [4], Michel Meignan [5], Judith Trotman [6]

Table 1. Baseline characteristics and demographics of patients with PET data, with or without HT

Characteristic	HT (n = 15)	No HT (n = 534)
Age, median, y	60	56
Males	7 (46.7)	238 (44.6)
ECOG PS		
0-1	13 (86.7)	519 (97.2)
2	2 (13.3)	15 (2.8)
FLIPI		
Low (0-1)	2 (13.3)	108 (20.2)
Intermediate (2)	5 (33.3)	212 (39.7)
High (≥3)	8 (53.3)	214 (40.1)
Extranodal involvement	13 (86.7)	363 (68.0)
FLIPI2		n = 522
Low (0-1)	1 (6.7)	53 (102)
Intermediate (2)	4 (26.7)	263 (50.4)
High (≥3)	10 (66.7)	206 (39.5)
Bone marrow involvement		n = 531
Positive	12 (80.0)	281 (52.9)
Negative	3 (20.0)	245 (46.1)
Indeterminate	0 (0)	5 (0.9)
LDH		n = 532
High	10 (66.7)	148 (27.8)
Normal/low	5 (33.3)	384 (72.2)
Hemoglobin		n = 533
Low	8 (53.3)	150 (28.1)
Normal/high	7 (46.7)	383 (71.9)

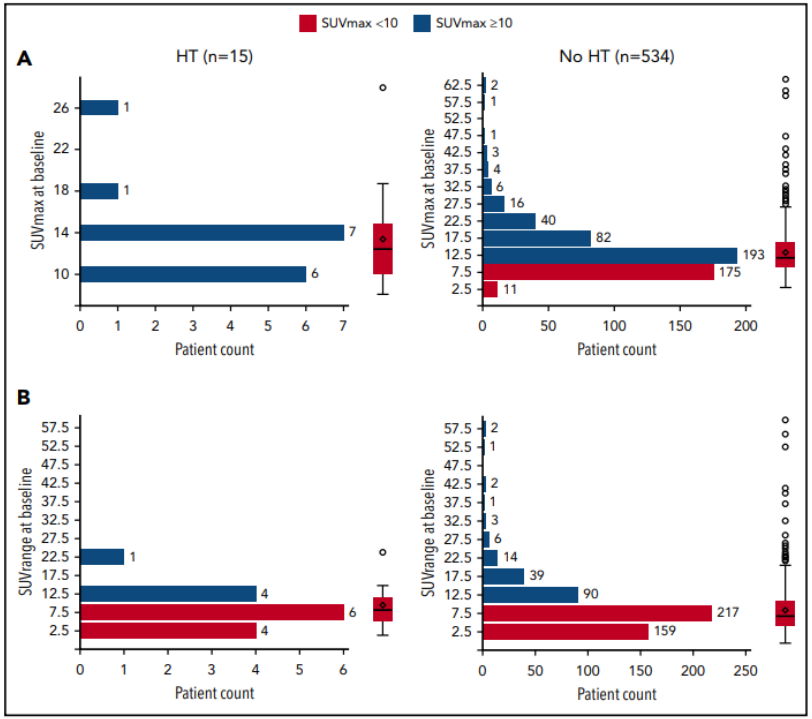


Figure 1. Distribution and probability plot of bSUVmax and bSUVrange by HT status. (A) bSUVmax. (B) bSUVrange.

Blood Reviews 71 (2025) 101270

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journal homepage: www.elsevier.com/locate/issn/0268960X

Review

PET scan for the detection of histological transformation of follicular lymphoma: A systematic review of diagnostic performance

Marc Sorigue [a,*], Milos Miljkovic [b], Pablo Mozas [c]

Table 3
PET results and diagnostic performance in the studies included in this systematic review.

Study	SUVmax in iNHL / FL	SUVrange in FL	SUVmax in HT	SUVrange in HT	SUVmax AUROCC	SUVrange AUROCC	SUVmax cutoffs	SUVrange cutoffs
Schoder et al. [11]	–	–	Ranges from 4.8 to 29.8	–		–	SUVmax >10 in 5/8 patients with HT (sens 0.63)	–
Bodet-Milin et al. [8]	Median 9.3 (IQR 8–12.6)[a]	Median: 6.4 (IQR 3–8.2)[a]	Median 18.1 (IQR 17–24)[a]	Median: 15.2 (IQR 8.6–20.4)[a]	0.95 (95 % CI 0.85–1)[a]	0.86 (95 % CI 0.70–1)[a]	Youden index: 14.6 (sens 0.89, spec 0.92)[a]. For PPV = 1 → 17 For NPV = 1 → 11.7	Youden index: 10.6 (sens 0.67, spec 0.91) For PPV = 1 → 11.5 For NPV = 1 → 6.1
Noy et al. [12]	–	–	Median 16.4 (IQR 9.7–22.5)[a]	Median 9.1 (IQR 5.9–13.4)[a]		–	SUVmax >10 in 15/21: sens 0.71[a] SUVmax >13 in 12/21: sens 0.57[a]	–
Wondergem et al. [13]	Median 10.9 (range: 5.3–21)	Median 4.6 (0–7.9)	Median 22.0 (14.7–42.2)	Median 15 (6–37.5)	0.97 (95 % CI: 0.91–1)	0.97 (95 % CI: 0.9–1)	For sens = 1 → 14.5 (spec 0.82)	For sens = 1 → 5.8 (spec 0.71).
Shichijo et al. [14]	First cohort: Median 9.2 (range 2.1–16.7) Second cohort: Median 12.2 (range 2.6–20.3)	–	First cohort: Median 16.7 (range 4.9–33.3) Second cohort: Median 27.5 (range 10.4–46.6)	–	First cohort: 0.83 (95 % CI: 0.72–0.95) Second cohort: 0.81 (95 % CI 0.62–1)	–	SUVmax ≥10 (sens 0.86–1, spec 0.37–0.57, PPV: 0.43–0.61, NPV: 0.84–1) SUVmax ≥16 (sens 0.59–0.67, spec 0.79–0.96, PPV: 0.6–0.93, NPV: 0.75–0.83) SUVmax ≥20 (sens 0.22–0.67, spec 0.95–1, PPV: 0.86–1, NPV: 0.62–0.86)	–
Rajamäki et al. [15]	Median 13.6 (range: 10–24.4)[b]	–	Median 27.1 (range: 10.5–34.9)	–	0.95 (95 % CI 0.86–1)	–	Youden index: 26.5 (sens 0.86, spec 1)	–
Wai et al. [16]	Median 10.7 (IQR 7.1–15.3)	–	Median 13.7 (IQR 10.6–26.3)	–	0.68	–	Youden index: 12 (sens 0.71, spec 0.61, PPV 0.7, NPV 0.65). SUVmax >25 (sens 0.26, spec 0.96, PPV 0.8, NPV 0.69)	–

