2nd edition

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

Turin, September 13-14, 2021

Starhotels Majestic

Scientific board:

Marco Ladetto (Alessandria)

Umberto Vitolo (Candiolo-TO)

BIOLOGY OF HIGH RISK FOLLICULAR LYMPHOMA

Simone Ferrero, MD

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UNIVERSITA DEGLI STUDI DI TORINO

DBMSS Dipartimento di Biotecnologie Molecolari e Scienze per la Salute

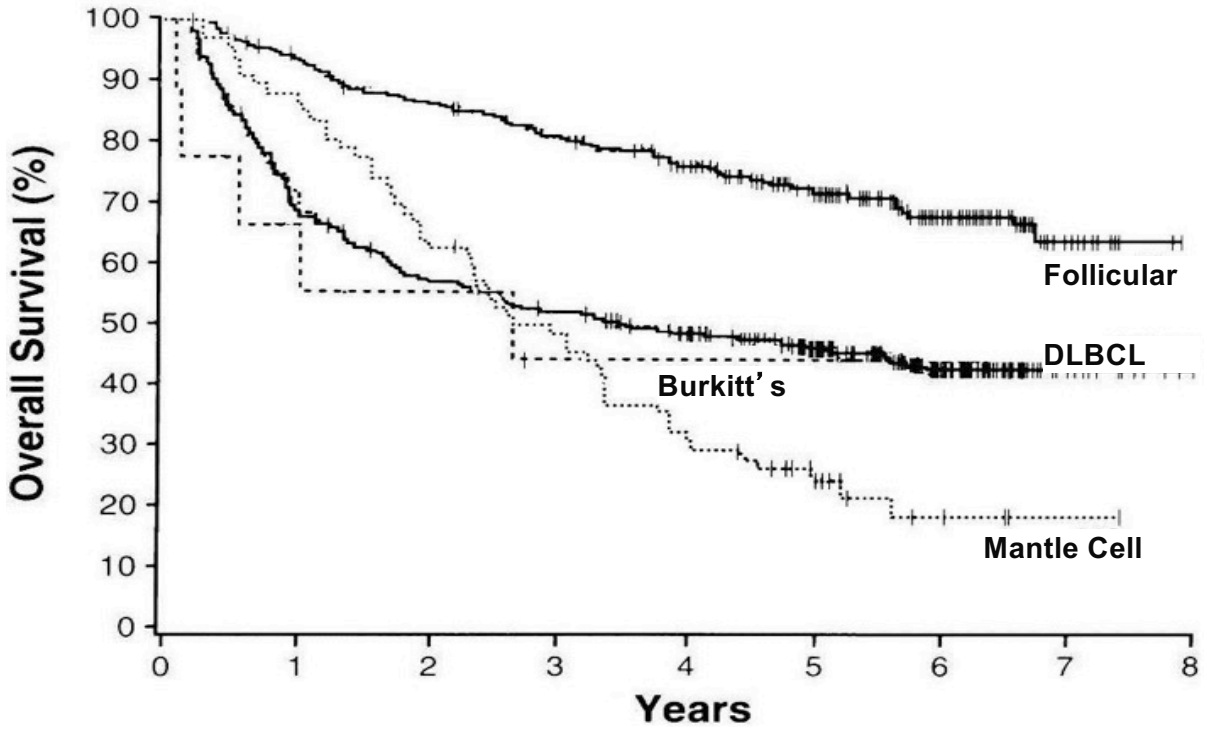
AZIENDA OSPEDALIERO - UNIVERSITARIA Città della Salute e della Scienza di Torino

FONDAZIONE ITALIANA LINFOMI

DISCLOSURES: Simone Ferrero

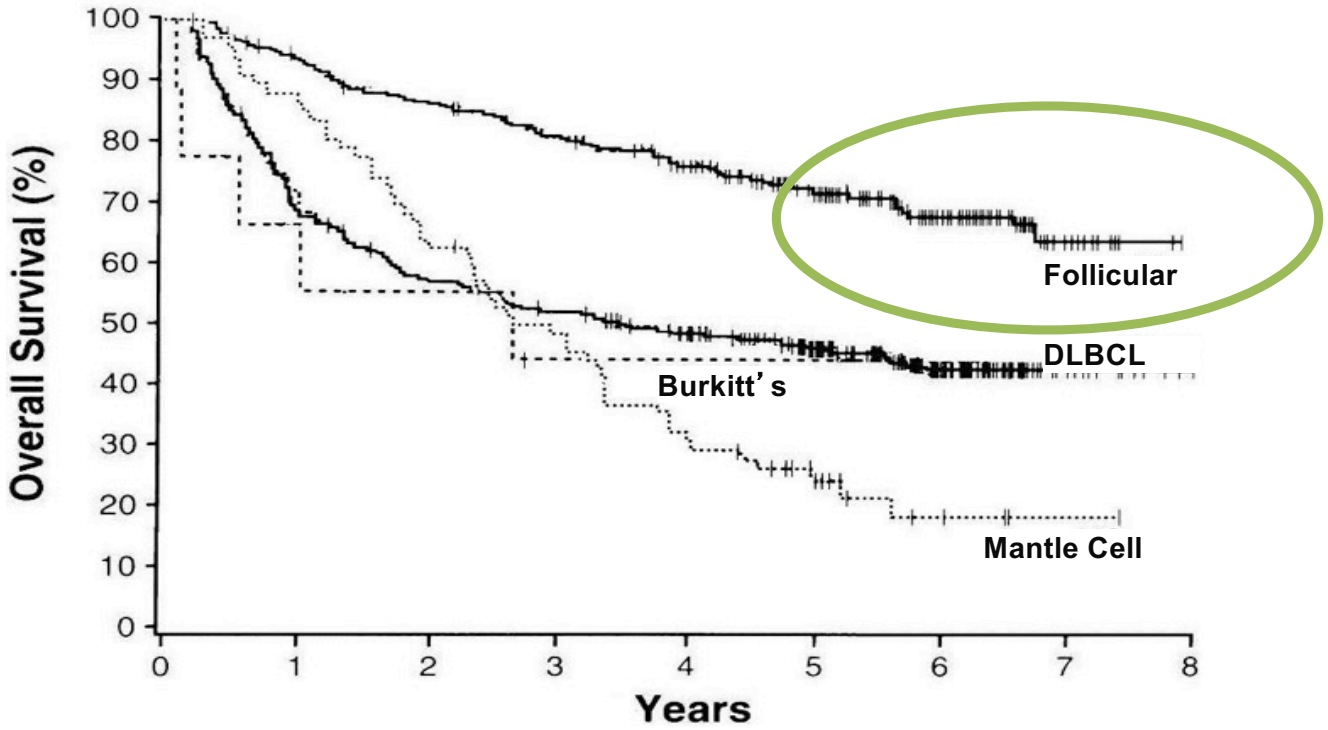
- **Janssen**: consultancy, advisory board, reasearch support, speakers honoraria
- **EUSA Pharma**: consultancy, advisory board, speakers honoraria
- **Morphosys, Gilead**: reasearch support
- **Incyte, Clinigen**: advisory board
- **Servier**: speakers honoraria

FL is a heterogeneous disease



The International Lymphoma Study Group. Blood 1997

FL is a heterogeneous disease



The International Lymphoma Study Group. Blood 1997

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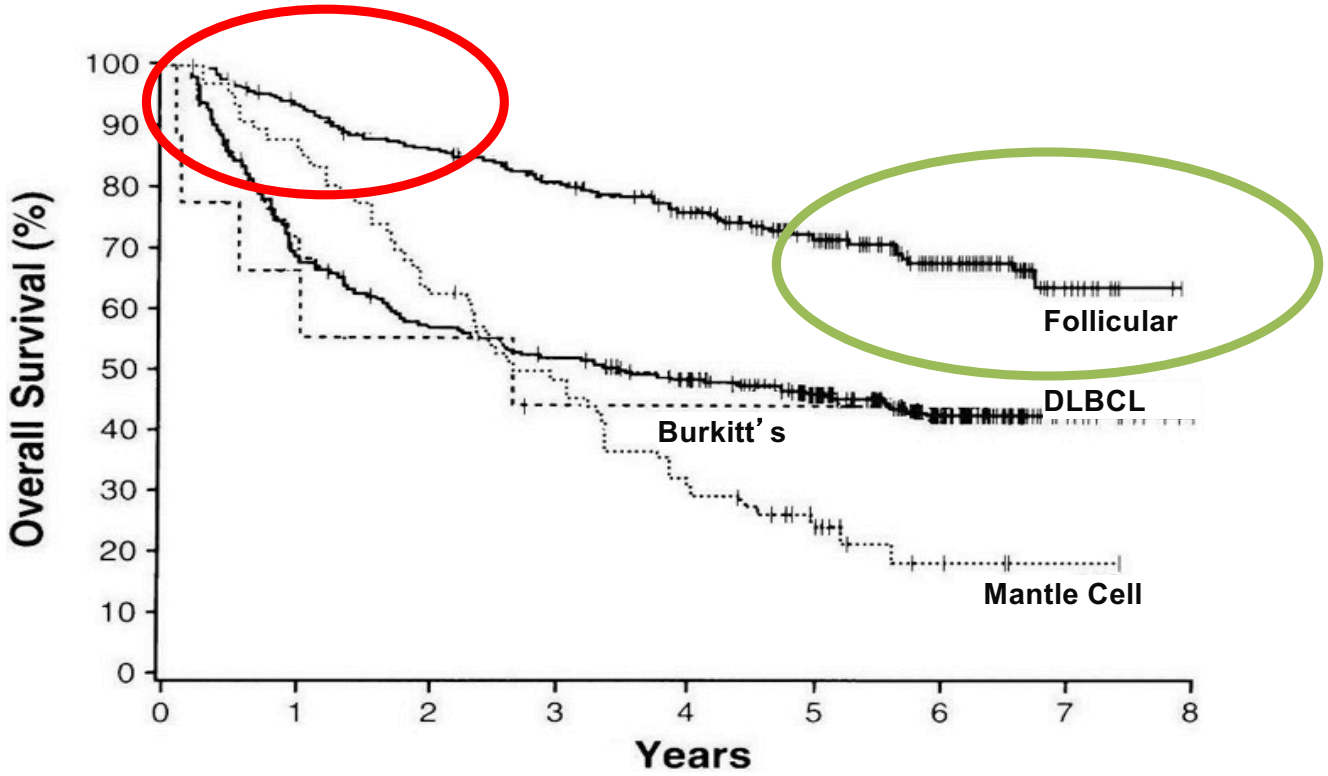


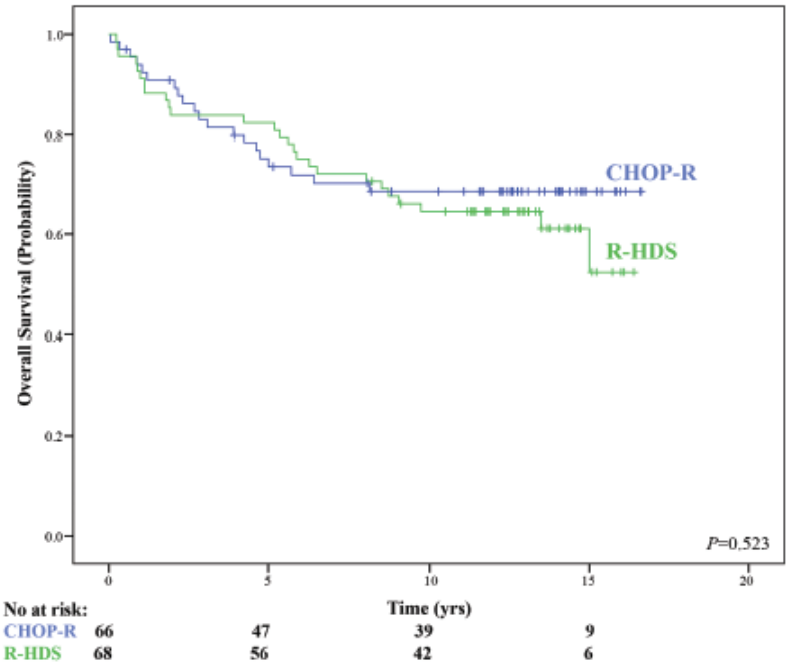
The International Lymphoma Study Group. Blood 1997

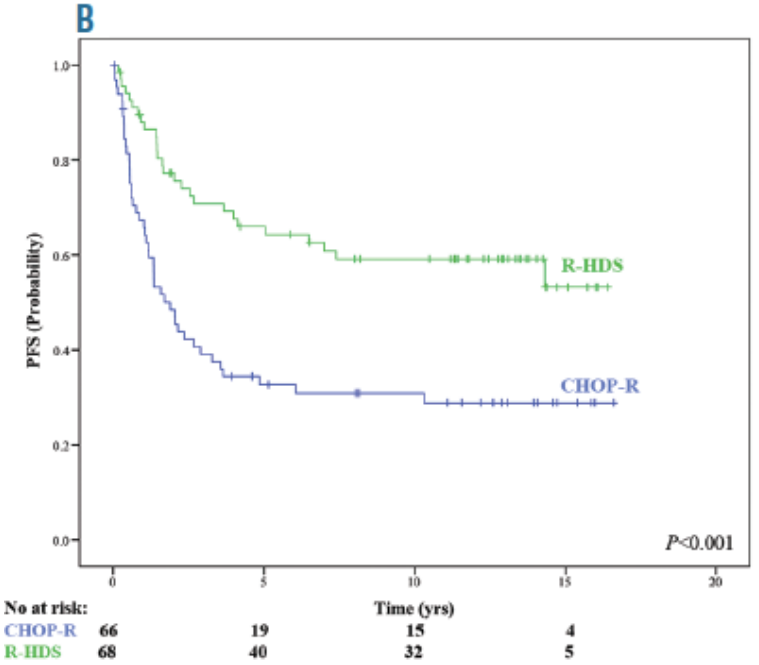
2nd edition
Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Prolonged survival in the absence of disease-recurrence in advanced-stage follicular lymphoma following chemo-immunotherapy: 13-year update of the prospective, multicenter randomized GITMO-IIL trial

Riccardo Bruna,[1§] Fabio Benedetti,[2] Carola Boccomini,[3] Caterina Patti,[4] Anna Maria Barbui,[5] Alessandro Pulsoni,[6] Maurizio Musso,[7] Anna Marina Liberati,[8] Guido Gini,[9] Claudia Castellino,[10] Fausto Rossini,[11] Fabio Ciceri,[12] Delia Rota-Scalabrini,[13] Caterina Stelitano,[14] Francesco Di Raimondo,[15] Alessandra Tucci,[16] Liliana Devizzi,[17] Valerio Zoli,[18] Francesco Zallio,[19] Franco Narni,[20] Alessandra Dondi,[21] Guido Parvis,[22^] Gianpietro Semenzato,[23] Francesco Lanza,[24°] Tommasina Perrone,[25] Francesco Angrilli,[26] Atto Billio,[27] Angela Gueli,[1] Barbara Mantoan,[28] Alessandro Rambaldi,[5,29] Alessandro Massimo Gianni,[1] Paolo Corradini,[17,29] Roberto Passera,[30] Marco Ladetto,[19] Corrado Tarella*[1,31]

Haematologica 2019
Volume 104(11):2241-2248





Turin, September 13-14, 2021
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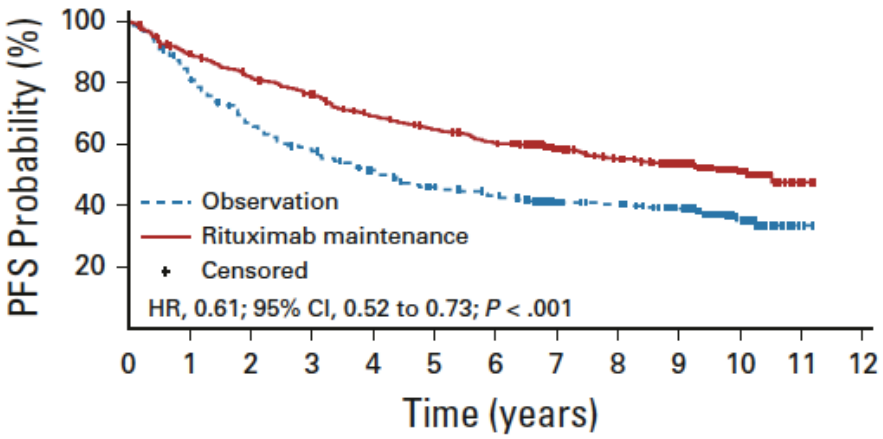
Sustained Progression-Free Survival Benefit of Rituximab Maintenance in Patients With Follicular Lymphoma: Long-Term Results of the PRIMA Study

Journal of Clinical Oncology®
Volume 37, Issue 31 2815

Emmanuel Bachy, MD, PhD[1]; John F. Seymour, MBBS, PhD[2]; Pierre Feugier, MD[3]; Fritz Offner, MD, PhD[4]; Armando López-Guillermo, MD[5]; David Belada, MD, PhD[6]; Luc Xerri, PhD, MD[7]; John V. Catalano, MD[8]; Pauline Brice, MD[9]; François Lemonnier, MD[10]; Alejandro Martin, MD, PhD[11]; Olivier Casasnovas, MD[12]; Lars M. Pedersen, MD[13]; Véronique Dorvaux, MD[14]; David Simpson, MD[15]; Sirpa Leppa, MD, PhD[16]; Jean Gabarre, MD[17]; Maria G. da Silva, MD, PhD[18]; Sylvie Glaisner, MD[19]; Loic Ysebaert, MD, PhD[20]; Anne Vekhoff, MD[21]; Tanin Intragumtornchai, MD[22]; Steven Le Gouill, MD, PhD[23]; Andrew Lister, MD[24]; Jane A. Estell, MD[25]; Gustavo Milone, MD[26]; Anne Sonet, MD[27]; Jonathan Farhi, MD[28]; Harald Zeuner[29]; Hervé Tilly, MD[30]; and Gilles Salles, MD, PhD[1]

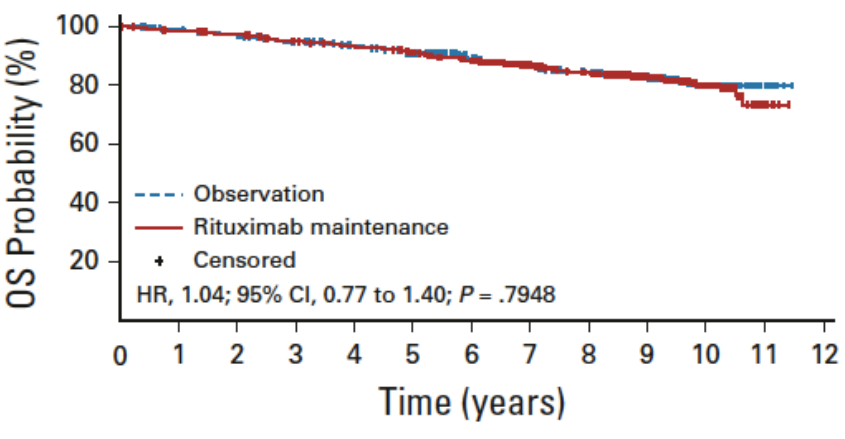
A



No. at risk:

Observation	513	415	336	290	251	217	200	155	147	122	41	1	0
Rituximab maintenance	505	445	406	372	333	309	284	231	208	170	67	4	0

D



No. at risk:

Observation	513	501	485	472	460	440	412	319	297	256	91	8	0
Rituximab maintenance	505	492	480	464	449	432	407	341	313	261	107	8	0