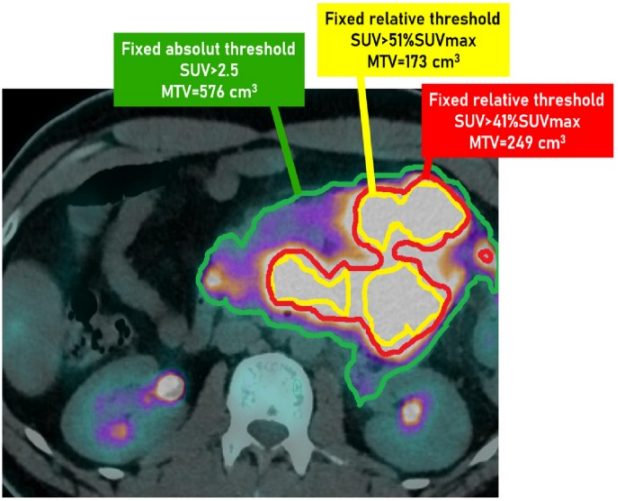
Abbreviations: PET: positron emission tomography; SUV: standardized uptake value; iNHL: indolent non-Hodgkin lymphoma; FL: follicular lymphoma; HT: histological transformation; AUROCC: area under the receiver operating characteristic curve; CI: confidence interval; sens: sensitivity; spec: specificity; IQR: interquartile range; PPV: positive predictive value; NPV: negative predictive value.

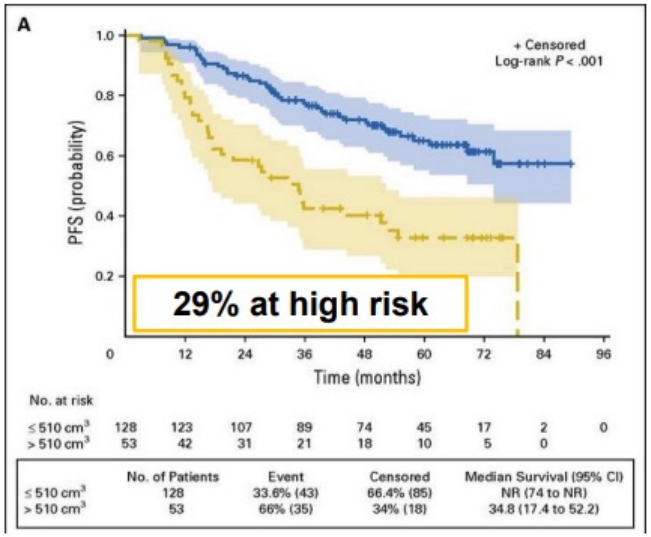
..Proposed SUVmax cutoffs should not be used to determine whether a patient has HT or to decide whether a biopsy should be obtained.

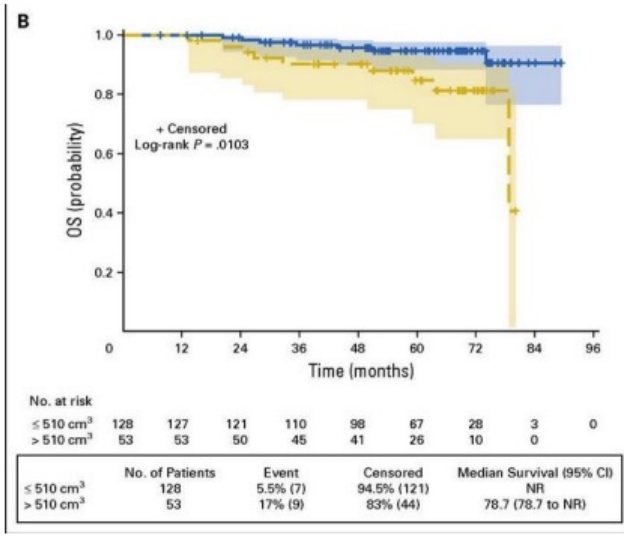
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Baseline Metabolic Tumor Volume Predicts Outcome in High–Tumor-Burden Follicular Lymphoma: A Pooled Analysis of Three Multicenter Studies

Michel Meignan, Anne Ségolène Cottereau, Annibale Versari, Loïc Chartier, Jehan Dupuis, Sami Boussetta, Ilaria Grassi, René-Olivier Casasnovas, Corinne Haioun, Hervé Tilly, Vittoria Tarantino, Julien Dubreuil, Massimo Federico, Gilles Salles, Stefano Luminari, and Judith Trotman







Michel Meignan et al. JCO doi:10.1200/JCO.2016.66.9440

American Journal of Hematology

WILEY

RESEARCH ARTICLE OPEN ACCESS

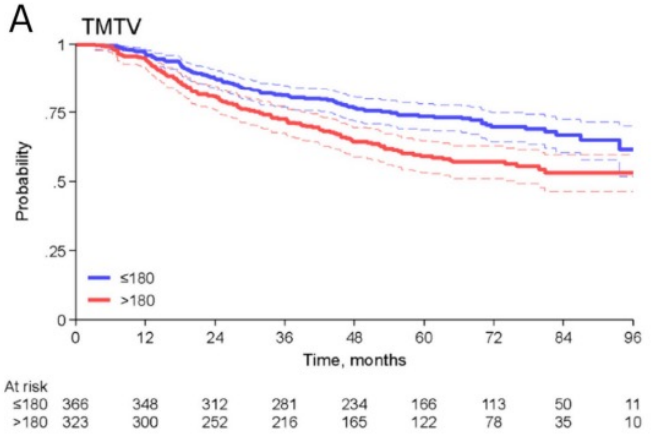
Total Metabolic Tumor Volume Is a Strong Independent Prognostic Factor in Follicular Lymphomas: Results From a Sub-Study of the FOLL12 Trial

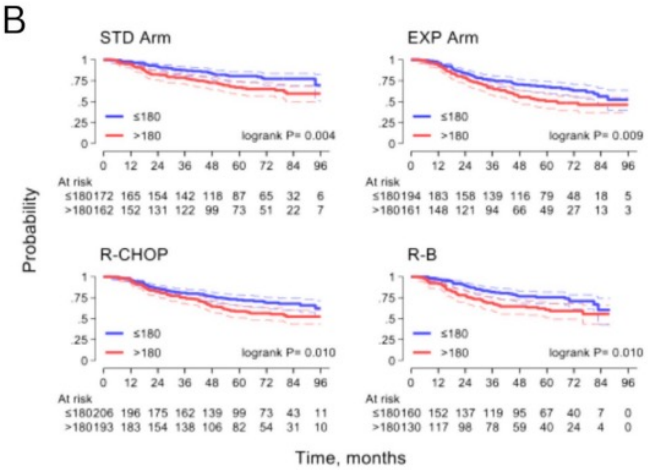
Rexhep Durmo[1] | Stephane Chauvie[2] | Carla Minoia[3] | Fabrizio Bergesio[2] | Federico Fallanca[4] | Simona Peano[5] | Luigi Marcheselli[6] | Antonella Anastasia[7] | Carola Boccomini[8] | Paolo Corradini[9] | Jacopo Olivieri[10] | Luca Arcaini[11] | Federica Cavallo[12] | Adalberto Ibatici[13] | Luca Nassi[14] | Vittoria Tarantino[15] | Antonello Pinto[16] | Caterina Stelitano[17] | Alessandro Pulsoni[18] | Francesca Ricci[19] | Salvatrice Mancuso[20] | Emanuele Cencini[21] | Nicola Di Renzo[22] | Clara Mannarella[23] | Angelo Palmas[24] | Pierluigi Zinzani[25,26] | Caterina Bocci[27] | Francesca Rossi[28] | Angelo Michele Carella[29] | Massimo Federico[30] | Annibale Versari[1] | Luca Guerra[31,32] | Stefano Luminari[30,33]

TABLE 1 | Univariable and multivariable Cox PH regression of progression-free survival ($n = 692$, fail 231).

	n (%)	Univariable		Multivariable			
Covariate		**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
TMTV > 180 mL	323 (47)	1.61 (1.24–2.09)	< 0.001	1.38 (1.05–1.81)	0.020	1.37 (1.03–1.81)	0.028
Age > 60	341 (50)	1.38 (1.06–1.79)	0.015			1.35 (1.03–1.76)	0.028
Sex male	317 (46)	1.23 (0.95–1.59)	0.119	1.32 (1.02–1.72)	0.036	1.39 (1.07–1.82)	0.015
B2M > ULN	378 (55)	1.57 (1.20–2.05)	0.001			1.26 (0.94–1.68)	0.124
BM+	381 (55)	1.57 (1.20–2.06)	0.001			1.49 (1.12–1.98)	0.007
LoDLIN > 6 cm	382 (55)	1.29 (0.99–1.68)	0.060			1.38 (1.04–1.83)	0.026
Hb < 12 mg/dL	111 (16)	1.74 (1.28–2.37)	0.001			1.77 (1.27–2.46)	0.001
FLIPI-2 High	278 (40)	2.25 (1.73–2.91)	< 0.001	2.11 (1.61–2.77)	< 0.001		
Experimental arm	355 (52)	1.70 (1.30–2.21)	< 0.001				
R-B	290 (42)	0.97 (0.74–1.26)	0.821	1.02 (0.78–1.34)	0.869	1.04 (0.79–1.37)	0.765

Note: In multivariable analysis the Cox PH regression was stratified by randomization arm; B2M, beta2 microglobuline; BM, bone marrow involvement; FLIPI, follicular lymphoma international prognostic index; Hb, hemoglobin; LoDLIN, longest diameter of the largest involved node; R-B, rituximab plus bendamustine; ULN, upper limit of normality.





- Beyond diagnosis - monitoring disease during and after treatment:
  - *Response-adapted prognostic factors*

How can I assess prognosis in Follicular Lymphoma?

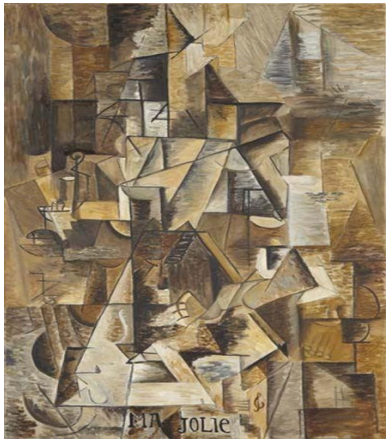
At relapse

Pablo Picasso - Science and Charity (1897)

CLINICAL SCORES

PET-based prognosticators

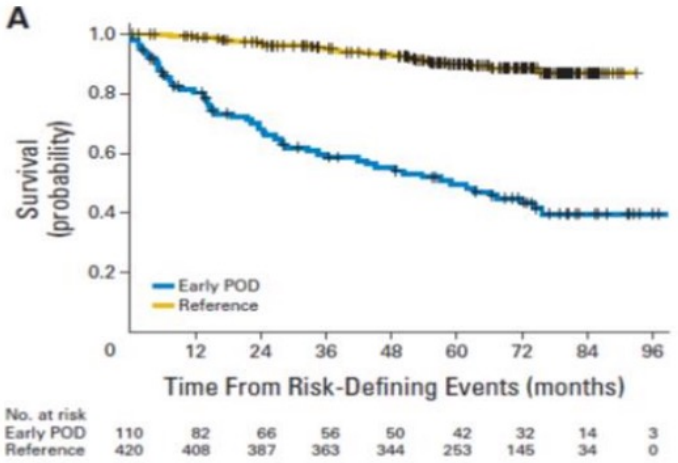
Minimal Residual Disease (MRD)



Pablo Picasso – Ma Jolie (1911–1912)

INNOVATIVE SCORES

POD24: A Major Prognostic Landmark



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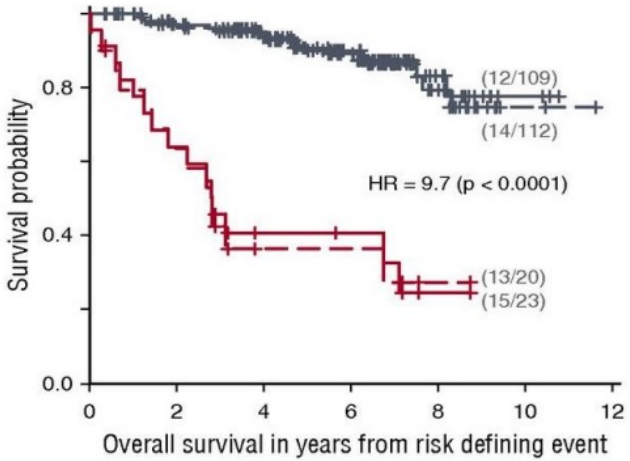
J Clin Oncol. 23: 2516-2522. 2015