VOLUME 33 · NUMBER 23 · AUGUST 10 2015

JOURNAL OF CLINICAL ONCOLOGY

Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study

Carla Casulo, Michelle Byrtek, Keith L. Dawson, Xiaolei Zhou, Charles M. Farber, Christopher R. Flowers, John D. Hainsworth, Matthew J. Maurer, James R. Cerhan, Brian K. Link, Andrew D. Zelenetz, and Jonathan W. Friedberg

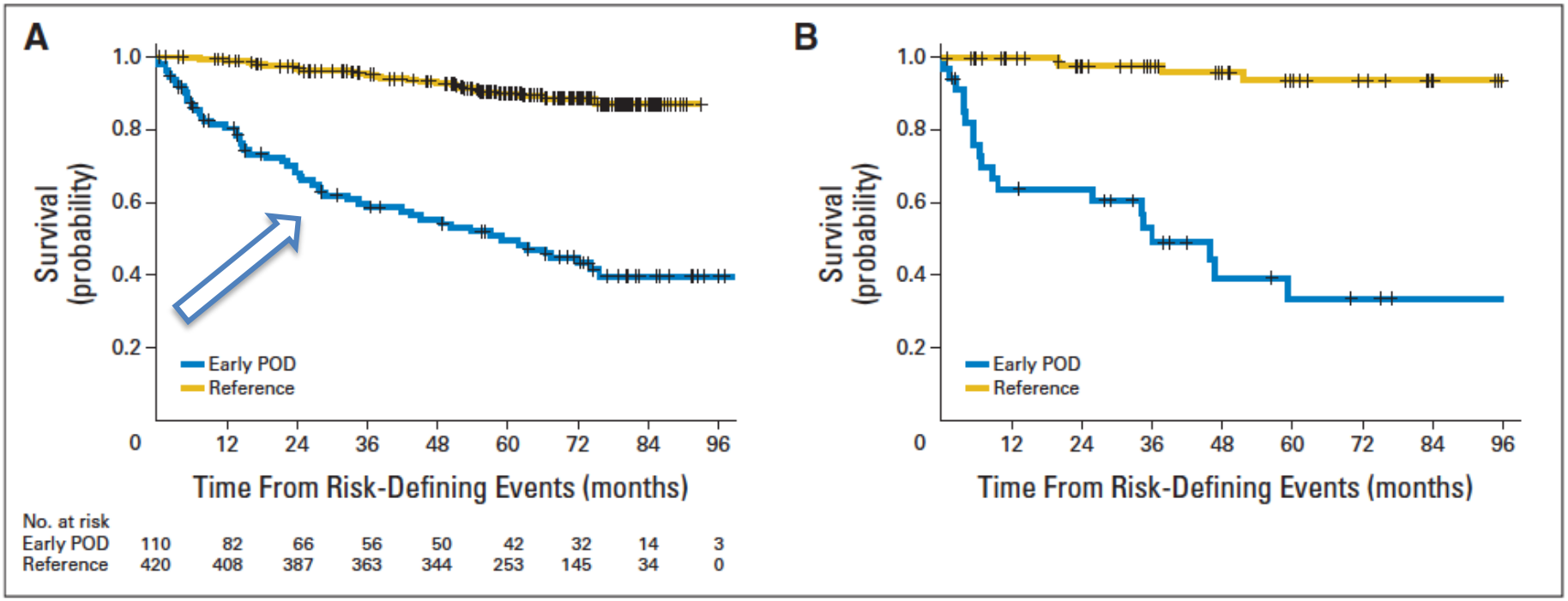
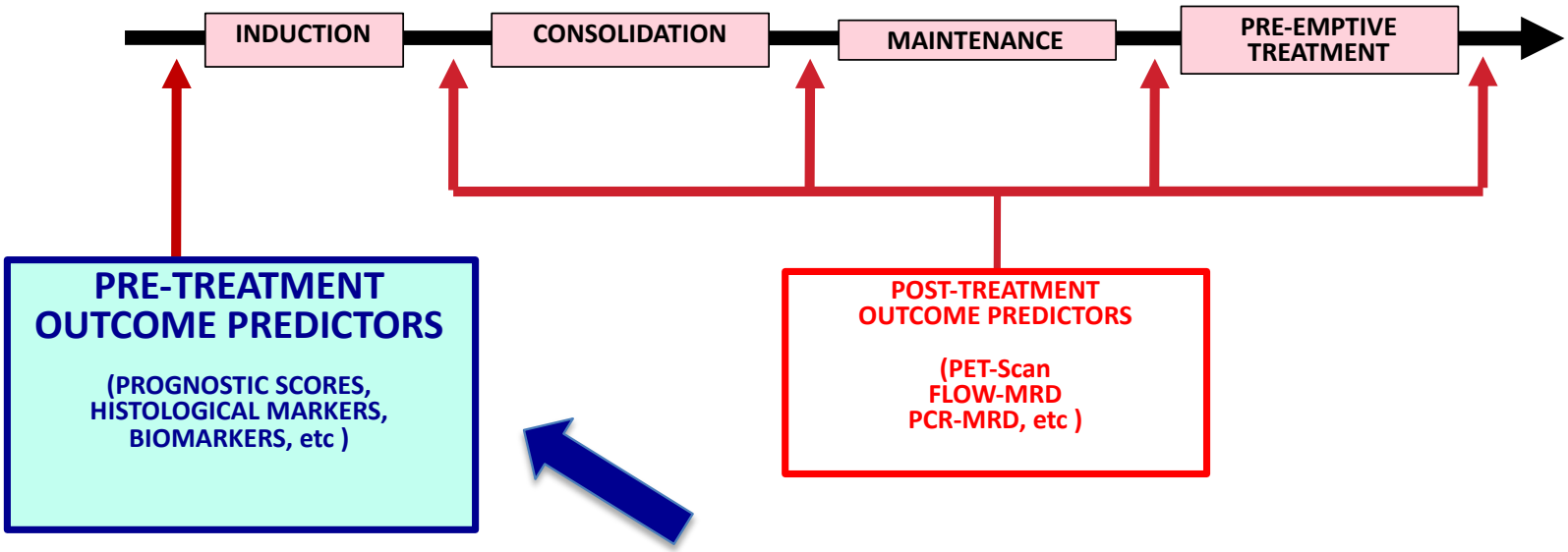


Fig 3. (A) Overall survival (OS) from a risk-defining event after diagnosis in patients who received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the National LymphoCare Study group. Patients with early progression of disease (POD) had poor survival. Two-year OS was 68% (95% CI, 58.2% to 76.3%). Five-year OS was 50% (95% CI, 39.4% to 59.2%). OS in the reference group was 97% (95% CI, 94.6% to 98.1%) at 2 years and 90% (95% CI 86.2% to 92.4%) at 5 years. (B) Patients in the validation set who received R-CHOP with early POD also had inferior OS.

Follicular lymphoma in 2021

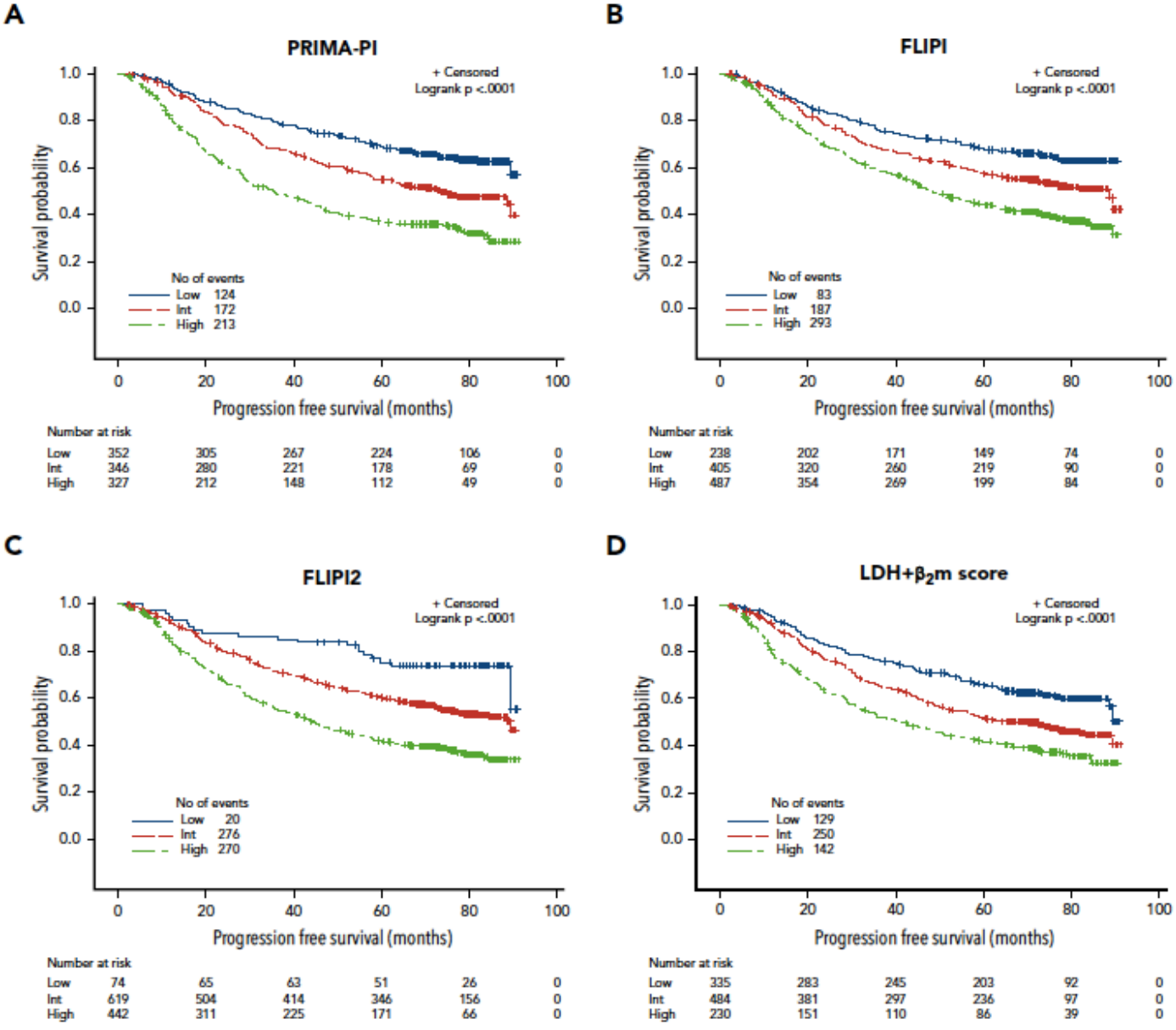
- Excellent outcome of advFL with available therapies (10-yrs OS 82%)
- 70-80% of patients have manageable FL
  - Consider the less toxic approach
  - Avoid late events
  - Some pt are cured (old, low risk)
- **20-30% have high risk disease**
  - **Early identification** (How?)
  - Consider experimental tx
    - **Reduce the rate of high risk patients**
    - **Overcome bad features of high risk patients**
- Risk adapted strategy seems appropriate

Outcome prediction in FL



Clinical prognostic scores

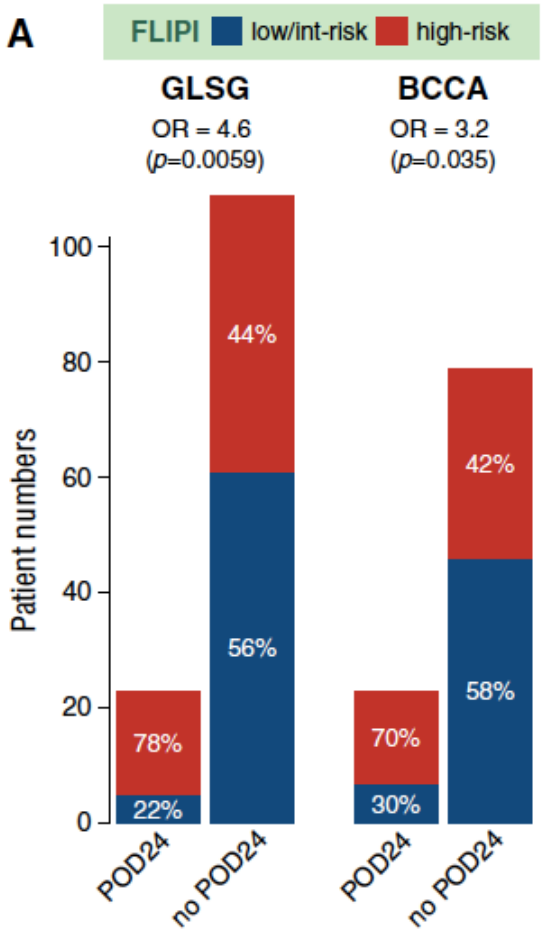
(both classical and new…)

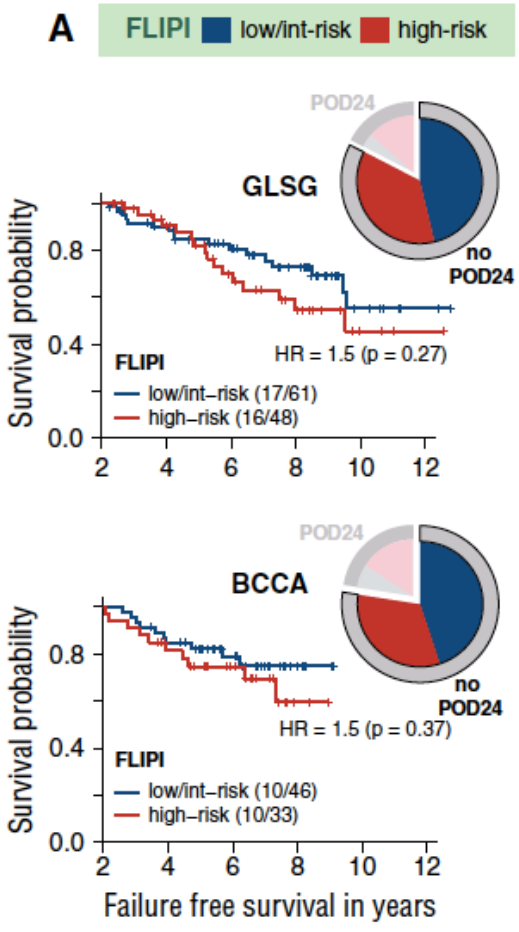


blood
2018 132: 49-58
doi:10.1182/blood-2017-11-816405 originally published online April 17, 2018

A simplified scoring system in de novo follicular lymphoma treated initially with immunochemotherapy

Emmanuel Bachy, Matthew J. Maurer, Thomas M. Habermann, Bénédicte Gelas-Dore, Delphine Maucort-Boulch, Jane A. Estell, Eric Van den Neste, Réda Bouabdallah, Emmanuel Gyan, Andrew L. Feldman, Joan Bargay, Alain Delmer, Susan L. Slager, Maria Gomes da Silva, Olivier Fitoussi, David Belada, Hervé Maisonneuve, Tanin Intragumtornchai, Stephen M. Ansell, Thierry Lamy, Peggy Dartigues, Brian K. Link, John F. Seymour, James R. Cerhan and Gilles Salles





FLIPI has a sensitivity of 70–78% but a **specificity of only 56–58% to predict POD24** in patients treated with R-CHOP or R-CVP, suggesting that <u>many patients</u> assigned into the high-risk FLIPI category <u>may not ultimately experience POD24</u>

blood®
2016 128: 1112-1120
doi:10.1182/blood-2016-05-717355 originally published online July 14, 2016

Clinicogenetic risk models predict early progression of follicular lymphoma after first-line immunochemotherapy

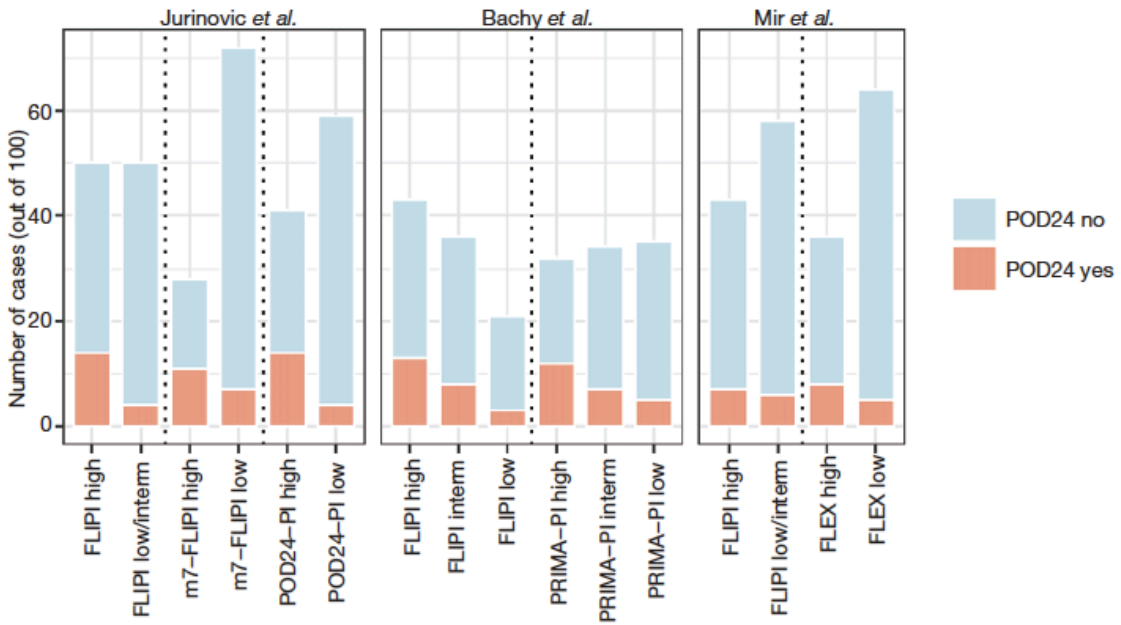
Vindi Jurinovic, Robert Kridel, Annette M. Staiger, Monika Szczepanowski, Heike Horn, Martin H. Dreyling, Andreas Rosenwald, German Ott, Wolfram Klapper, Andrew D. Zelenetz, Paul M. Barr, Jonathan W. Friedberg, Stephen Ansell, Laurie H. Sehn, Joseph M. Connors, Randy D. Gascoyne, Wolfgang Hiddemann, Michael Unterhalt, David M. Weinstock and Oliver Weigert

Review Article

Predicting early progression in follicular lymphoma

Qin Liu[1], Anjali Silva[1,2], Robert Kridel[1,3,4]

Ann Lymphoma 2021 | http://dx.doi.org/10.21037/aol-20-46



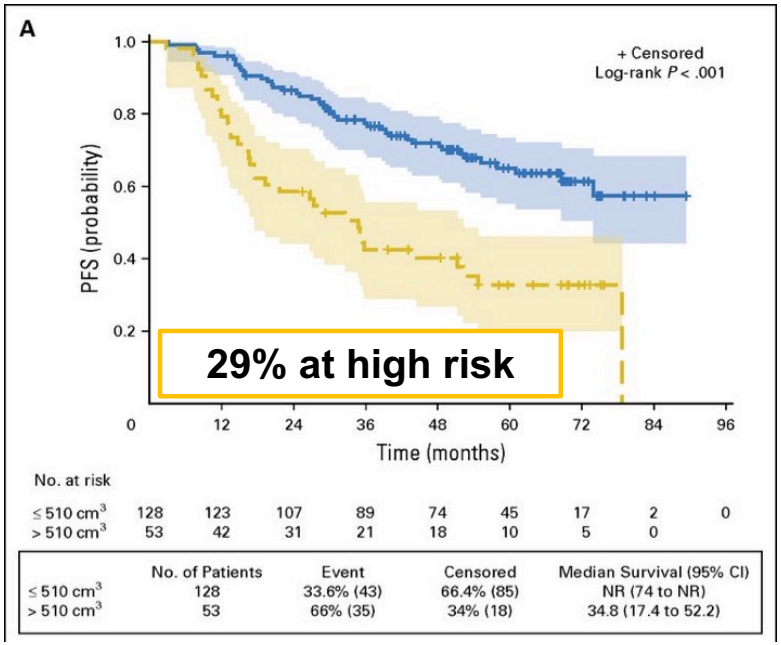
Neither of the available indices **has thus far had a definitive role in altering clinical management**, mostly because their accuracy to identify high-risk situations remains imperfect