Jurinovic et al.
Blood. 2016; 128: 1112-1120, 2016

Pablo Picasso - Science and Charity (1897)

- *Binary endpoint that oversimplifies disease biology*
- *Retrospective definition, not available at diagnosis*
- *Influenced by treatment choice and follow-up strategy*
- *Does not capture depth or quality of response*
- *Limited guidance for early risk-adapted interventions*

Response-Based Prognostic Tools

- ✓ *Dynamic prognostication*
- ✓ *End-of-treatment matters*
- ✓ *Metabolic response outperforms anatomic response*
- ✓ *Identifies high-risk patients early despite therapy*
- ✓ *Complements FLIPI / FLIPI2 for risk stratification*

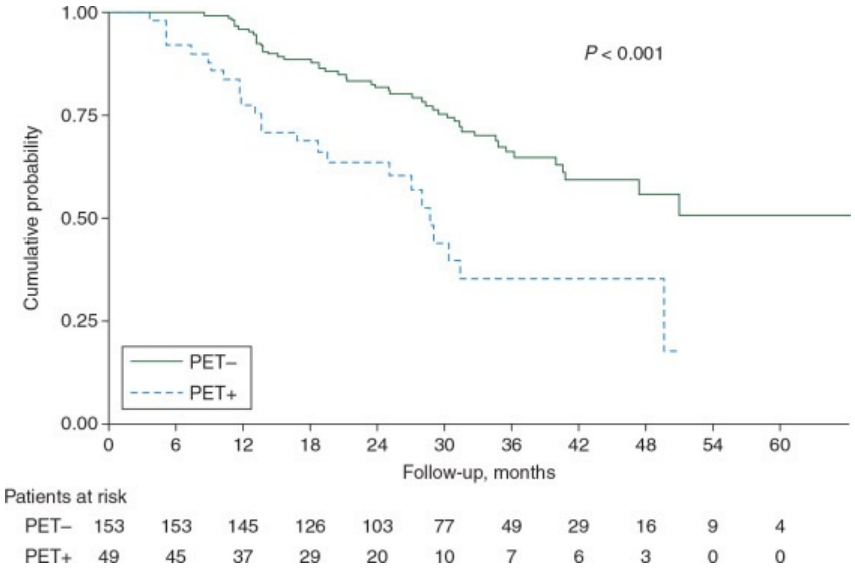
PET-based prognosticators

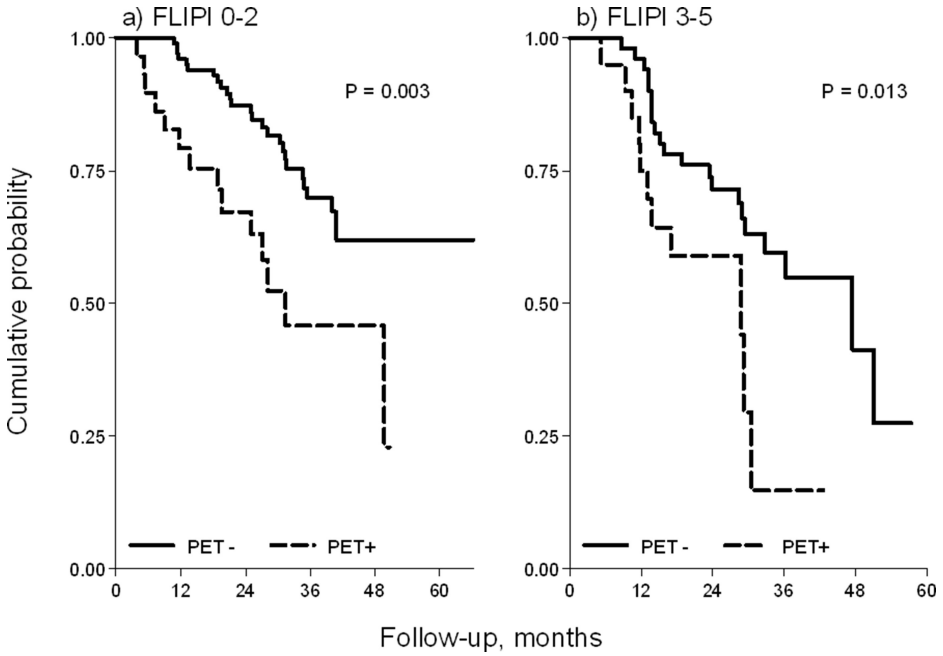
Pablo Picasso – Ma Jolie (1911–1912)

Minimal Residual Disease (MRD)

End of induction [18F]FDG PET

FOLL05 trial





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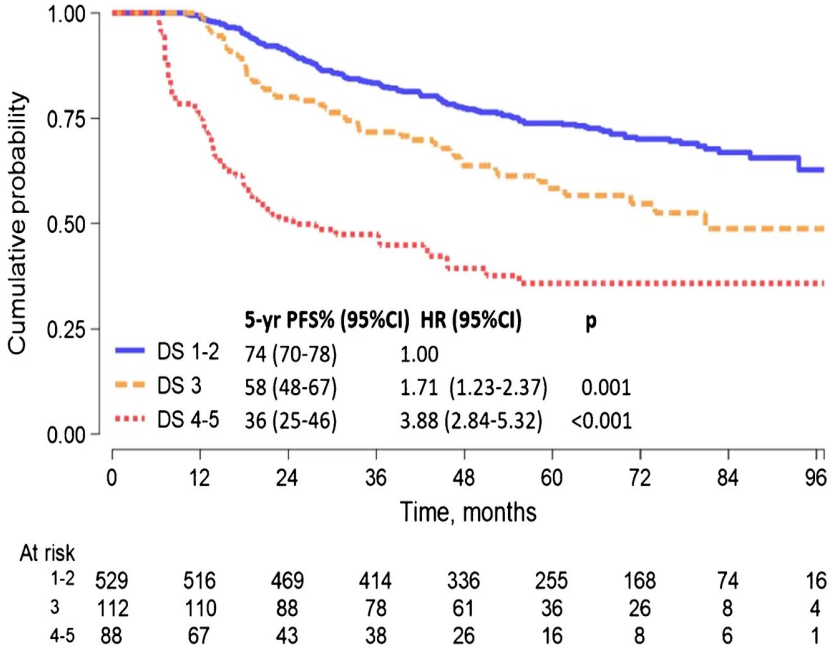
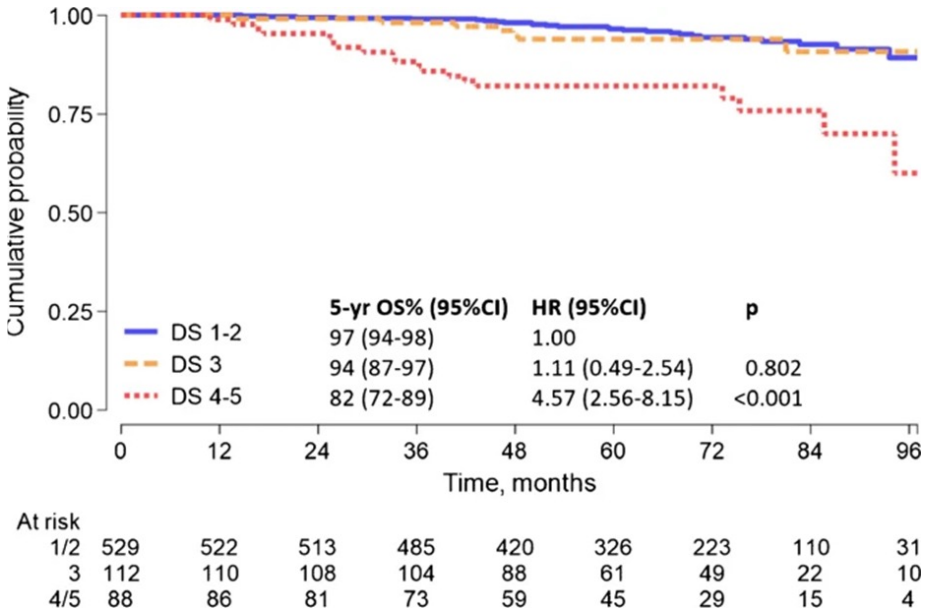
End of induction [18F]FDG PET

FOLL12 trial





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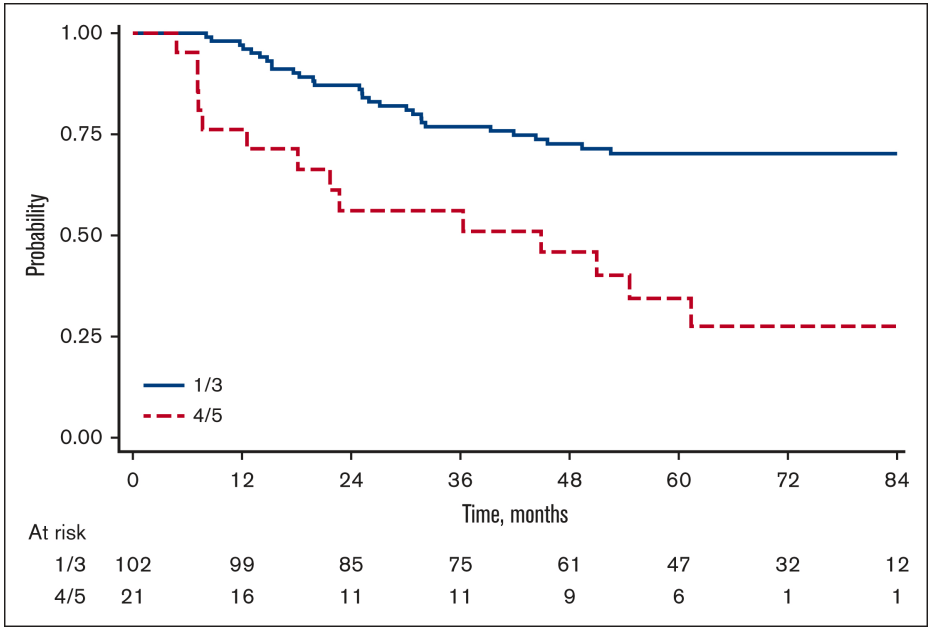
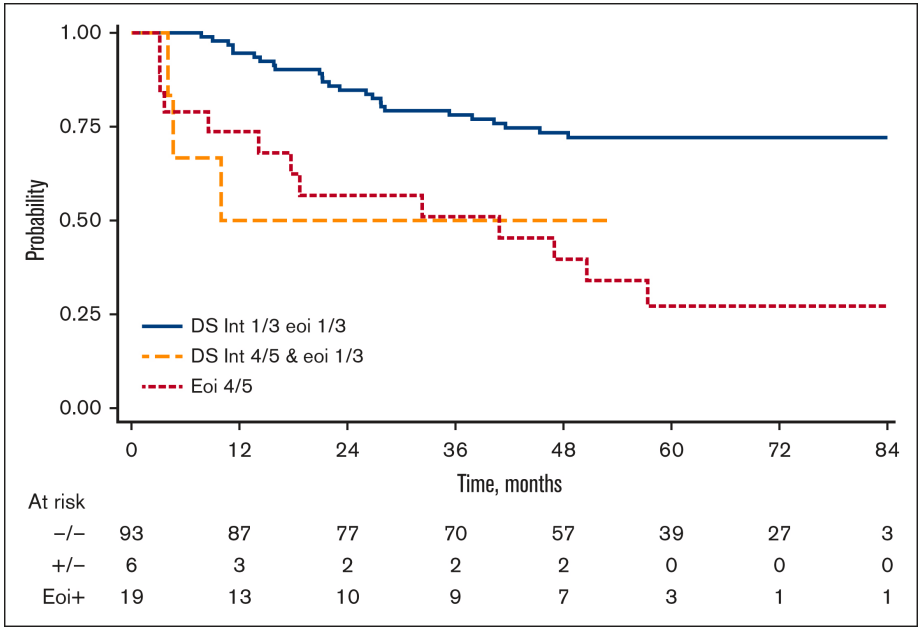
Interim [18F]FDG PET