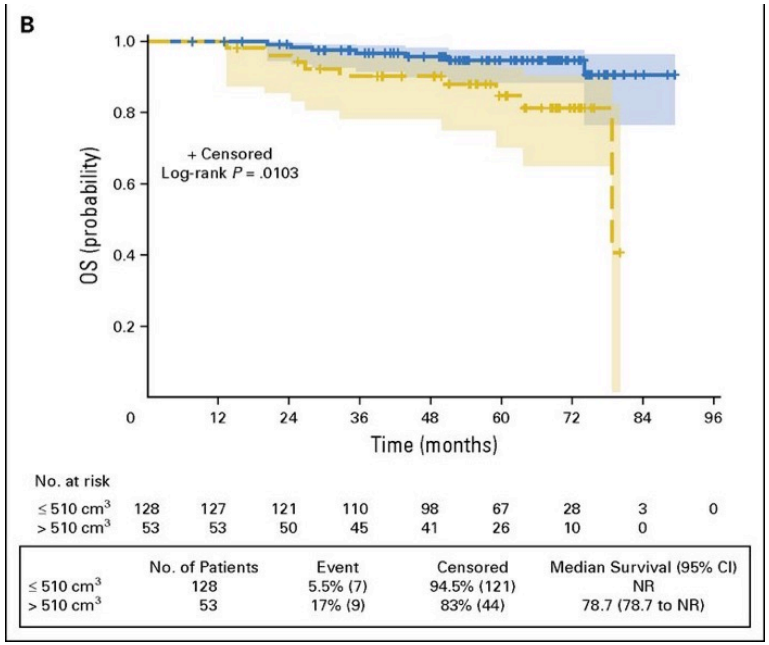
Figure 1 Number of follicular lymphoma patients experiencing POD24 in risk categories defined by the FLIPI, the m7-FLIPI, the POD24-PI, the PRIMA-PI or the FLEX scores. As the reported studies had varying sample sizes, the numbers shown here were normalized to represent numbers of patients out of 100. For each study, only the results from the training cohorts are shown. In Jurinovic *et al.*, POD24 was defined as progression or relapse within 24 months of first-line treatment (15). Bachy *et al.* reported EFS24, defined as event-free survival within 24 months of diagnosis (26). Mir *et al.* defined POD24 as progression or disease-related death within 24 months of randomization (29).

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





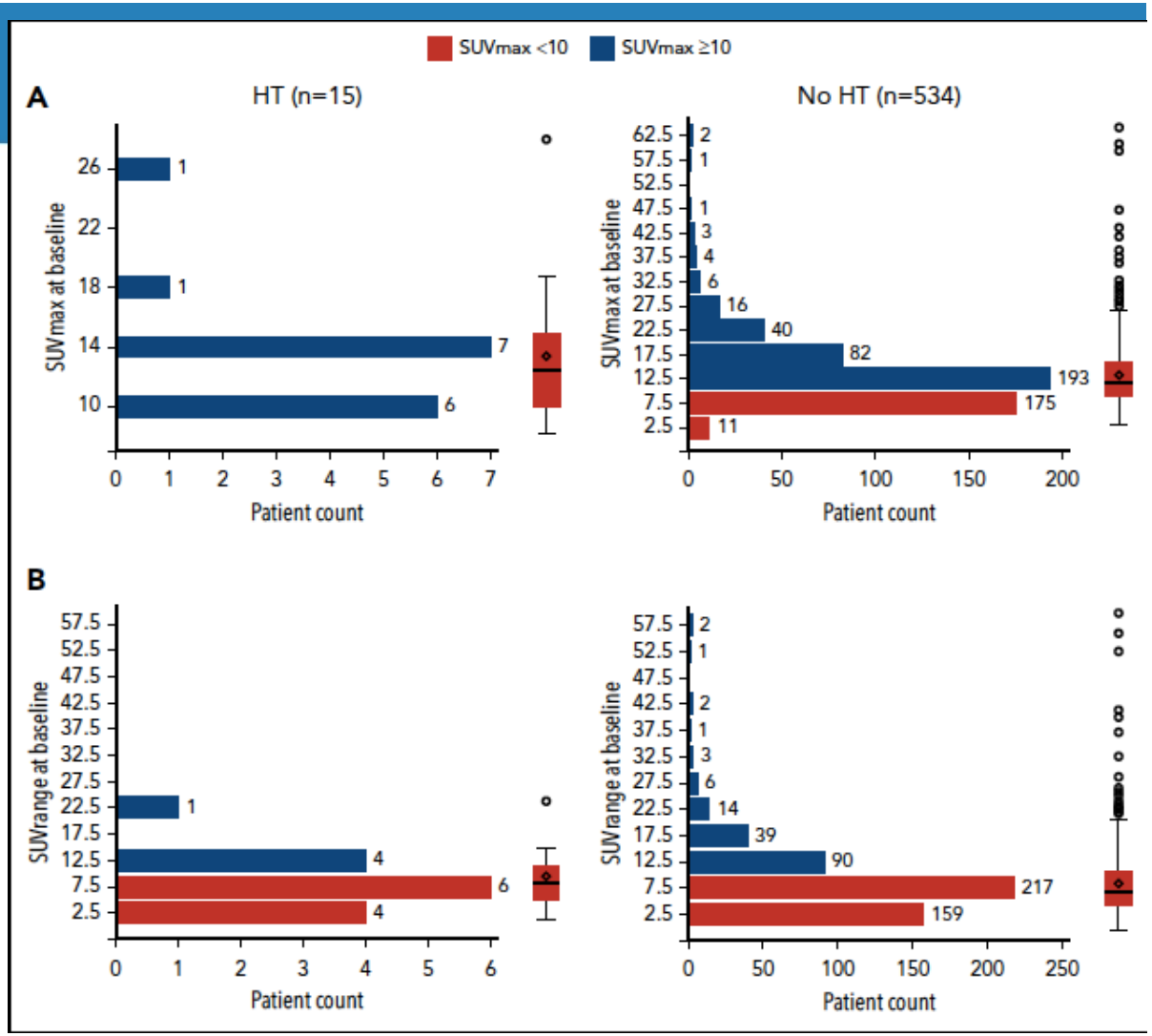
Michel Meignan et al. JCO doi:10.1200/JCO.2016.66.9440

CLINICAL TRIALS AND OBSERVATIONS

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] and Judith Trotman[6]

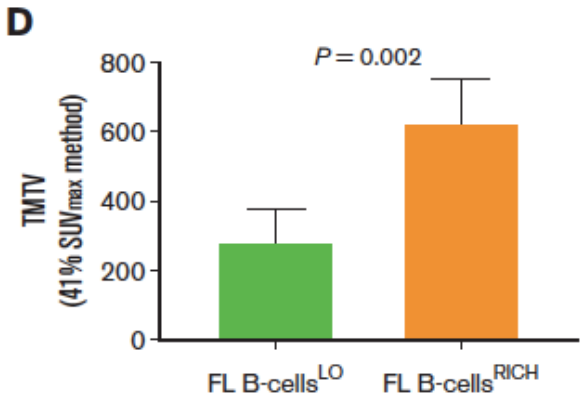
blood® 9 APRIL 2020 | VOLUME 135, NUMBER 15

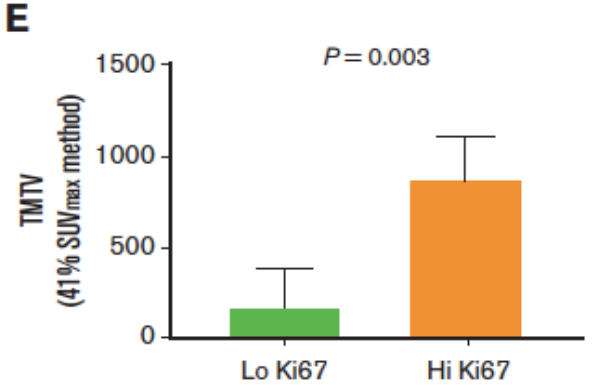


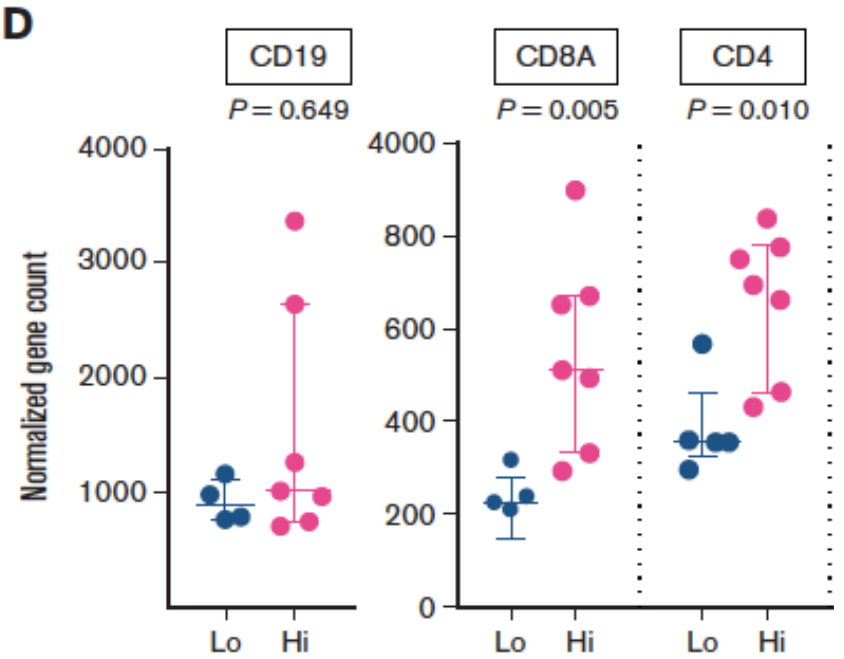
blood advances 22 JUNE 2021 • VOLUME 5, NUMBER 12

Intratumoral T cells have a differential impact on FDG-PET parameters in follicular lymphoma

Karthik Nath,[1] Soi-Cheng Law,[1] Muhammed B. Sabdia,[1] Jay Gunawardana,[1] Lilia M. de Long,[1] David Sester,[2] Mohamed Shanavas,[1] Hennes Tsang,[1] Joshua W. D. Tobin,[1] Sarah-Jane Halliday,[3] Annette Hernandez,[3] Donna Cross,[3] Robert J. Bird,[3] Sanjiv Jain,[4] Colm Keane,[1,3] Dipti Talaulikar,[5,6] Judith Trotman,[7,8] Phillip Law,[9] and Maher K. Gandhi[1,3]



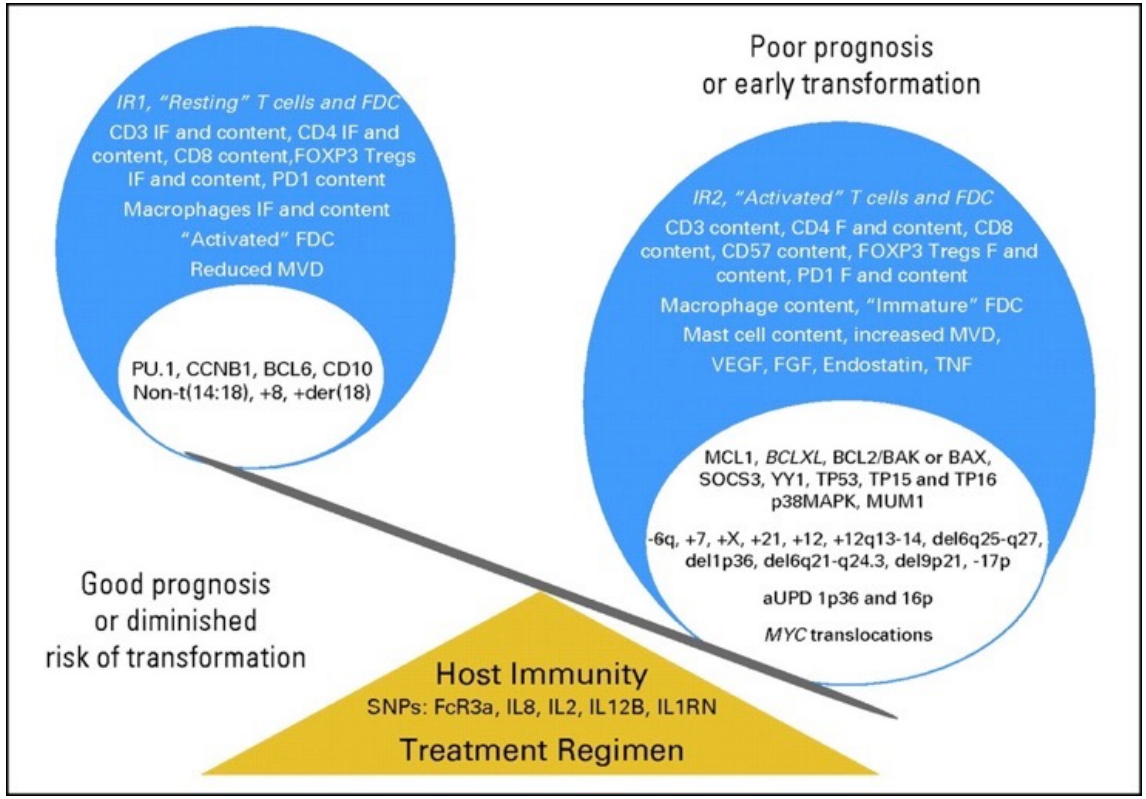




TMTV -> FL cells

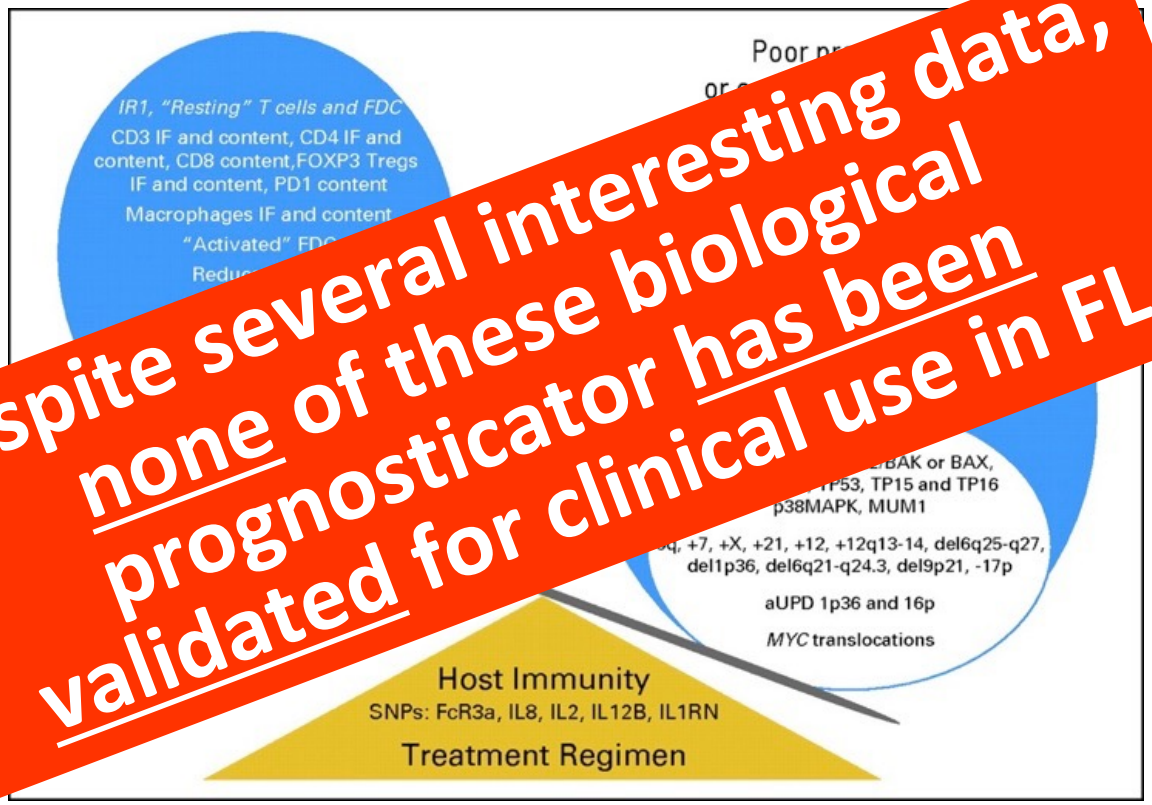
SUVmax -> ME T-cells

Biomarkers impacting survival or transformation in follicular lymphoma (FL).



Relander T et al. JCO 2010;28:2902-2913

Biomarkers impacting survival or transformation in follicular lymphoma (FL).