FOLL12 trial





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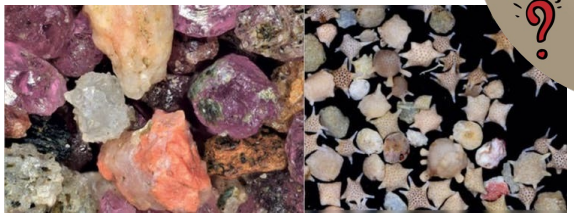
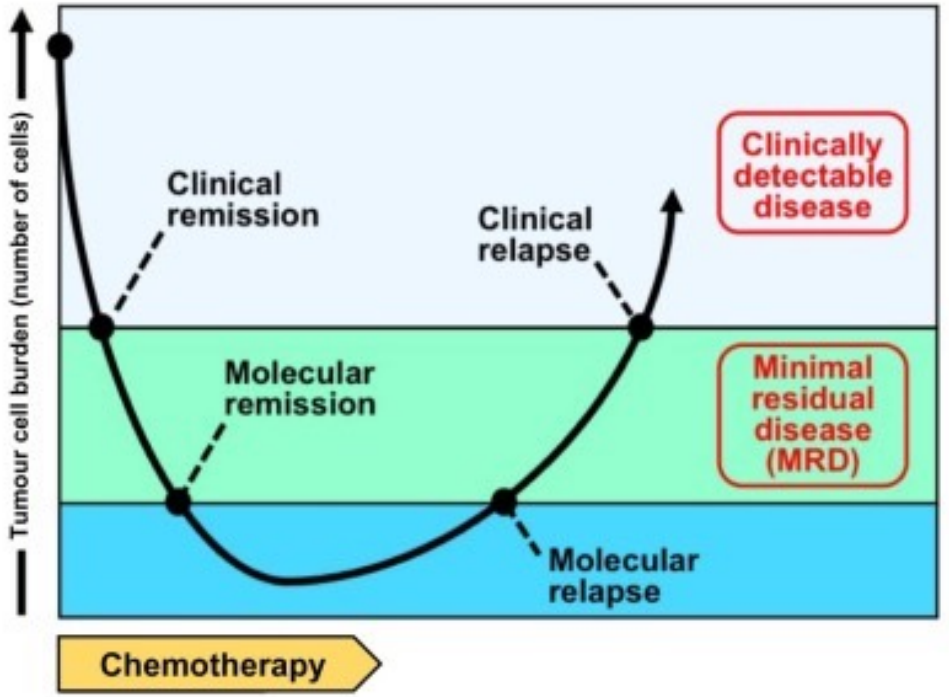




Masahiko Sato, et al. Minimal residual disease in canine lymphoma: An objective marker to assess tumour cell burden in remission, The Veterinary Journal, Volume 215, 2016, Pages 38-42,

Is the prolonged molecular follow-up of clinical relevance?

Study	Advanced disease	Patients	Therapy	Tissue	Method	Marker	Tumor burden / Notes	MRD− %	Clinical impact	Follow-up
Rambaldi et al.13	BCL2/IGH+ FL, untreated	128 (79 R)	CHOP×6 ± R	BM ± PB	Nested PCR	BCL2/IGH	—	After CHOP: BM 36%, PB 35%; After R up to 74%	3-yr FFR 52% BM MRD− after CHOP; 57% vs 20% MRD+ after R	17 mo
Rambaldi et al.14	BCL2/IGH+ FL, untreated	86	—	BM	RQ-PCR	BCL2/IGH	Low/intermediate vs high	—	FFR 64% MRD− vs 32% MRD+ (P<.006)	56 mo
Ladetto et al.15	High-risk FL <60 y	134	R-HDS vs CHOP-R	BM	Nested PCR	BCL2/IGH, IGH	—	44% CHOP-R vs 80% R-HDS	MRD− predicts PFS regardless of treatment	51 mo
Bruna et al.16	High-risk FL <60 y	134	R-HDS vs CHOP-R	BM	Nested PCR	—	—	65% overall	13-yr OS: 82% MRD− vs 52% MRD+	13 y
Ladetto et al.17	FL >60 y	227	R-FND + R maintenance	BM	RQ-PCR	BCL2/IGH	Baseline burden stratifies PFS	84% at end consolidation	3-yr PFS 72% MRD− vs 39% MRD+	42 mo
Galimberti et al.18	Untreated FL	415	R-CHOP / R-CVP / R-FN	BM	Nested, RQ-PCR	BCL2/IGH	High vs low RQ-PCR	71% at EOI	MRD− at 12–24 mo predicts PFS	NA
Zohren et al.19	Untreated FL	114	R-CHOP vs R-B	PB	RQ-PCR	BCL2/IGH	High ratio → worse PFS	85%	High baseline burden predicts shorter PFS	41 mo
Pott et al.20,21	Untreated FL	1101	G- vs R-chemo + maintenance	PB ± BM	RQ-PCR / Nested	BCL2/IGH, IGH	Higher in stage IV, high FLIPI	Up to 94%	MRD− strongly predicts PFS and OS	57 mo
Delfau-Larue et al.22	Untreated FL	440	R2 vs R-CHOP	PB ± BM	ddPCR	BCL2/IGH	Higher in MRD+	PB 98%, BM 78%	3-yr PFS 84% MRD− vs 55% MRD+	NA
Pott et al.23	R-refractory FL	319	G-B vs B	PB ± BM	RQ-PCR	BCL2/IGH, IGH	—	86% G-B vs 55% B	MRD− improves PFS and OS	31.8 mo
Genuardi et al.38	FL marker-negative at baseline	20	—	BM	TLA	BCL2/TLA	New markers in 40% of "marker-negative"	4/5 suitable for RQ-PCR MRD	MRD sensitivity good; allows tracking in previously marker-negative patients	NA
Cavalli et al.40	Early-stage FL	67	—	PB, BM	ddPCR	BCL2/IGH	ddPCR identifies MBR in 44% nested PCR-negative; baseline ≥10^{-5} predicts PFS	—	ddPCR more sensitive than RQ-PCR; tumor burden predictive of PFS	NA
Sarkozy et al.42	FL, PRIMA trial	34	—	Tumor biopsy, plasma	NGS	IGH	Subclonal diversity: 54–75% overlap between plasma/tumor	—	High ctDNA predicts shorter PFS (MVA)	NA
Delfau-Larue et al.43	FL	133 (PET TMTV), 68 PB CTC, 61 PB cfDNA	—	PB	ddPCR	BCL2/IGH	Correlation TMTV ↔ CTCs/cfDNA	—	Total cfDNA & TMTV independent outcome predictors; CTCs predictive in univariate analysis	NA