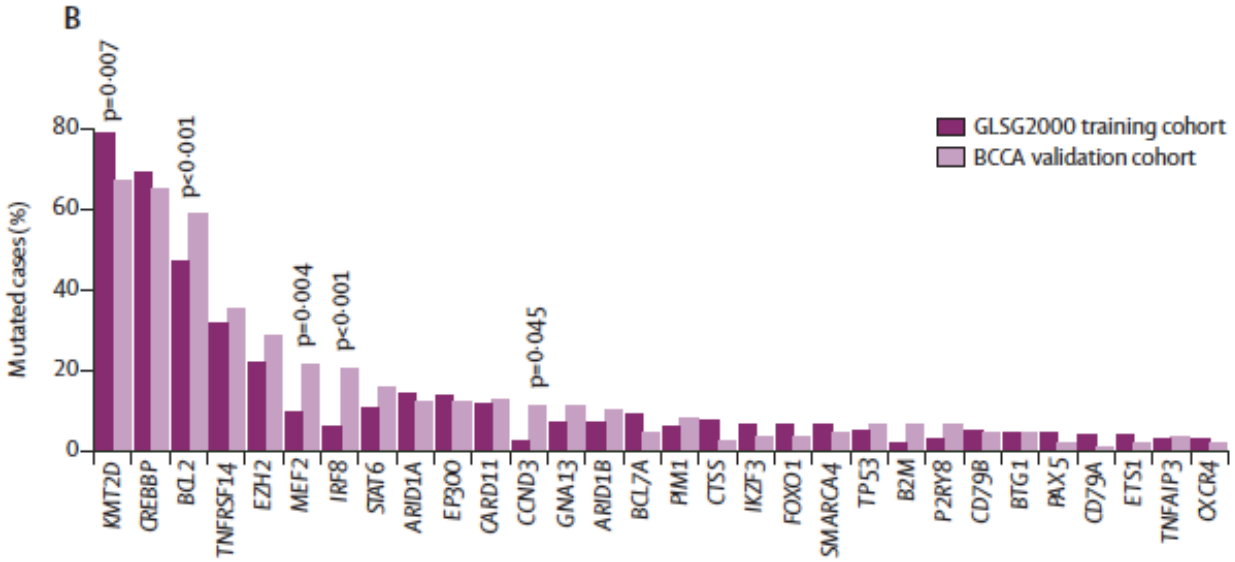
Despite several interesting data, none of these biological prognosticator has been validated for clinical use in FL

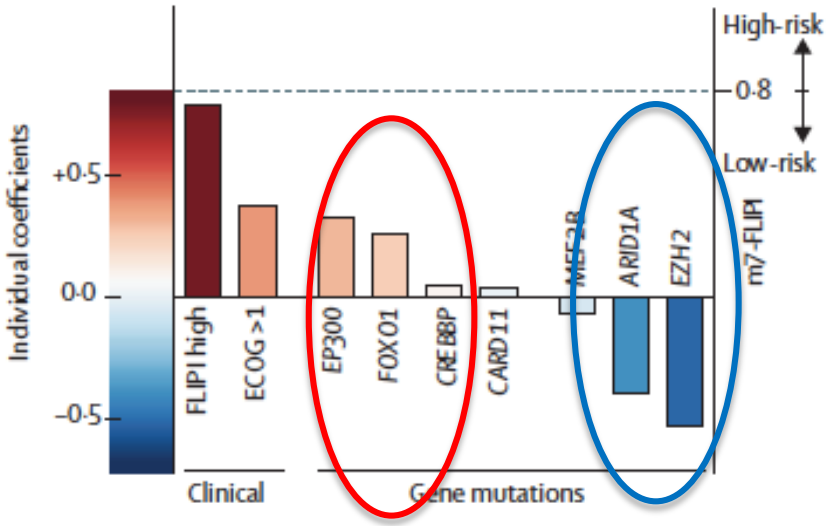
Relander T et al. JCO 2010;28:2902-2913

Several genomic mutations have been described in FL

Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry

Alessandro Pastore*, Vindi Jurinovic*, Robert Kridel*, Eva Hoster*, Annette M Staiger, Monika Szczepanowski, Christiane Pott, Nadja Kopp, Mark Murakami, Heike Horn, Ellen Leich, Alden A Moccia, Anja Mottok, Ashwini Sunkavalli, Paul Van Hummelen, Matthew Ducar, Daisuke Ennishi, Hennady P Shulha, Christoffer Hother, Joseph M Connors, Laurie H Sehn, Martin Dreyling, Donna Neuberg, Peter Möller, Alfred C Feller, Martin L Hansmann, Harald Stein, Andreas Rosenwald, German Ott, Wolfram Klapper, Michael Unterhalt, Wolfgang Hiddemann, Randy D Gascoyne*, David M Weinstock*, Oliver Weigert*



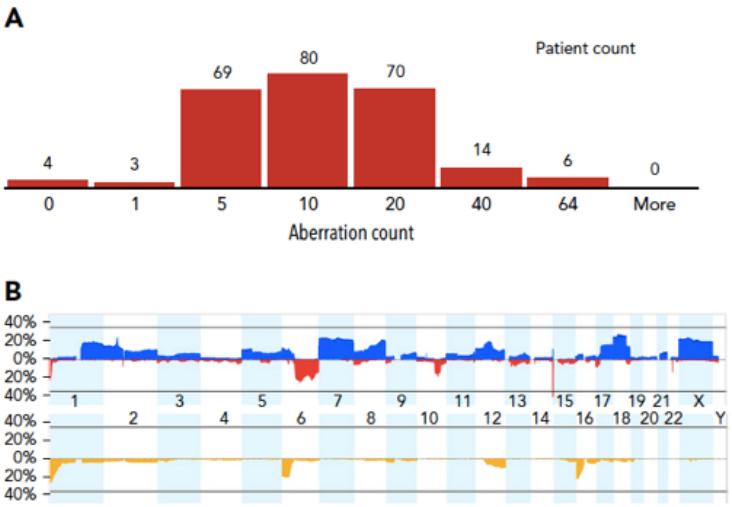


Lancet Oncol 2015

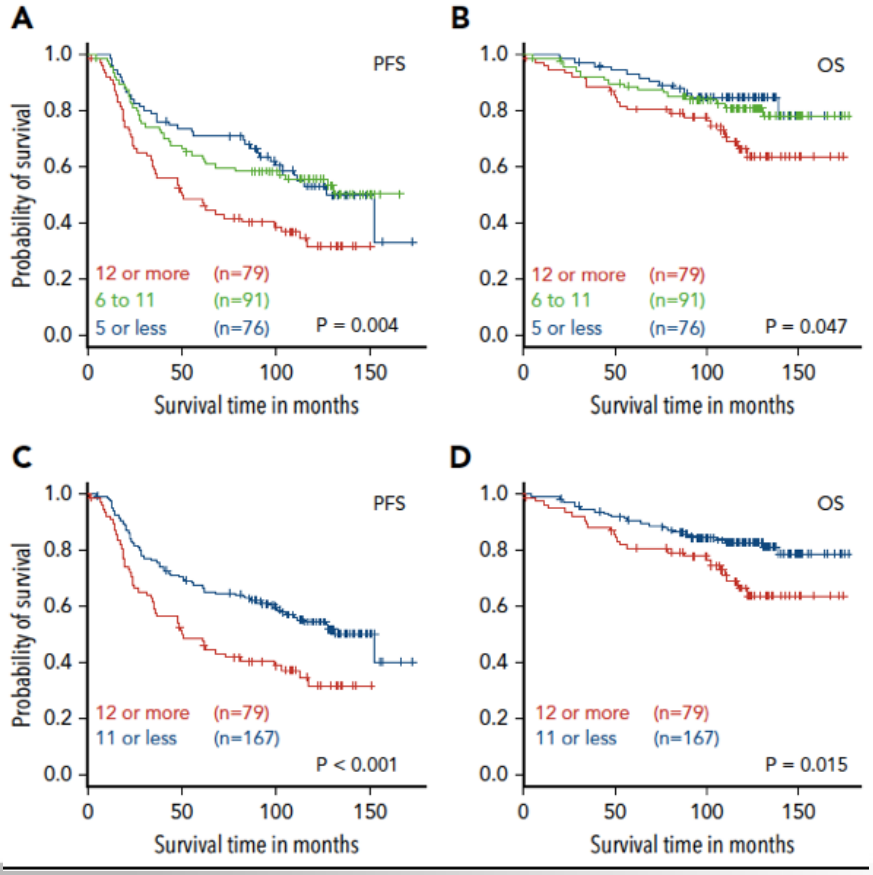
Genomic alterations important for the prognosis in patients with follicular lymphoma treated in SWOG study S0016

Xiaoyu Qu,[1] Hongli Li,[2] Rita M. Braziel,[3] Verena Passerini,[4,5] Lisa M. Rimsza,[6] Eric D. Hsi,[7] John P. Leonard,[8] Sonali M. Smith,[9] Robert Kridel,[10] Oliver Press,[1] Oliver Weigert,[4,5] Michael LeBlanc,[2] Jonathan W. Friedberg,[11] and Min Fang[1]

The **increased number of genetic alterations** was associated with a greater propensity of progression within 2 years



Gain or cnLOH of 2p is correlated with 2-year progression; ***CDKN2A/B*** **deletion** with worse PFS; ***CREBBP*** **and** ***TP53*** **deletions** predict worse OS



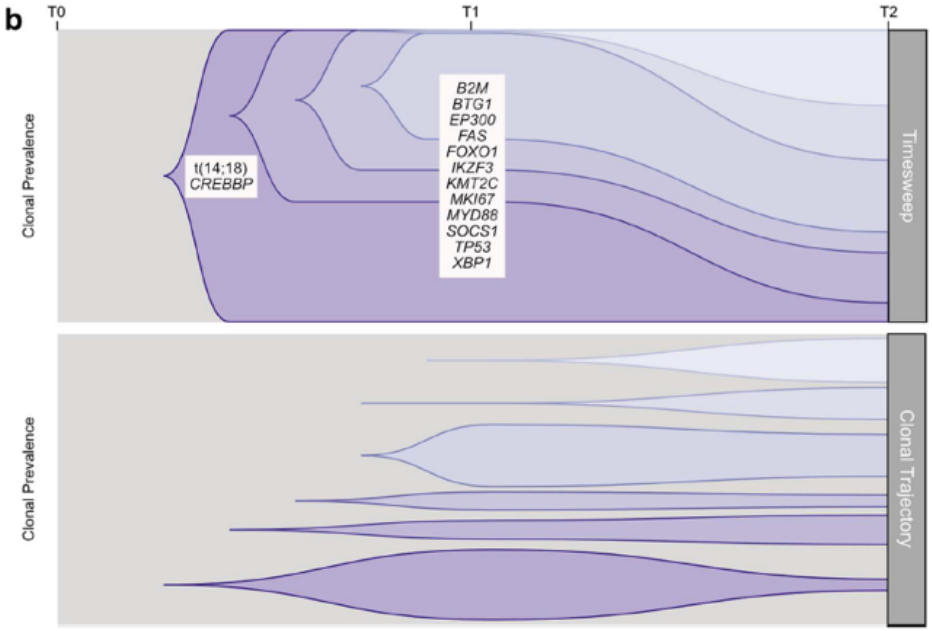
blood® 3 JANUARY 2019 | VOLUME 133, NUMBER 1

A study using whole-genome sequencing of paired lymphoma samples found that **the clonal evolution underlying early progression was limited**, at least when compared to clonal changes underlying transformation

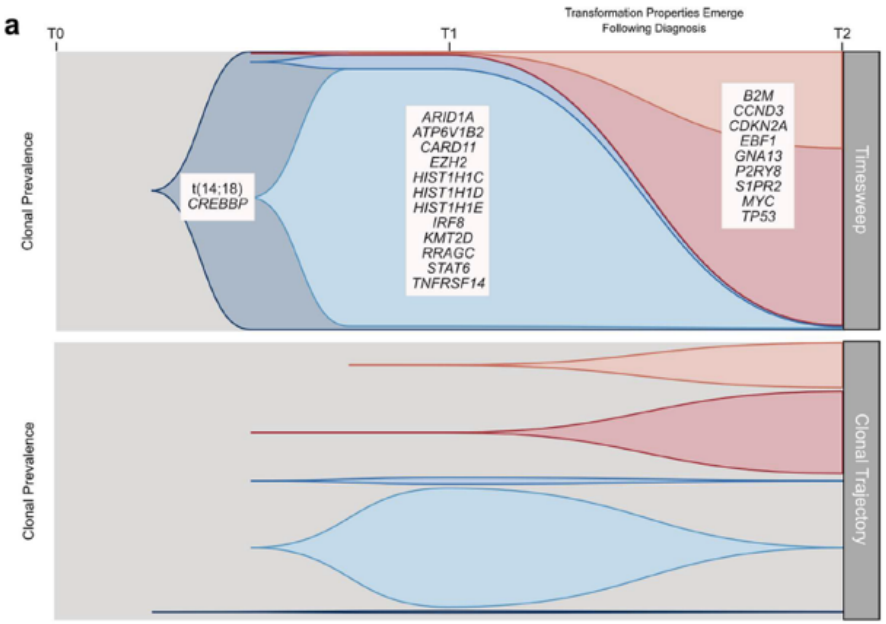
Histological Transformation and Progression in Follicular Lymphoma: A Clonal Evolution Study

Robert Kridel[1☯¤a], Fong Chun Chan[1,2☯], Anja Mottok[1,3], Merrill Boyle[1], Pedro Farinha[1], King Tan[1], Barbara Meissner[1], Ali Bashashati[4], Andrew McPherson[4], Andrew Roth[2,4], Karey Shumansky[4], Damian Yap[4], Susana Ben-Neriah[1], Jamie Rosner[4], Maia A. Smith[2,4], Cydney Nielsen[4], Eva Giné[1], Adele Telenius[1], Daisuke Ennishi[1], Andrew Mungall[5], Richard Moore[5], Ryan D. Morin[5,6], Nathalie A. Johnson[7], Laurie H. Sehn[1], Thomas Tousseyn[8,9], Ahmet Dogan[10,11], Joseph M. Connors[1], David W. Scott[1], Christian Steidl[1,3], Marco A. Marra[5], Randy D. Gascoyne[1,3], Sohrab P. Shah[3,4]*

early progression



transformation

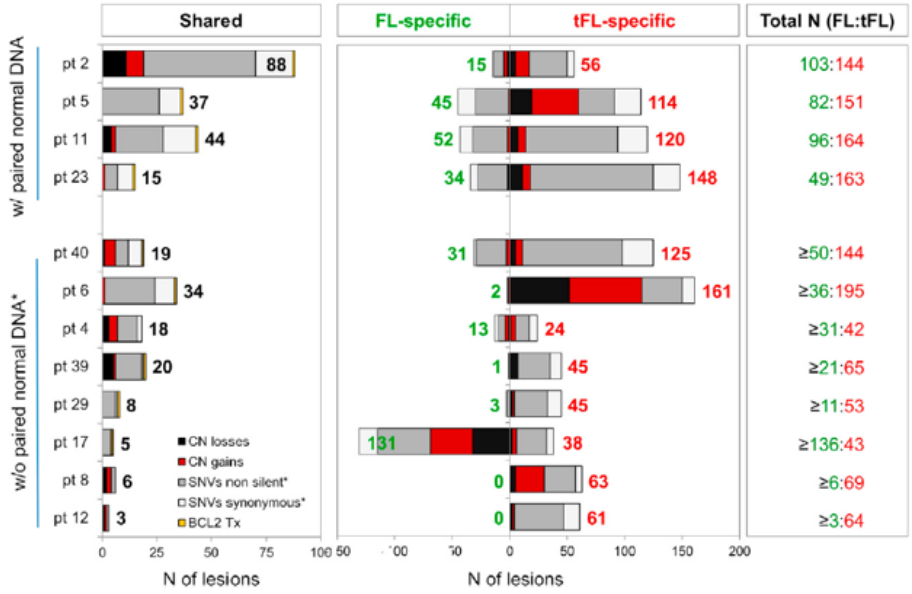


PLOS Medicine | DOI:10.1371/journal.pmed.1002197 December 13, 2016

Genetics of Follicular Lymphoma Transformation

Laura Pasqualucci,[1,2,3,*] Hossein Khiabanian,[4] Marco Fangazio,[1] Mansi Vasishtha,[1] Monica Messina,[1] Antony B. Holmes,[1] Peter Ouillette,[5] Vladimir Trifonov,[4] Davide Rossi,[6] Fabrizio Tabbò,[7] Maurilio Ponzoni,[8] Amy Chadburn,[9] Vundavalli V. Murty,[1,2,3] Govind Bhagat,[2,3] Gianluca Gaidano,[6] Giorgio Inghirami,[7] Sami N. Malek,[5] Raul Rabadan,[4] and Riccardo Dalla-Favera[1,2,3,10,11,*]

Cell Reports
Article



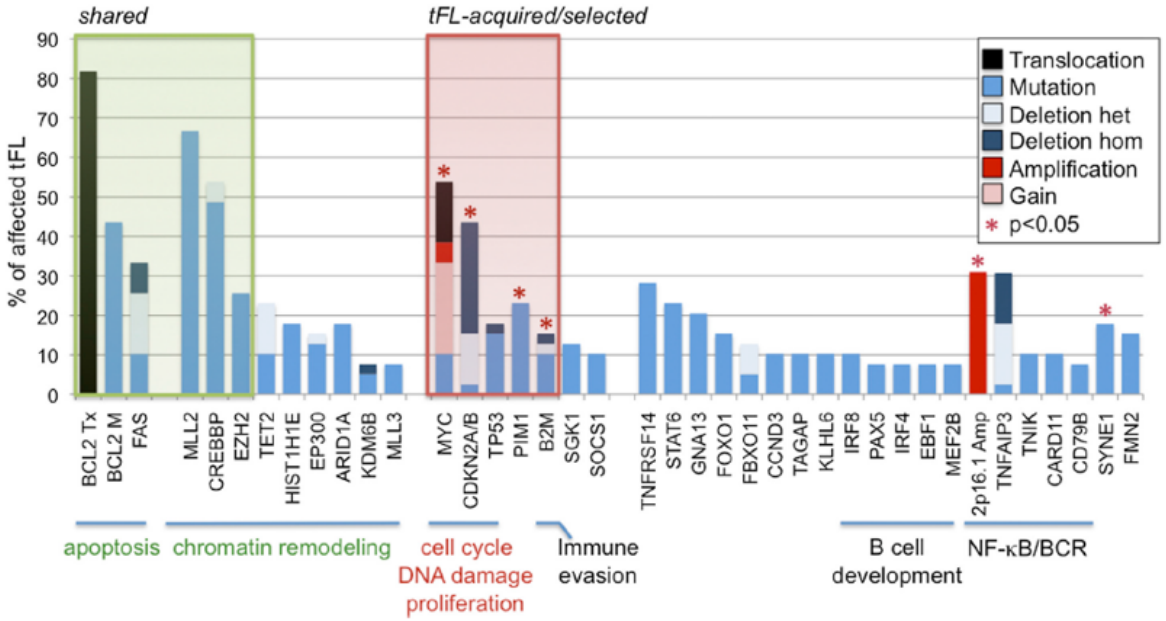


Figure 3. Recurrently Mutated Genes in tFL

blood
2017 130: 258-266
doi:10.1182/blood-2017-03-691345 originally published online April 13, 2017

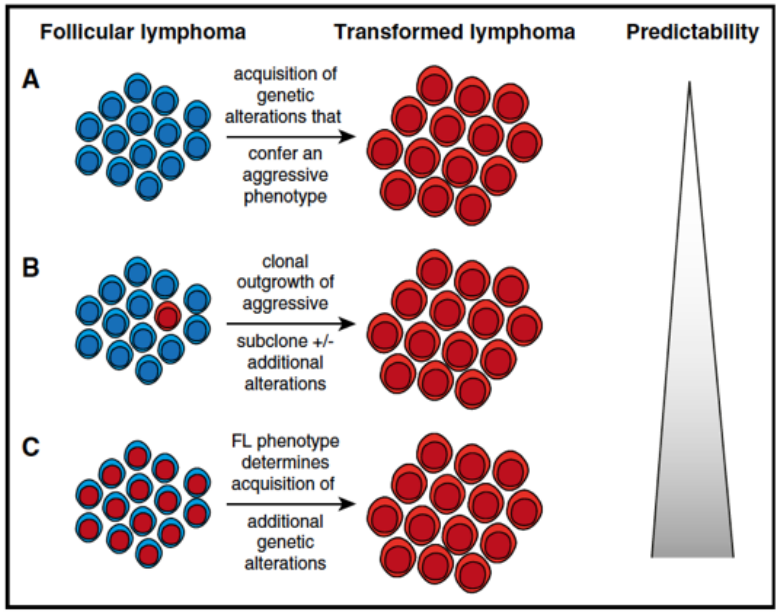
Can histologic transformation of follicular lymphoma be predicted and prevented?