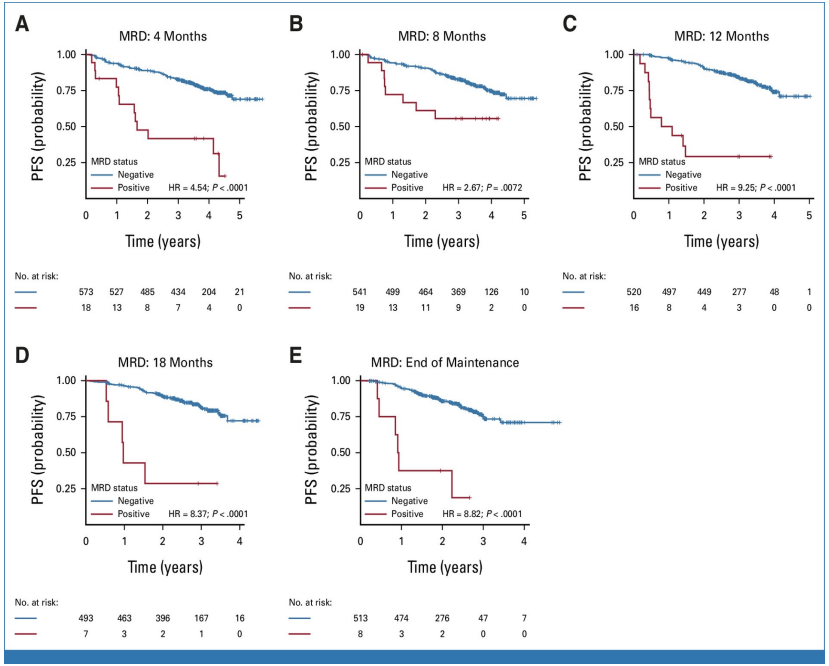
Adapted from Del Giudice I et al. Does MRD have a role in the management of iNHL? Hematology Am Soc Hematol Educ Program (2021) 2021 (1): 320–330.

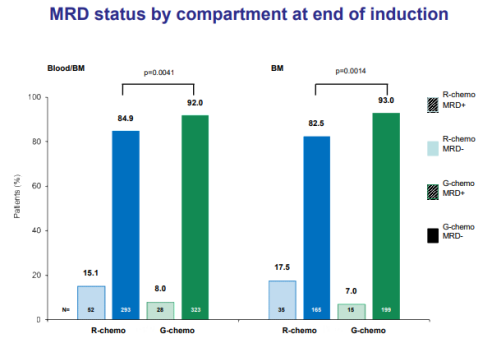
OPEN ACCESS | ORIGINAL REPORTS | December 14, 2023

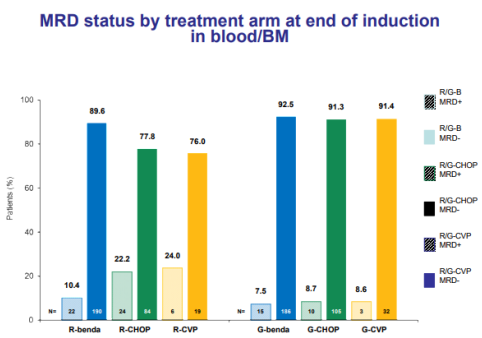
Minimal Residual Disease Status Predicts Outcome in Patients With Previously Untreated Follicular Lymphoma: A Prospective Analysis of the Phase III GALLIUM Study

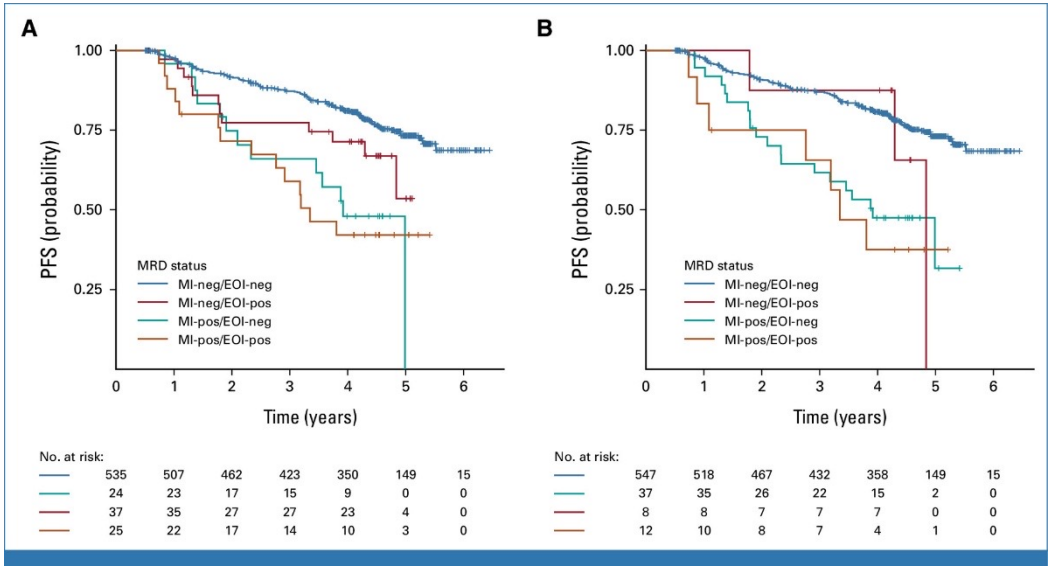
Authors: Christiane Pott, MD, PhD, Vindi Jurinovic, PhD, Judith Trotman, MBChB, Britta Kehden, PhD, Michael Unterhalt, MD, PhD, Michael Herold, MD, Richard van der Jagt, MD, ... SHOW ALL ..., and Eva Hoster, PhD AUTHORS INFO & AFFILIATIONS

J Clin Oncol **42**, 550-561(2024) • Volume 42, Number 5 • DOI: 10.1200/JCO.23.00838





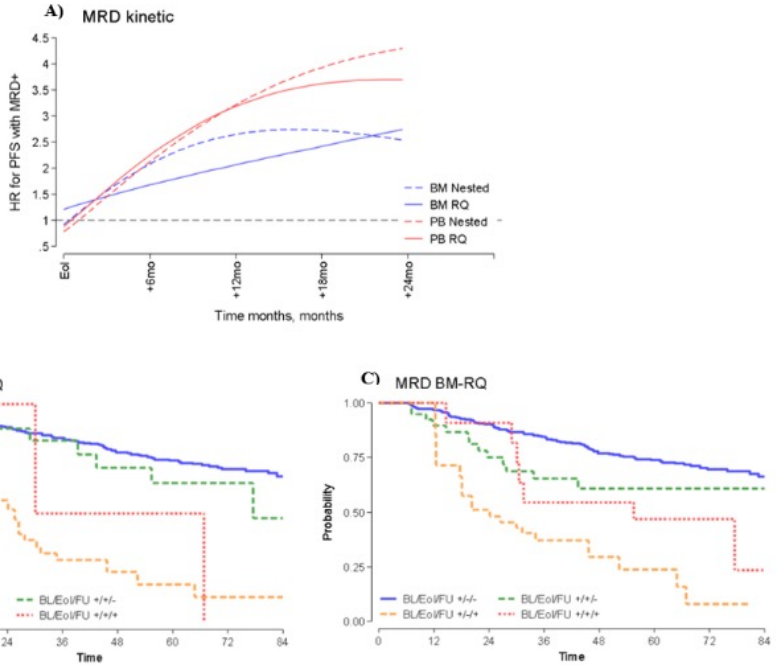




EPIDEMIOLOGICAL | NOVEMBER 6, 2024

Impact of Minimal Residual Disease Analysis in the Era of Rituximab Maintenance in Follicular Lymphoma: Data from "FOLL12" Phase III Trial of the Fondazione Italiana Linfomi

Simone Ferrero, Ilaria Del Giudice, Sara Galimberti, Valter Gattei, Luigi Marcheselli, Elisa Genuardi, Daniela Drandi, Mariapia Pironti, Irene Dogliotti, Aurora Maria Civita, Irene Della Starza, Giovanni Manfredi Assanto, Francesca Guerrini, Clara Bono, Riccardo Bomben, Carola Boccomini, Lucia Farina, Jacopo Olivieri, Luca Arcaini, Federica Cavallo, Filippo Ballerini, Gloria Margiotta Casaluci, Vittorio Ruggero Zilioli, Manuela Zanni, Gerardo Musuraca, Anna Merli, Benedetta Bianchi, Silvia Bolis, Vincenzo Pavone, Annalisa Chiarenza, Annalisa Arcari, Catello Califano, Samantha Pozzi, Massimo Massaia, Annarita Conconi, Tommasina Perrone, Donato Mannina, Alessandro Re, Maria Elena Nizzoli, Dimitri Dardanis, Stefano Luminari, Marco Ladetto

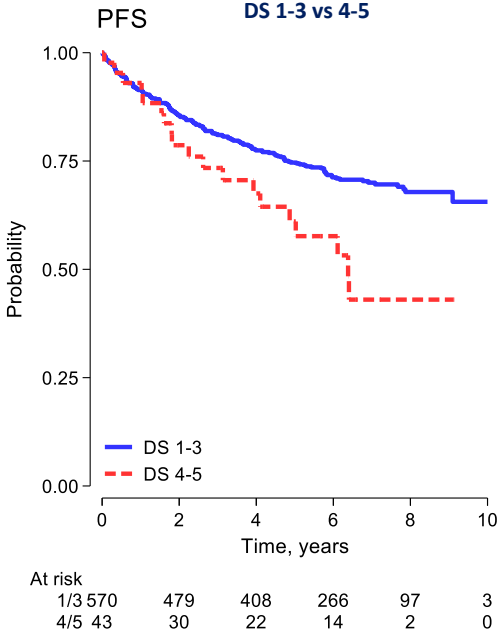


Courtesy of Prof. Ferrero - S. Ferrero et al., ASH 2024 – Article under submission

PET and MRD are confirmed as strong prognostic factors and can be combined together to increase their prognostic accuracy

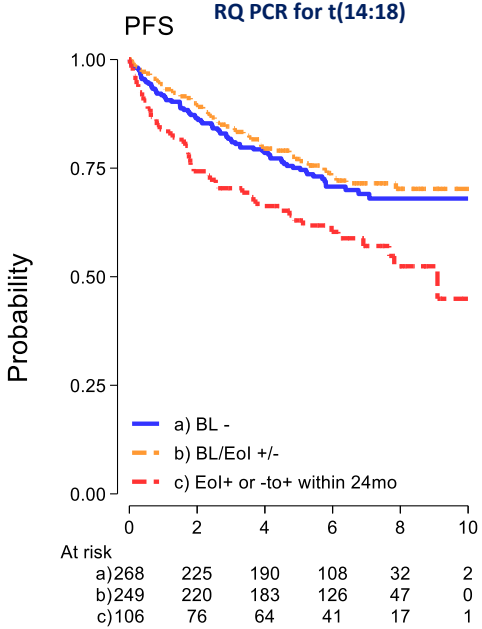
PET only

DS 1-3 vs 4-5

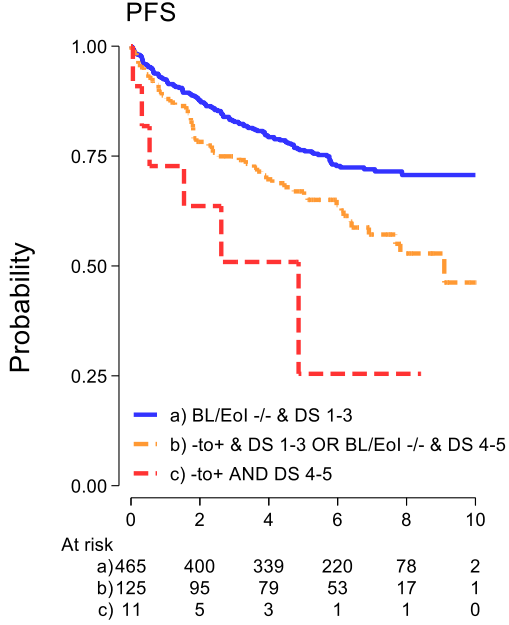


MRD only

RQ PCR for t(14:18)



MRD + PET



PFS	8yr PFS% (95%CI)	HR (95%CI)	p
A	71 (66-75)	1.00	
B	53 (42-63)	1.68 (1.21-2.33)	0.002
C	25 (2-64)	3.68 (1.62-8.38)	0.002

MRD, Minimal residual disease: DS, Deauville score: BL baseline molecular marker: EoI, End of induction

Courtesy of Prof. Luminari - S. Luminari et al., ASH 2025

Key Take-Home Messages

- Follicular lymphoma is highly variable in both its clinical presentation and underlying biology, making each patient’s disease course unique.
- Established models like FLIPI, FLIPI2, or PRIMA-PI can still provide useful prognostic guidance at diagnosis.
- PET-CT with Deauville scoring is recommended at the end of systemic therapy to assess response, providing important prognostic information.
- At retreatment, early progression is the strongest predictor of outcome.
- No single model can fully capture the complexity of follicular lymphoma. The future of prognostic assessment lies in combining clinical features, biological markers, and treatment response to provide a more accurate, dynamic, and personalized prediction of patient outcomes.

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A tutti voi per l’ascolto!