Robert Kridel, Laurie H. Sehn and Randy D. Gascoyne

This observation may suggest that the **determinants of early progression are potentially present in the diagnostic tissue specimen**, whereas transformation to aggressive histology may be much more difficult to predict

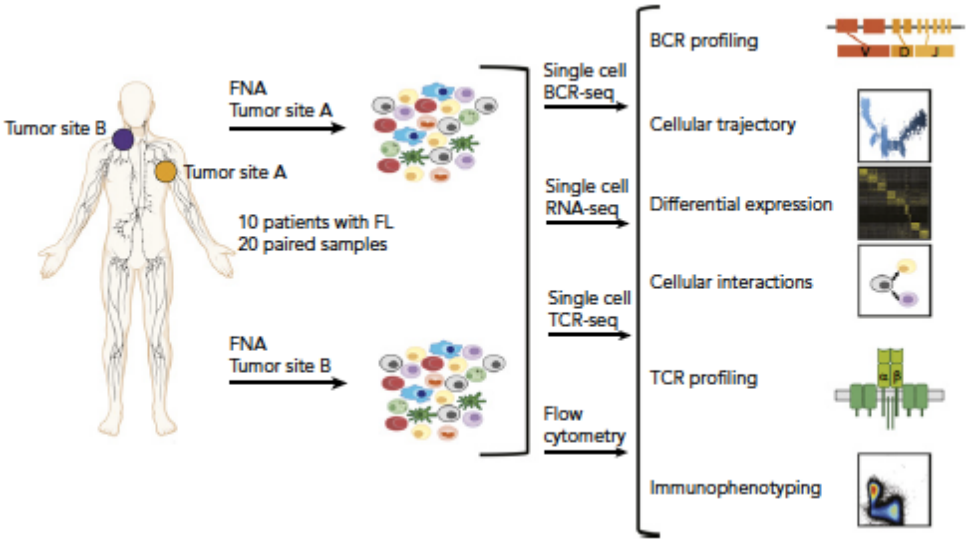
Predicting transformation remains a challenge, with no robust biomarker currently available in routine clinical practice. Indeed, several genetic alterations, gene signatures, or immunohistochemical markers have been reported in the literature to be associated with transformation, but have not been sufficiently validated to warrant their assessment outside of the research setting. Future studies are important to address this unmet need. We anticipate that large-scale

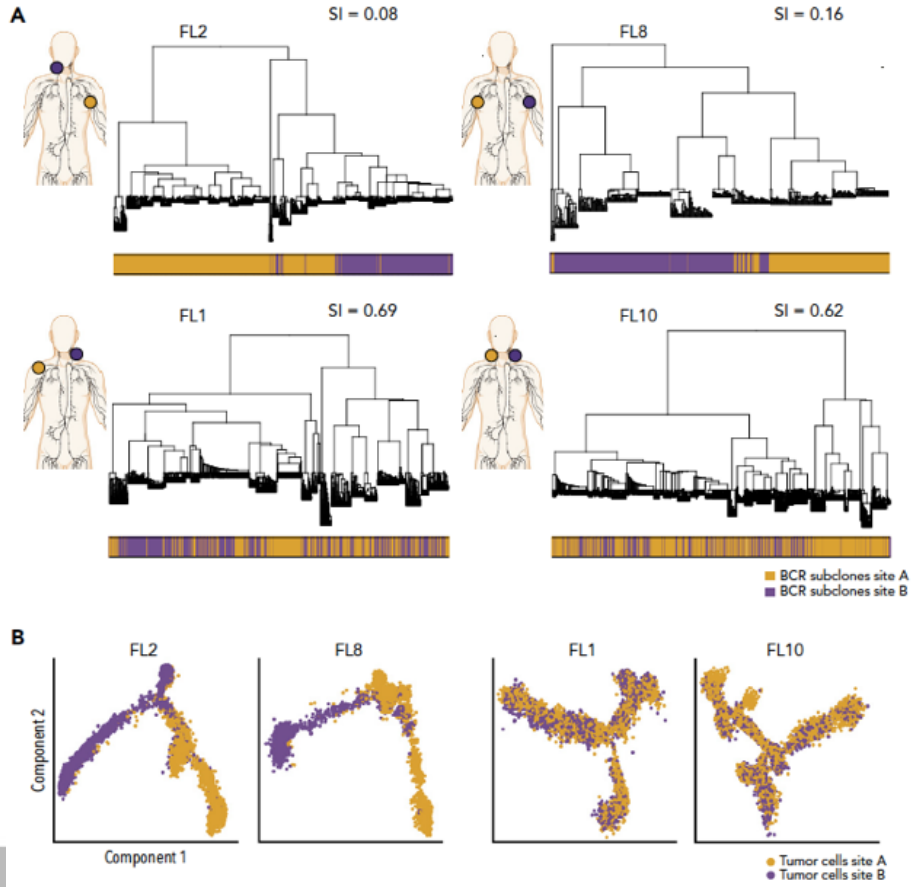
far, no treatment strategy appears to mitigate the risk of transformation. Only a deeper understanding of tumor biology and evolution will allow us to eventually predict transformation, which could open new avenues for the investigation of strategies aiming at circumventing it.



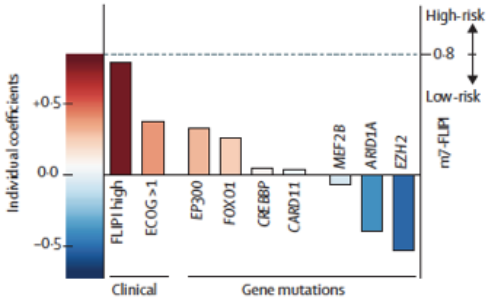
Single-cell analysis can define distinct evolution of tumor sites in follicular lymphoma

Sarah Haebe,[1,*] Tanaya Shree,[1,*] Anuja Sathe,[1] Grady Day,[1] Debra K. Czerwinski,[1] Susan M. Grimes,[2] HoJoon Lee,[1] Michael S. Binkley,[3] Steven R. Long,[4] Brock Martin,[4] Hanlee P. Ji,[1,2] and Ronald Levy[1]





Clinicogenetic risk model: m7-FLIPI



Lancet Oncol 2015

Published Online
August 7, 2015
http://dx.doi.org/10.1016/
S1470-2045(15)00169-2

Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry

Alessandro Pastore, Vindi Jurinovic*, Robert Kridel*, Eva Hoster*, Annette M Staiger, Monika Szczepanowski, Christiane Pott, Nadja Kopp, Mark Murakami, Heike Horn, Ellen Leich, Alden A Moccia, Anja Mottok, Ashwini Sunkavalli, Paul Van Hummelen, Matthew Ducar, Daisuke Ennishi, Hennady P Shulha, Christoffer Hother, Joseph M Connors, Laurie H Sehn, Martin Dreyling, Donna Neuberg, Peter Möller, Alfred C Feller, Martin L Hansmann, Harald Stein, Andreas Rosenwald, German Ott, Wolfram Klapper, Michael Unterhalt, Wolfgang Hiddemann, Randy D Gascoyne*, David M Weinstock*, Oliver Weigert**

- **Mutation status of seven genes**

(*EZH2*, *ARID1A*, *MEF2B*, *EP300, FOXO1, CREBBP*, *CARD11*)

+

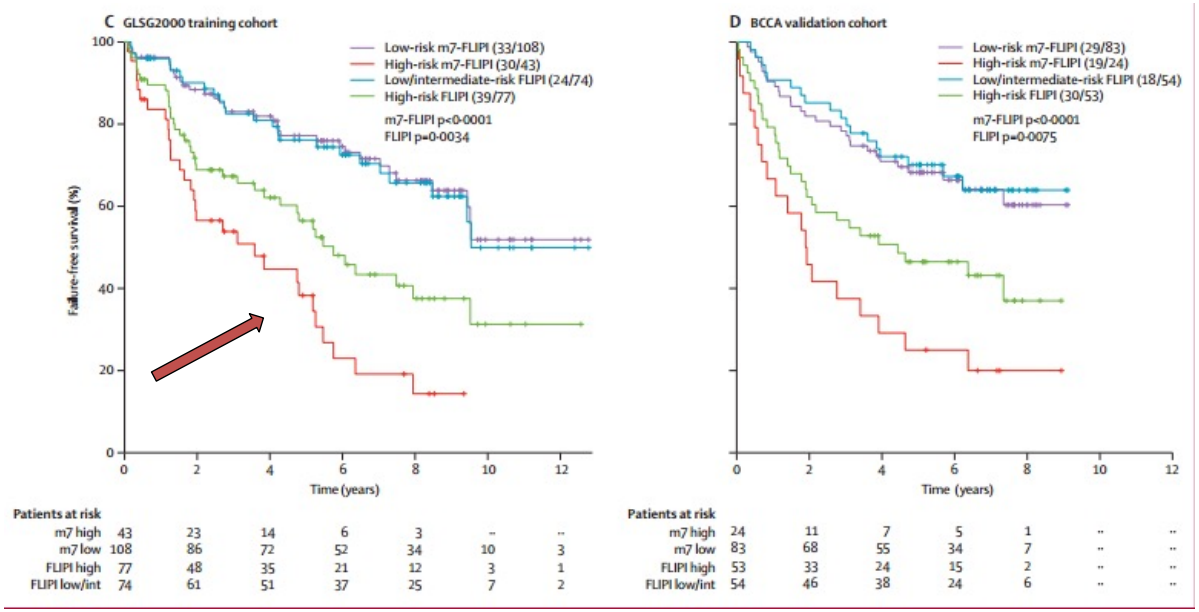
- Follicular Lymphoma International Prognostic Index **(FLIPI)**

+

- Eastern Cooperative Oncology Group **(ECOG)** performance status

Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry

Alessandro Pastore, Vindi Jurinovic*, Robert Kridel*, Eva Hoster*, Annette M Staiger, Monika Szczepanowski, Christiane Pott, Nadja Kopp, Mark Murakami, Heike Horn, Ellen Leich, Alden A Moccia, Anja Mottok, Ashwini Sunkavalli, Paul Van Hummelen, Matthew Ducar, Daisuke Ennishi, Hennady P Shulha, Christoffer Hother, Joseph M Connors, Laurie H Sehn, Martin Dreyling, Donna Neuberg, Peter Möller, Alfred C Feller, Martin L Hansmann, Harald Stein, Andreas Rosenwald, German Ott, Wolfram Klapper, Michael Unterhalt, Wolfgang Hiddemann, Randy D Gascoyne*, David M Weinstock*, Oliver Weigert**



Lancet Oncol 2015

the **m7-FLIPI** was found to have the highest accuracy and positive predictive value for POD24 and identified a smaller group of high-risk patients

blood

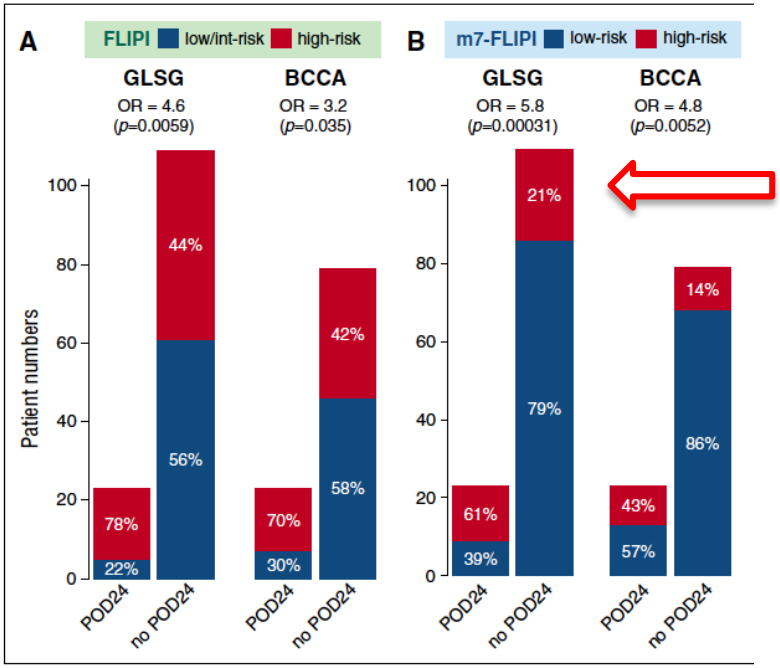


Figure 2. Accuracy of 3 pretreatment risk models to predict POD24 status. (A) Follicular Lymphoma Internatior Prognostic Index (POD24-PI).

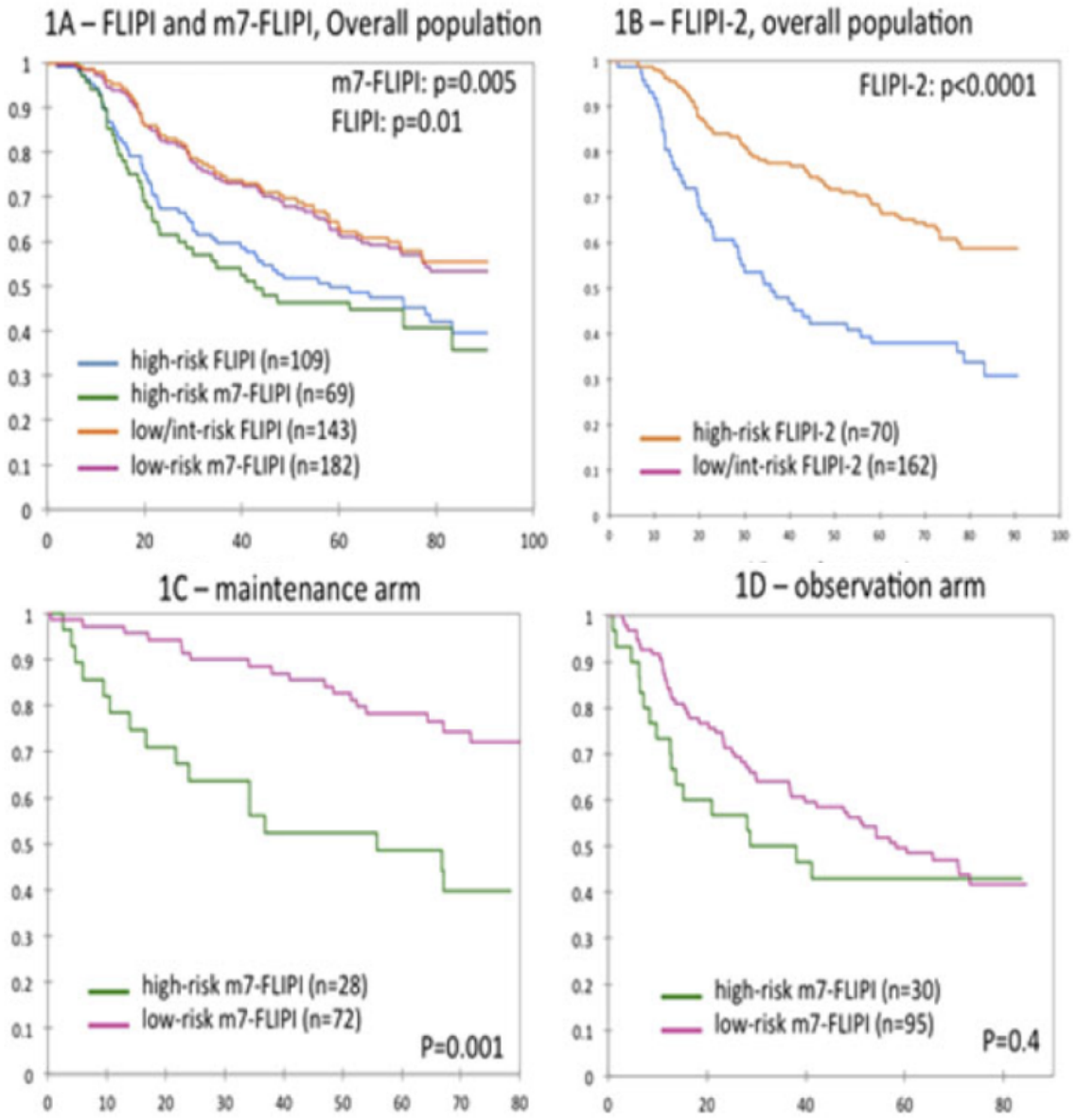
PRIMA TRIAL

EVALUATION OF CLINICOGENETIC RISK MODELS FOR OUTCOME OF FOLLICULAR LYMPHOMA PATIENTS IN THE PRIMA TRIAL

S. Huet[1*] | E. Szafer-Glusman[2] | L. Xerri[3] | C. Bolen[2] | E. Punnoose[2] | L. Tonon[4] | H. Tilly[5] | P. Brice[6] | P. Feugier[7] | B. Tesson[8] | A. Viari[4] | J.M. Venstrom[2] | G. Salles[9]

14-ICML

Conclusions: We confirmed in a large cohort, using a clinically validated assay, the applicability of composite scores m7-FLIPI and POD24-PI. Nevertheless, these scores showed some limitations, and need further evaluation to better discriminate risk group categories identified with FLIPI-1 or -2 in larger cohorts and in patients treated with other approaches.



Turin, September 13-14, 2021
Starhotels Majestic

GALLIUM TRIAL

Whereas the m7-FLIPI predicted outcome in patients treated with rituximab-based regimens, it was **not prognostic** for patients treated with **obinutuzumab**. Furthermore, it was prognostic in patients who were treated with CHOP/CVP, but not in patients receiving **bendamustine**

m7-FLIPI appeared to be driven mainly by *EZH2* mutation status

GALLIUM TRIAL

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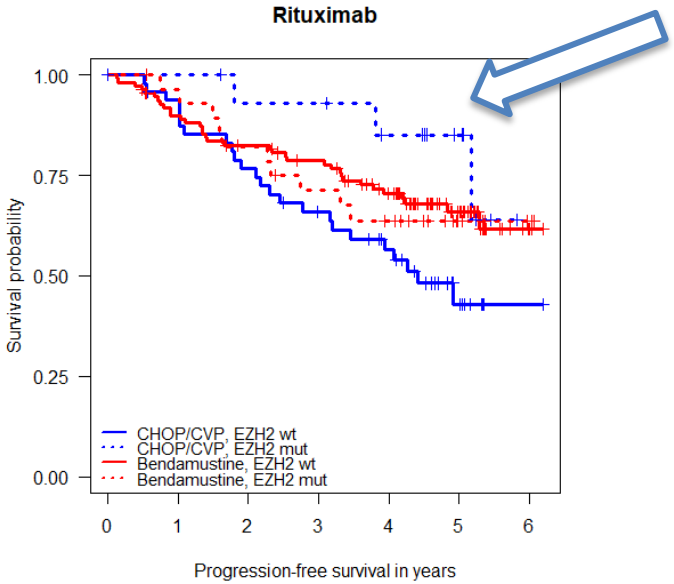
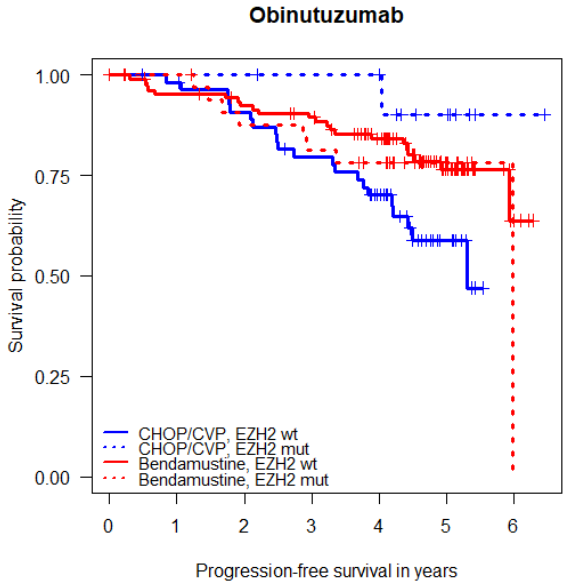
m7-FLIPI appeared to be driven mainly by *EZH2* mutation status



CHOP/CVP, EZH2 wt	49	44	36	29	22	8	1
CHOP/CVP, EZH2 mut	15	15	13	13	10	6	0
Bendamustine, EZH2 wt	111	97	87	80	63	29	2
Bendamustine, EZH2 mut	29	27	23	19	16	6	2



CHOP/CVP, EZH2 wt	56	54	49	42	31	10	0
CHOP/CVP, EZH2 mut	15	14	14	13	13	6	1
Bendamustine, EZH2 wt	109	100	95	90	74	33	3
Bendamustine, EZH2 mut	34	33	28	26	23	6	0

EZH2 mutated patients seemed to benefit from CHOP/CVP backbone schedules -> predictive marker?

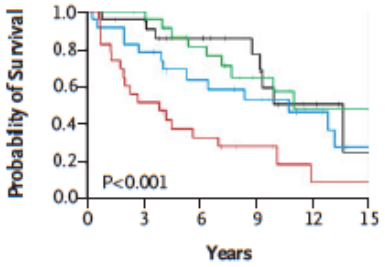
Jurinovic V et al., ASH 2019

The NEW ENGLAND JOURNAL of MEDICINE

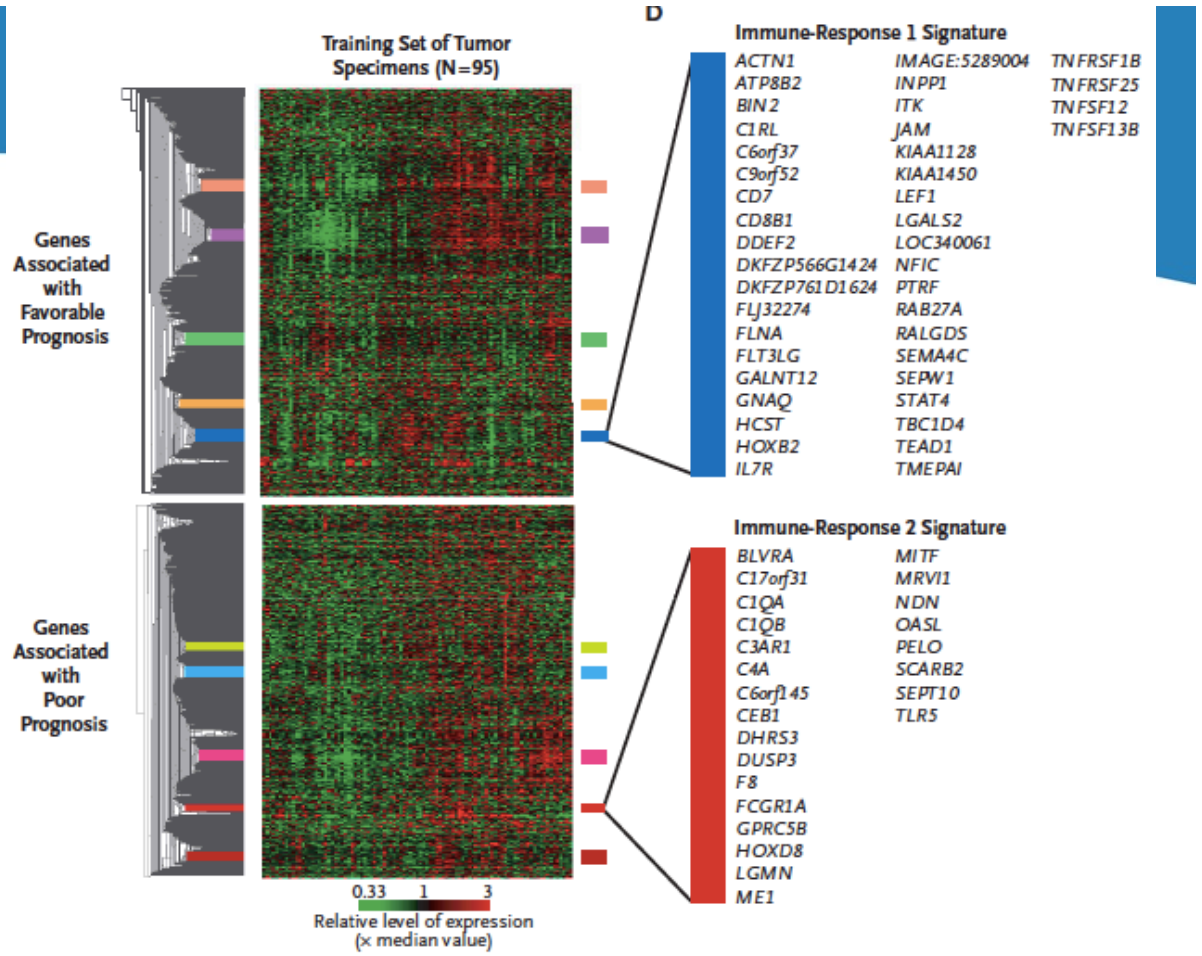
ESTABLISHED IN 1812 NOVEMBER 18, 2004 VOL. 351 NO. 21

Prediction of Survival in Follicular Lymphoma Based on Molecular Features of Tumor-Infiltrating Immune Cells

Sandeep S. Dave, M.D., George Wright, Ph.D., Bruce Tan, M.D., Andreas Rosenwald, M.D., Randy D. Gascoyne, M.D., Wing C. Chan, M.D., Richard I. Fisher, M.D., Rita M. Braziel, M.D., Lisa M. Rimsza, M.D., Thomas M. Grogan, M.D., Thomas P. Miller, M.D., Michael LeBlanc, Ph.D., Timothy C. Greiner, M.D., Dennis D. Weisenburger, M.D., James C. Lynch, Ph.D., Julie Vose, M.D., James O. Armitage, M.D., Erlend B. Smeland, M.D., Ph.D., Stein Kvaloy, M.D., Ph.D., Harald Holte, M.D., Ph.D., Jan Delabie, M.D., Ph.D., Joseph M. Connors, M.D., Peter M. Lansdorp, M.D., Ph.D., Qin Ouyang, Ph.D., T. Andrew Lister, M.D., Andrew J. Davies, M.D., Andrew J. Norton, M.D., H. Konrad Muller-Hermelink, M.D., German Ott, M.D., Elias Campo, M.D., Emilio Montserrat, M.D., Wyndham H. Wilson, M.D., Ph.D., Elaine S. Jaffe, M.D., Richard Simon, Ph.D., Liming Yang, Ph.D., John Powell, M.S., Hong Zhao, M.S., Neta Goldschmidt, M.D., Michael Chiorazzi, B.A., and Louis M. Staudt, M.D., Ph.D.



Quartile of SPS	Survival		
	Median (yr)	5 yr (%)	10 yr (%)
1	13.6	86	51
2	11.1	86	58
3	10.8	69	54
4	3.9	38	29



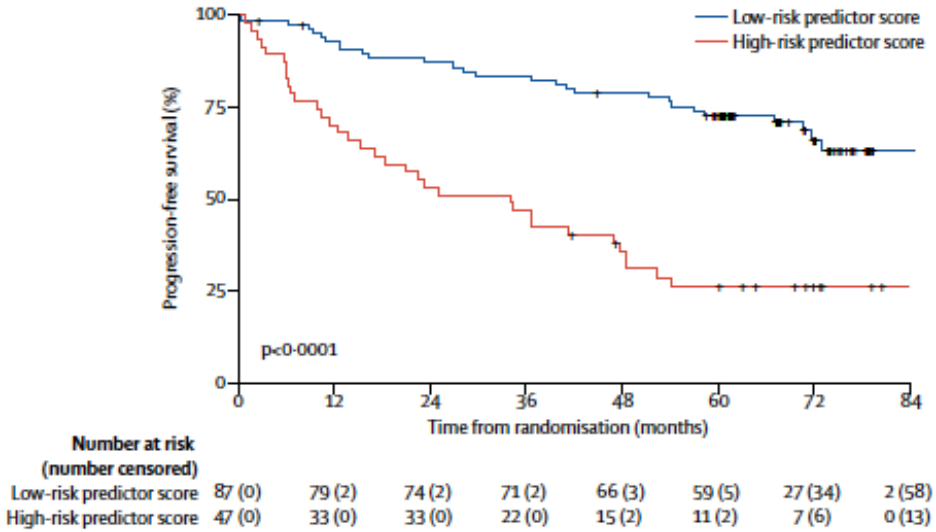
Given the emerging signal that **outcome correlations are tightly related to the specific treatments** received, it is not surprising that these and other immune signatures <u>have not been universally validated</u>.

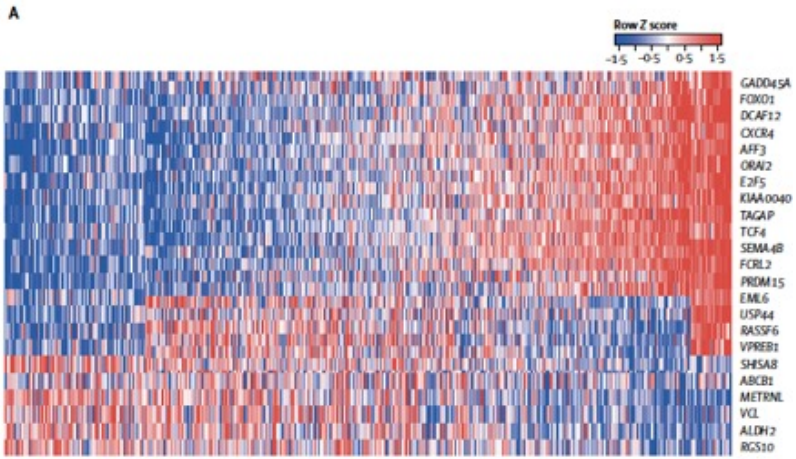
A gene-expression profiling score for prediction of outcome in patients with follicular lymphoma: a retrospective training and validation analysis in three international cohorts

Sarah Huet, Bruno Tesson*, Jean-Philippe Jais, Andrew L Feldman, Laura Magnano, Emilie Thomas, Alexandra Traverse-Glehen, Benoit Albaud, Marjorie Carrère, Luc Xerri, Stephen M Ansell, Lucile Baseggio, Cécile Reyes, Karin Tarte, Sandrine Boyault, Corinne Haioun, Brian K Link, Pierre Feugier, Armando Lopez-Guillermo, Hervé Tilly, Pauline Brice, Sandrine Hayette, Fabrice Jardin, Fritz Offner, Pierre Sujobert, David Gentien, Alain Viari, Elias Campo, James R Cerhan, Gilles Salles*

PRIMA TRIAL

Conclusion: Using the largest study evaluating molecular prognostic biomarkers in FL patients, we developed a robust 23-gene expression–based predictor of PFS, applicable to routinely available FFPE biopsies from FL patients at diagnosis. In patients treated initially with rituximab-chemotherapy, this model identifies patients with a high risk of early progression.



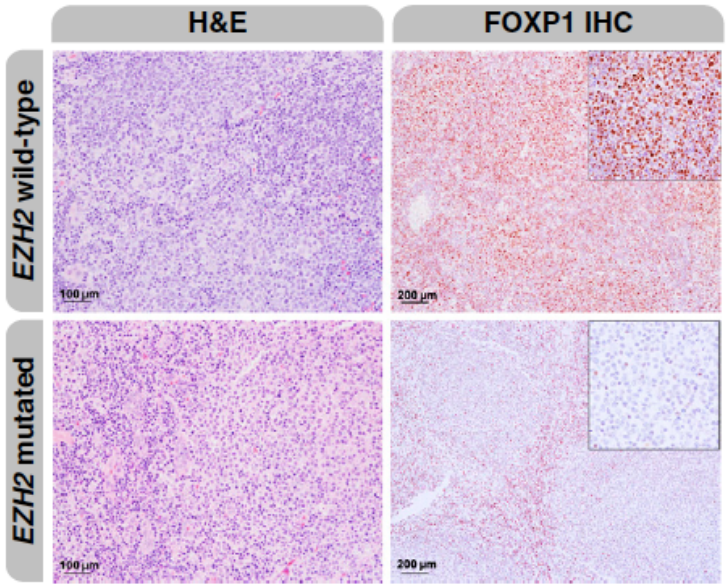


using an adapted gene expression predictor, Silva et al. **validated** the prognostic relevance of a modified "23" gene predictor in 137 patients treated with **R-CVP**, with or without maintenance

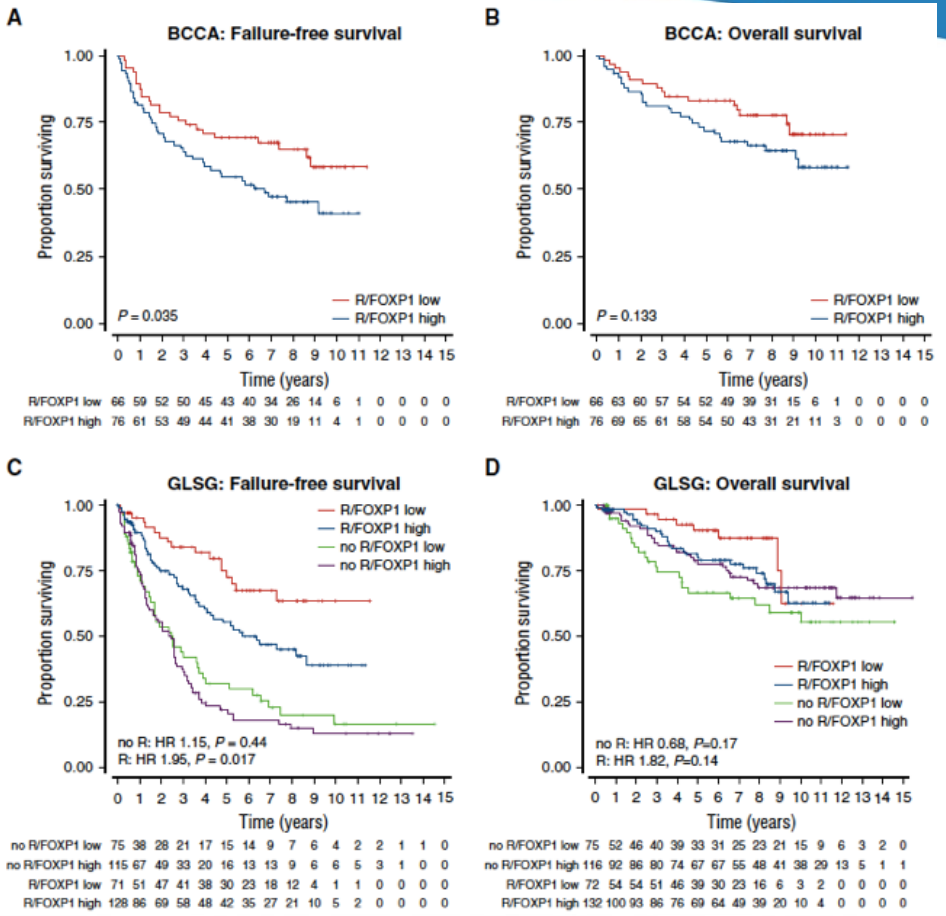
Lancet Oncol 2018

FOXP1 expression is a prognostic biomarker in follicular lymphoma treated with rituximab and chemotherapy

Anja Mottok,[1-3,*] Vindi Jurinovic,[4,5,*] Pedro Farinha,[1,2] Andreas Rosenwald,[3] Ellen Leich,[3] German Ott,[6,7] Heike Horn,[7,8] Wolfram Klapper,[9] Michael Boesl,[4] Wolfgang Hiddemann,[4] Christian Steidl,[1,2] Joseph M. Connors,[1] Laurie H. Sehn,[1] Randy D. Gascoyne,[1,2] Eva Hoster,[4,5,*] Oliver Weigert,[4,*] and Robert Kridel[10,*]



FOXP1 high and low expressors differ in specific gene mutations and gene expression changes.

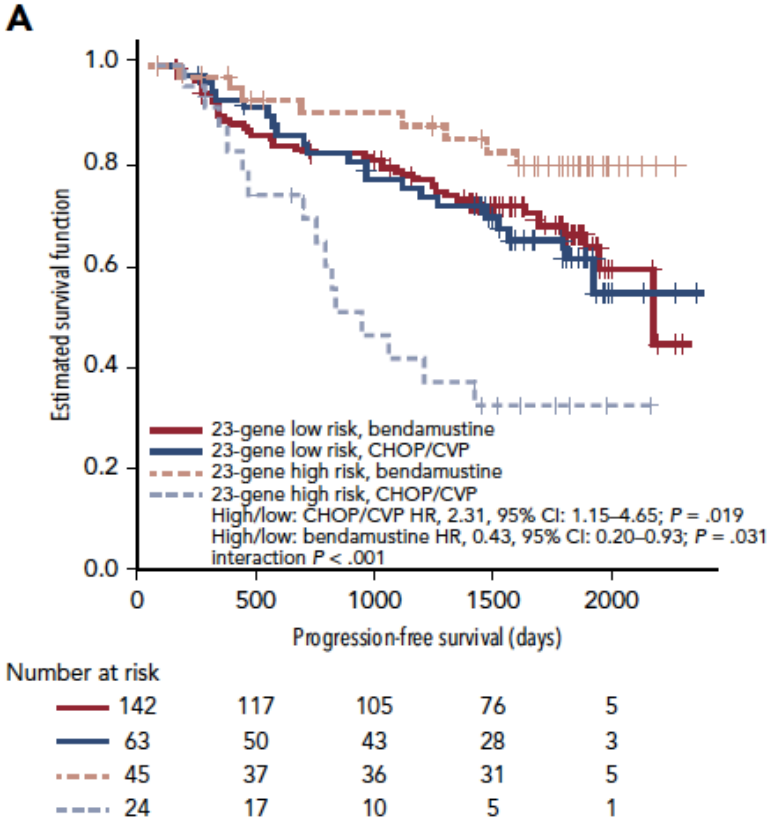


GALLIUM TRIAL

TO THE EDITOR:

Treatment dependence of prognostic gene expression signatures in de novo follicular lymphoma

Christopher R. Bolen,[1] Federico Mattiello,[2] Michael Herold,[3] Wolfgang Hiddemann,[4] Sarah Huet,[5-7] Wolfram Klapper,[8] Robert Marcus,[9] Farheen Mir,[10] Gilles Salles,[5,11] Oliver Weigert,[12-14] Tina Nielsen,[2] Mikkel Z. Oestergaard,[15] and Jeffrey M. Venstrom[16]



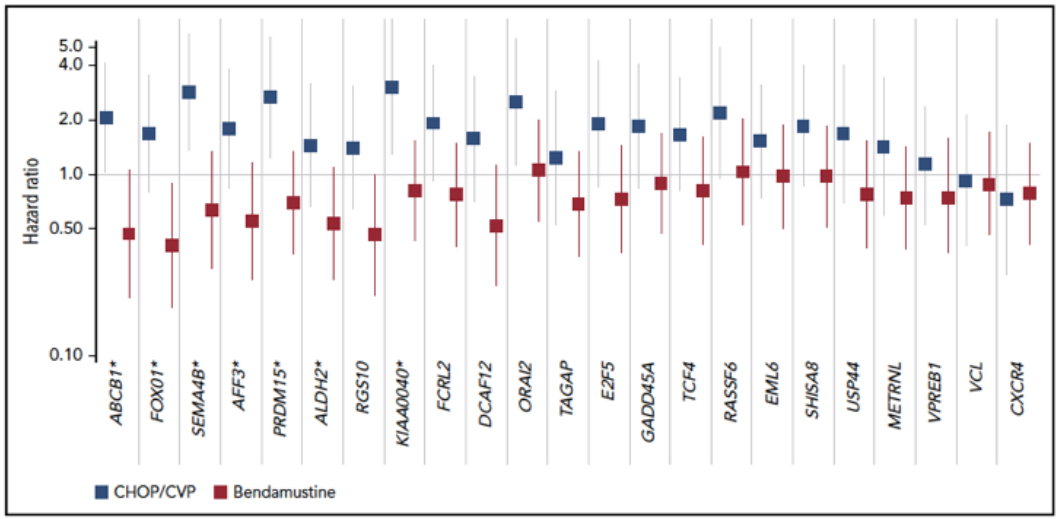


Figure 2. Evidence of differential prognostic association across all subsets of the 23-gene signature. The association of each gene was tested among patients treated with either CHOP/CVP (blue) or bendamustine (red). PFS HRs and 95% CIs from a multivariate Cox proportional-hazards model are plotted. *Demonstrated significant chemotherapy dependence (interaction, $P < .05$). CI, confidence interval; HR, hazard ratio.

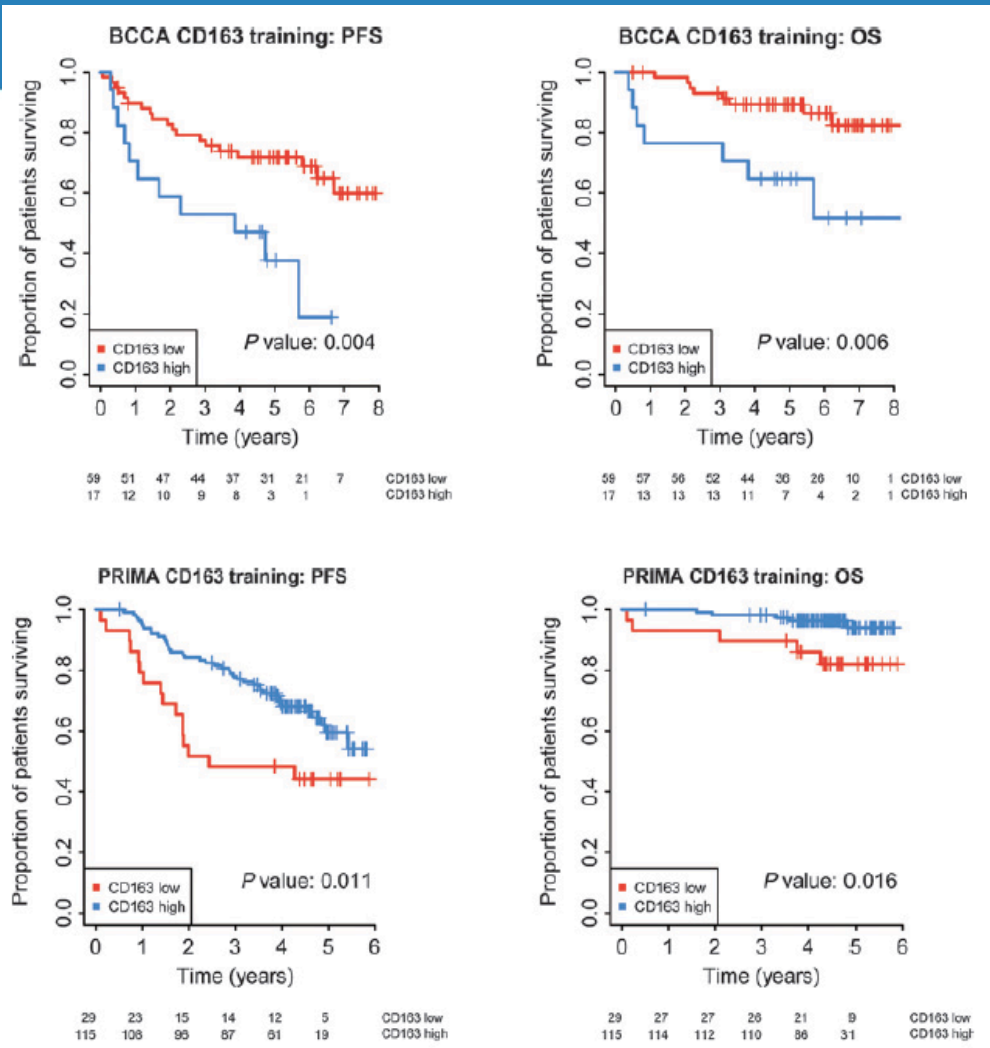
Personalized Medicine and Imaging

Clinical Cancer Research

The Prognostic Impact of CD163-Positive Macrophages in Follicular Lymphoma: A Study from the BC Cancer Agency and the Lymphoma Study Association

Robert Kridel[1], Luc Xerri[2], Bénédicte Gelas-Dore[3], King Tan[1], Pierre Feugier[4], Ayesha Vawda[1], Danielle Canioni[5], Pedro Farinha[1], Sami Boussetta[3], Alden A. Moccia[1], Pauline Brice[6], Elizabeth A. Chavez[1], Alastair H. Kyle[7], David W. Scott[1], Ashley D. Sanders[8], Bettina Fabiani[9], Graham W. Slack[1], Andrew I. Minchinton[7], Corinne Haioun[10], Joseph M. Connors[1], Laurie H. Sehn[1], Christian Steidl[1], Randy D. Gascoyne[1], and Gilles Salles[11]

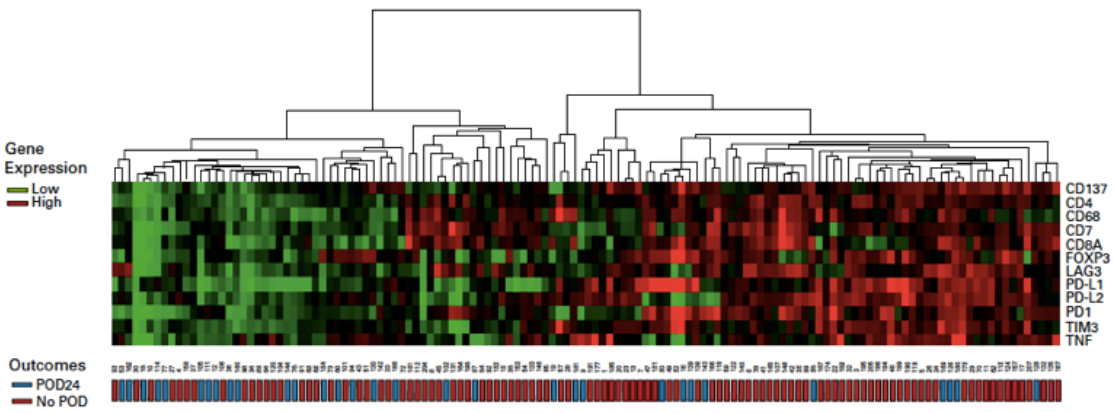
Conclusions: CD163-positive macrophages predict outcome in follicular lymphoma, but their prognostic impact is highly dependent on treatment received. *Clin Cancer Res; 21(15); 3428–35.*

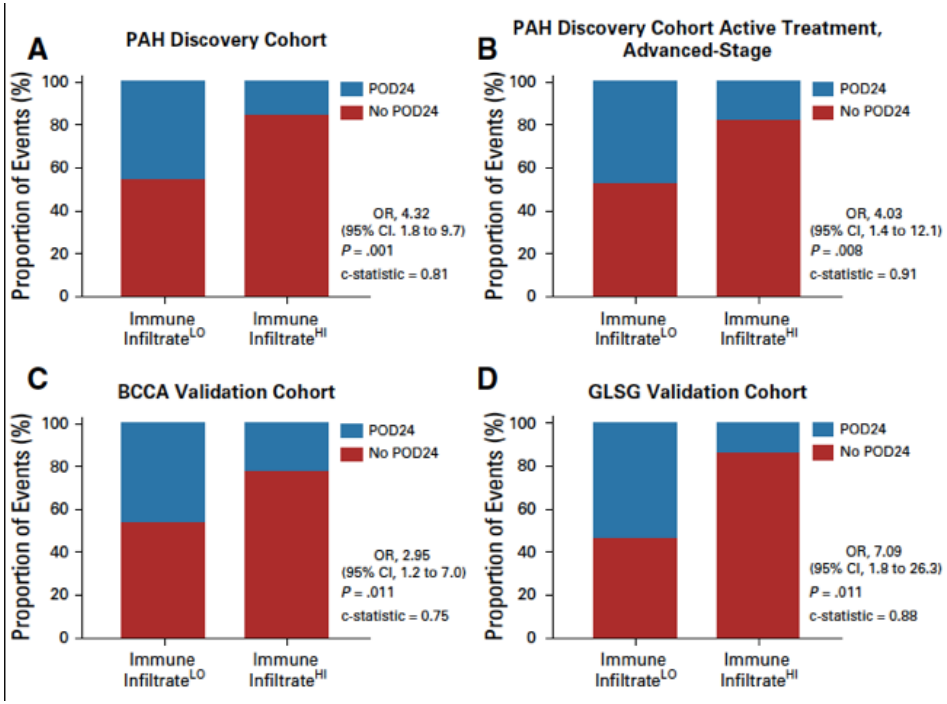


Progression of Disease Within 24 Months in Follicular Lymphoma Is Associated With Reduced Intratumoral Immune Infiltration

Journal of Clinical Oncology®

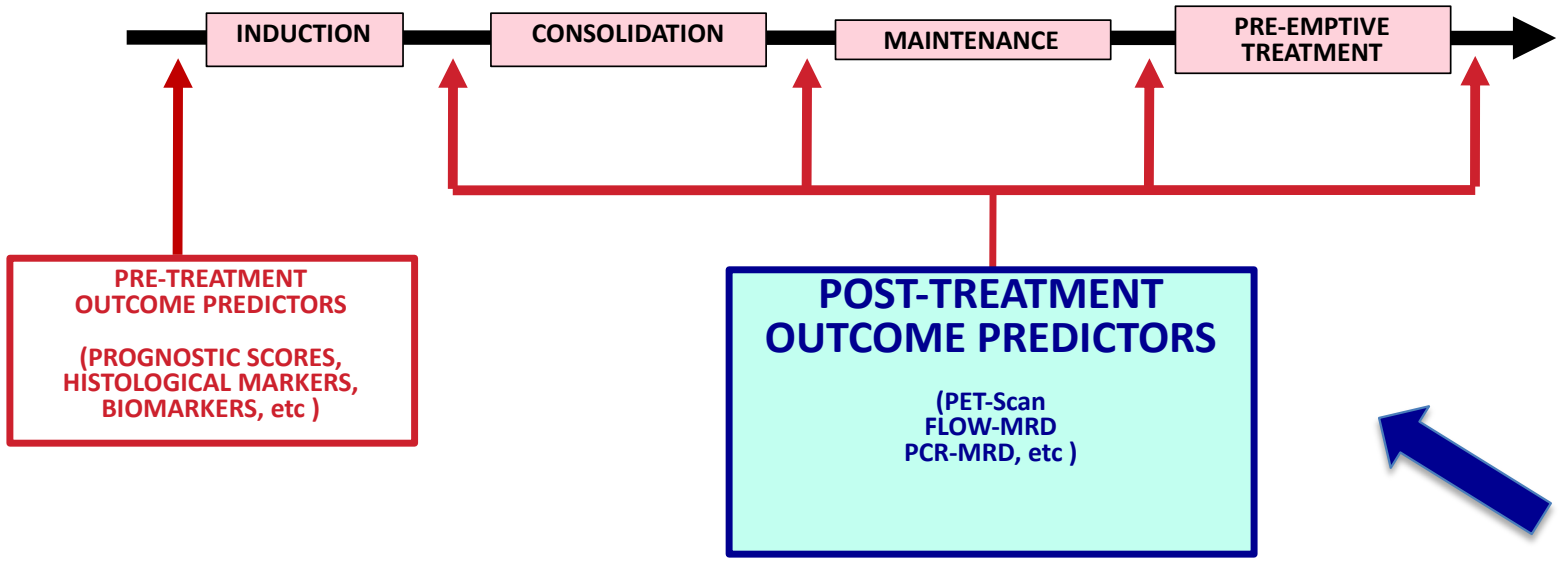
Joshua W.D. Tobin, MD[1,2]; Colm Keane, MD[1,2]; Jay Gunawardana, PhD[1]; Peter Mollee, MBBS, MMedSc[2]; Simone Birch, MD, PhD[2]; Thanh Hoang, MB[3]; Justina Lee[3]; Li Li, MD, PhD[4]; Li Huang, MD[4]; Valentine Murigneux, MSc[3]; J. Lynn Fink, PhD[3]; Nicholas Matigian, BAppSci[3]; Frank Vari, PhD[11]; Santiyagu Francis, PhD[3]; Robert Kridel, MD, PhD[5]; Oliver Weigert, MD[6,7,8]; Sarah Haebe, MD[6,7,8]; Vindi Jurinovic, MD[6,7,8]; Wolfram Klapper, MD[9]; Christian Steidl, MD[10]; Laurie H. Sehn, MD, MPH[10]; Soi-Cheng Law, PhD[1]; Michelle N. Wykes, PhD[11]; and Maher K. Gandhi, MD, PhD[1,2]





J Clin Oncol 37:3300-3309. © 2019 by American Society of Clinical Oncology

Outcome prediction in FL



VOLUME 29 · NUMBER 23 · AUGUST 10 2011

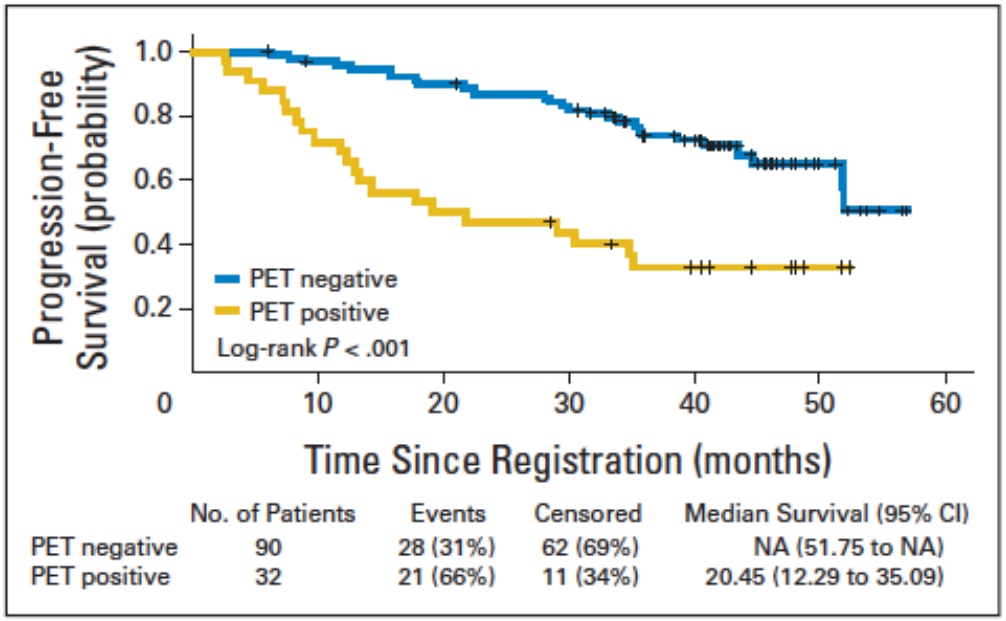
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

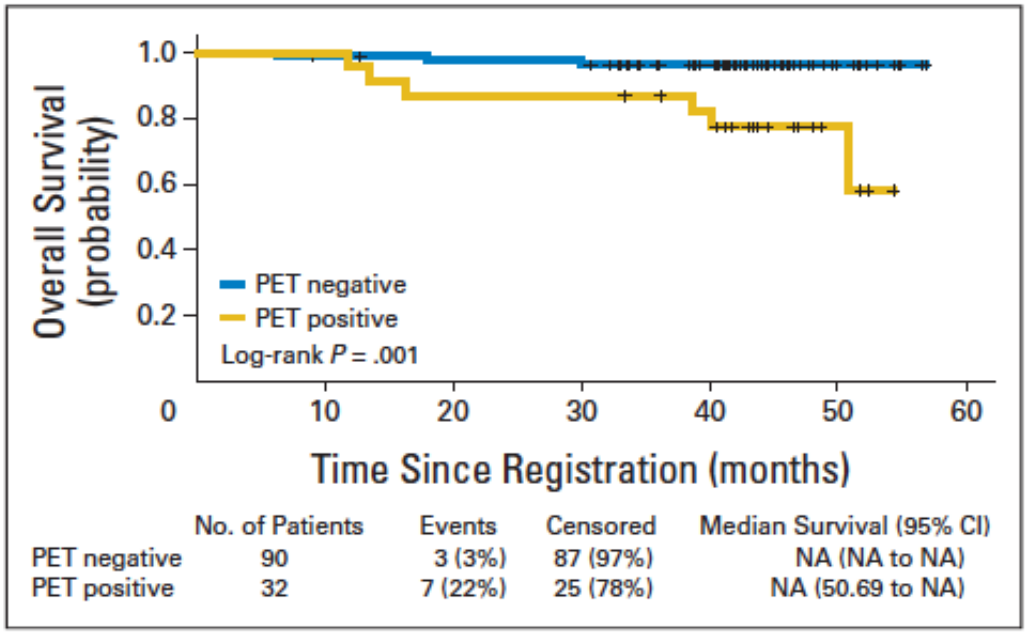
PRIMA TRIAL

Positron Emission Tomography–Computed Tomography (PET-CT) After Induction Therapy Is Highly Predictive of Patient Outcome in Follicular Lymphoma: Analysis of PET-CT in a Subset of PRIMA Trial Participants

Judith Trotman, Marion Fournier, Thierry Lamy, John Francis Seymour, Anne Sonet, Andrea Janikova, Ofer Shpilberg, Emmanuel Gyan, Hervé Tilly, Jane Estell, Cecily Forsyth, Didier Decaudin, Bettina Fabiani, Jean Gabarre, Bruno Salles, Eric Van Den Neste, Danielle Canioni, Etienne Garin, Michael Fulham, Thierry Vander Borght, and Gilles Salles



	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	28 (31%)	62 (69%)	NA (51.75 to NA)
PET positive	32	21 (66%)	11 (34%)	20.45 (12.29 to 35.09)

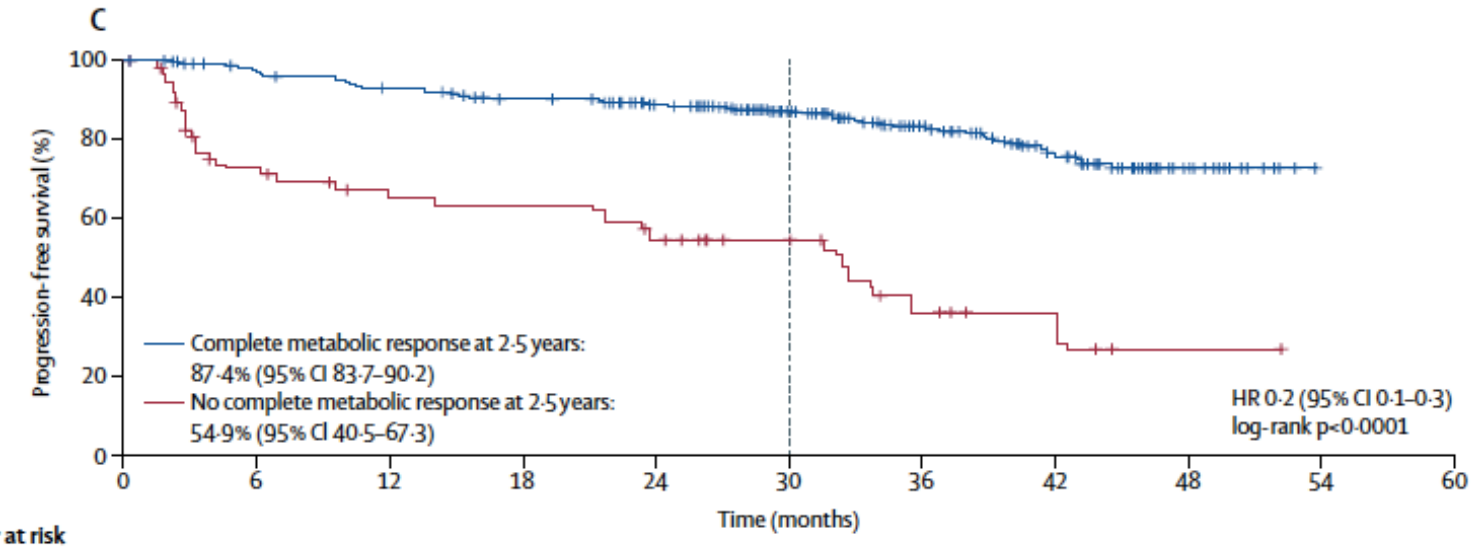


	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	3 (3%)	87 (97%)	NA (NA to NA)
PET positive	32	7 (22%)	25 (78%)	NA (50.69 to NA)

Prognostic value of end-of-induction PET response after first-line immunochemotherapy for follicular lymphoma (GALLIUM): secondary analysis of a randomised, phase 3 trial

GALLIUM TRIAL

Judith Trotman, Sally F Barrington, David Belada, Michel Meignan, Robert MacEwan, Carolyn Owen, Václav Ptáčník, András Rosta, Günter R Fingerle-Rowson, Jiawen Zhu, Tina Nielsen, Deniz Sahin, Wolfgang Hiddemann, Robert E Marcus, Andrew Davies, for the PET investigators from the GALLIUM study



Number at risk (number censored)											
Complete response	448 (0)	414 (21)	393 (26)	373 (33)	329 (72)	247 (149)	161 (225)	88 (288)	23 (349)	0 (349)	0 (349)
No complete response	60 (0)	39 (5)	32 (9)	31 (9)	26 (10)	20 (16)	9 (22)	4 (27)	1 (29)	0 (29)	0 (29)

Lancet Oncol 2018

In vitro purging of Bone Marrow Grafts: the MDR- value in Follicular Lymphoma

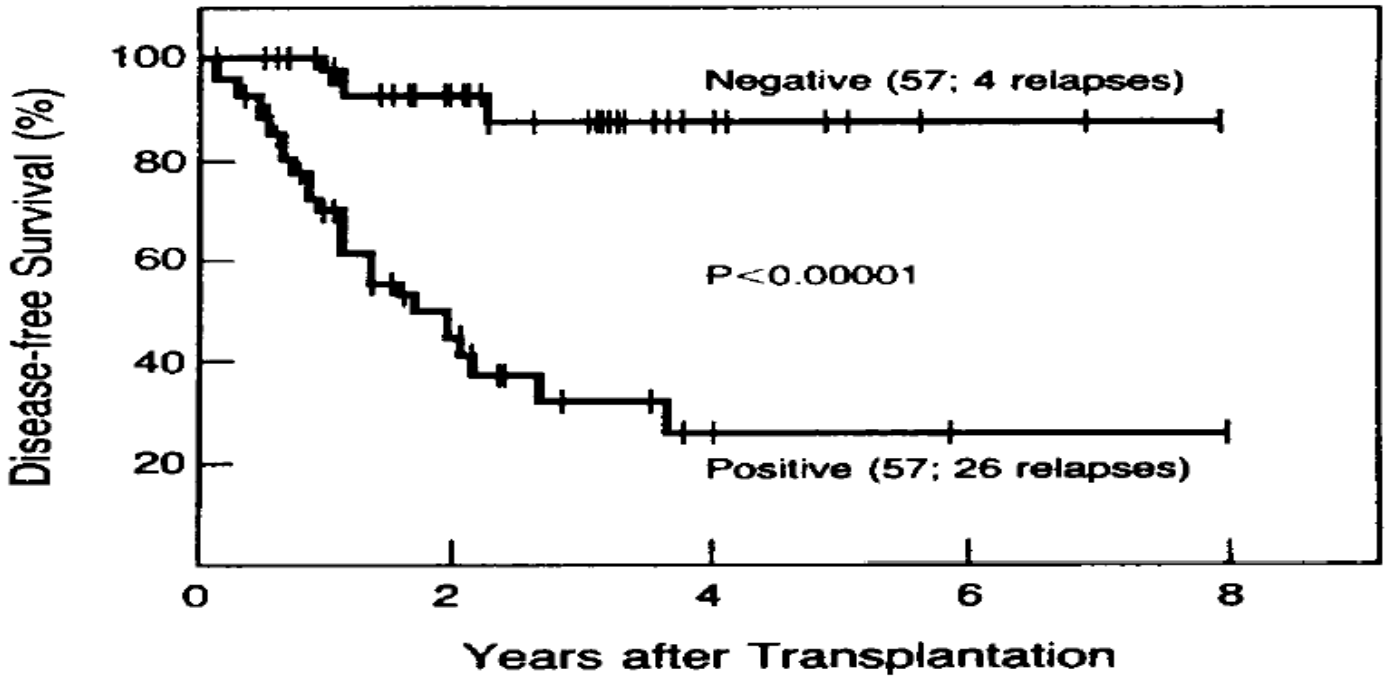


Figure 3. Actuarial Probability of Disease-free Survival after Autologous Bone Marrow Transplantation in 114 Patients with B-Cell Non-Hodgkin's Lymphoma.

"Negative" denotes the patients in whom PCR did not detect residual lymphoma cells after purging, and "positive" the patients in whom PCR did detect residual disease.

Gribben et al. N Engl J Med, 1991

M8: Predictive value for PFS

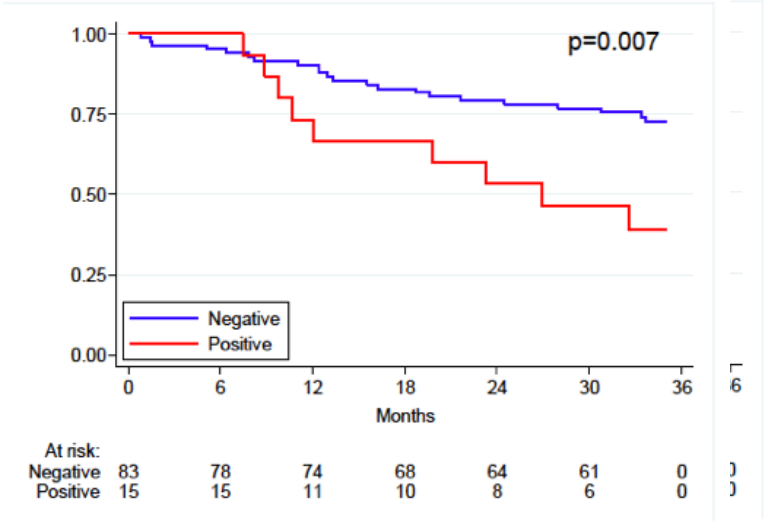
blood
2013 122: 3759-3766
Prepublished online October 1, 2013;
doi:10.1182/blood-2013-06-507319

Persistence of minimal residual disease in bone marrow predicts outcome in follicular lymphomas treated with a rituximab-intensive program

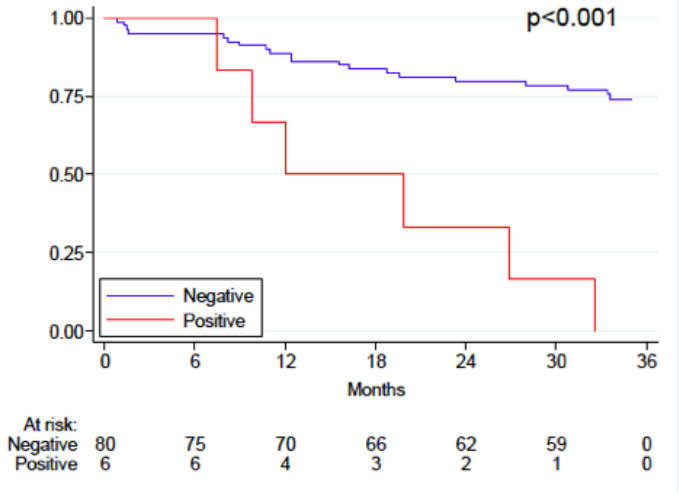
Marco Ladetto, Chiara Lobetti-Bodoni, Barbara Mantoan, Manuela Ceccarelli, Carola Boccomini, Elisa Genuardi, Annalisa Chiappella, Luca Baldini, Giuseppe Rossi, Alessandro Pulsoni, Francesco Di Raimondo, Luigi Rigacci, Antonello Pinto, Sara Galimberti, Alessia Bari, Delia Rota-Scalabrini, Angela Ferrari, Francesco Zaja, Andrea Gallamini, Giorgina Specchia, Pellegrino Musto, Francesca Gaia Rossi, Enrica Gamba, Andrea Evangelista and Umberto Vitolo

Median follow-up of 34 months

N-PCR
72% vs 39%



RQ-PCR
74% vs NA



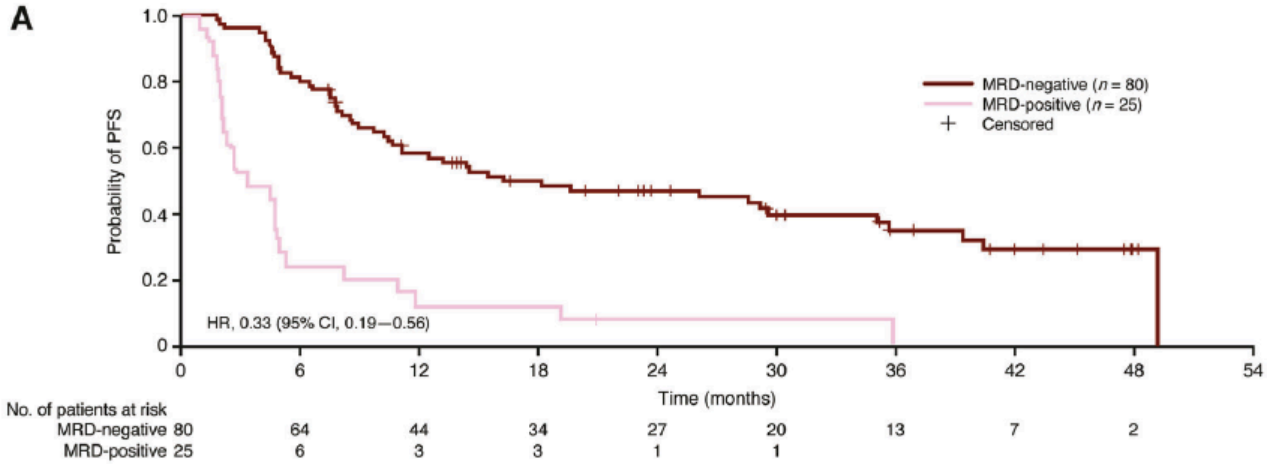
FONDAZIONE ITALIANA LINFOMI

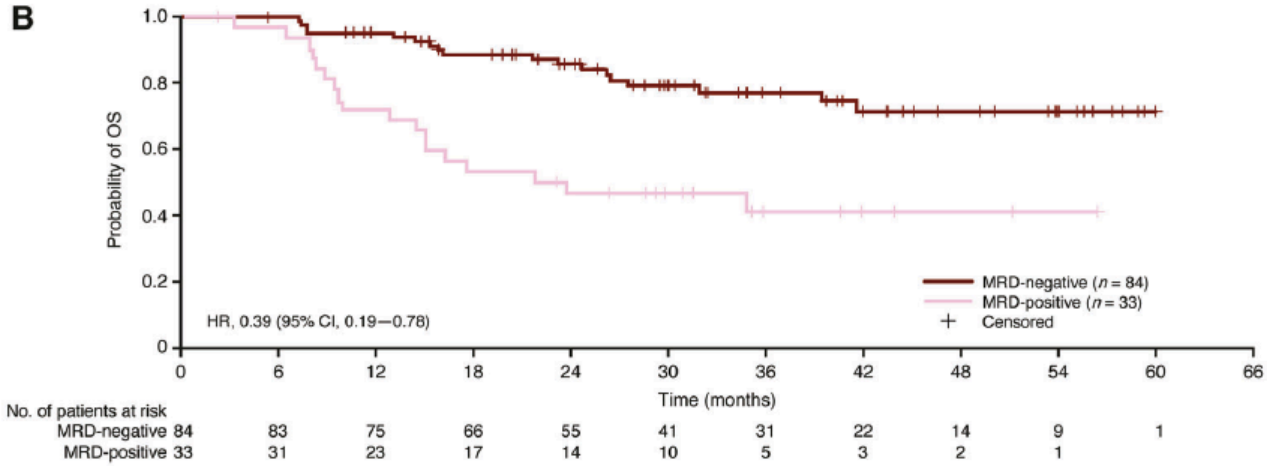
Ladetto, M. et al. Blood 2013

MRD response in relapsed/refractory FL after obinutuzumab plus bendamustine or bendamustine alone in the GADOLIN trial

GADOLIN TRIAL

Christiane Pott[1] · Laurie H. Sehn[2] · David Belada[3] · John Gribben[4] · Eva Hoster[5] · Brad Kahl[6] · Britta Kehden[1] · Emmanuelle Nicolas-Virelizier[7] · Nathalie Spielewoy[8] · Guenter Fingerle-Rowson[8] · Chris Harbron[9] · Kirsten Mundt[8] · Elisabeth Wassner-Fritsch[8] · Bruce D. Cheson[10]





Leukemia
https://doi.org/10.1038/s41375-019-0559-9

Received: 25 March 2019 / Revised: 25 June 2019 / Accepted: 15 July 2019

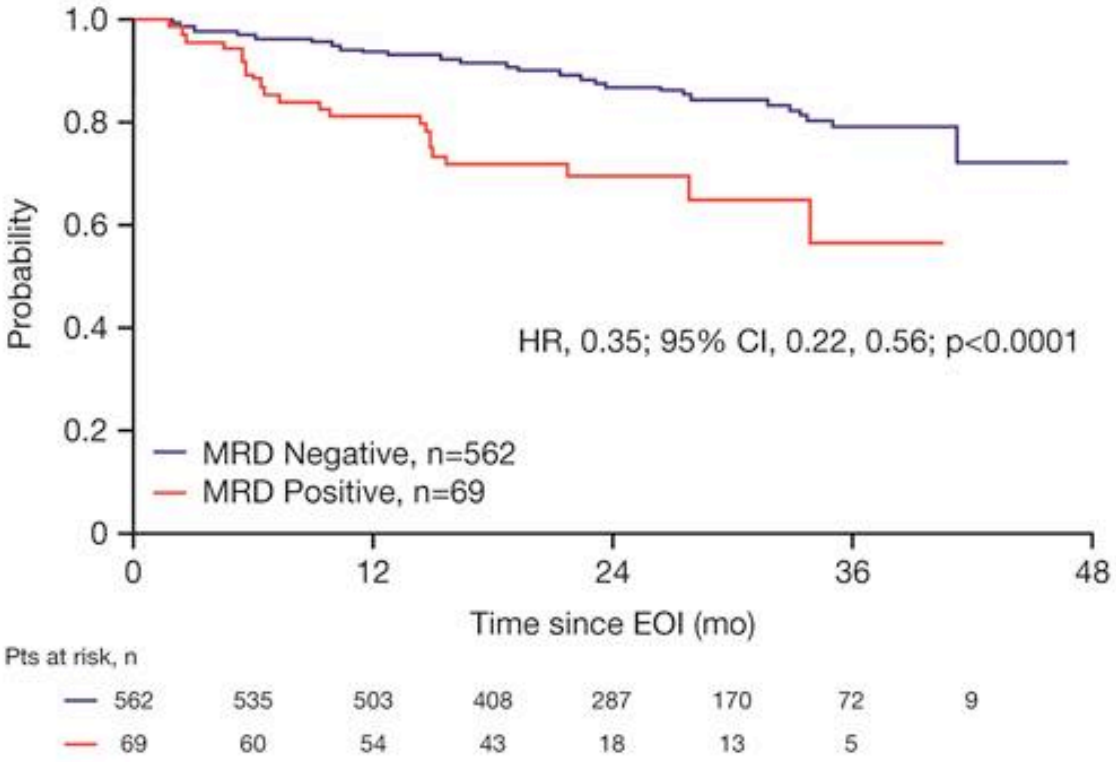
GALLIUM TRIAL

613 Minimal Residual Disease in Patients with Follicular Lymphoma Treated with Obinutuzumab or Rituximab As First-Line Induction Immunochemotherapy and Maintenance in the Phase 3 GALLIUM Study

Mantle Cell, Follicular, and Other Indolent B-Cell Lymphoma—Clinical Studies
Program: Oral and Poster Abstracts
Type: Oral
Session: 623. Mantle Cell, Follicular, and Other Indolent B-Cell Lymphoma—Clinical Studies: Chemoimmunotherapy in Follicular Lymphoma

Monday, December 5, 2016: 7:00 AM
Room 6DE (San Diego Convention Center)

Christiane Pott[1*], *Eva Hoster, PhD*[2*], *Britta Kehden*[1*], *Michael Unterhalt, Ph.D.*[2*], *Michael Herold*[3], *Richard H van der Jagt*[4], *Ann Janssens, MD*[5*], *Michael Kneba*[6], *Jiri Mayer, MD*[7], *Chris Pocock, PhD FRCPath FRCP*[8], *Nathalie Danesi, PhD*[9*], *Günter Fingerle-Rowson*[9], *Chris Harbron*[9*], *Kirsten Mundt*[10*], *Robert E Marcus*[11*] *and Wolfgang Hiddemann*[2]



ASH | 58th Annual Meeting & Exposition
San Diego, CA · December 3-6, 2016

Table 1. MRD status by treatment arm at EOI in PB and/or BM

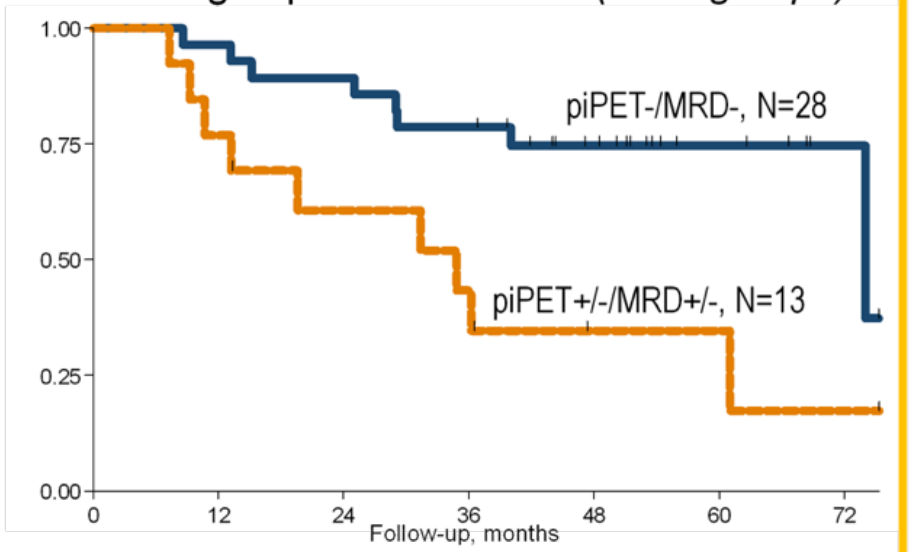
MRD status at EOI in PB and/or BM, n (%)	R-chemo (n=345)	G-chemo (n=351)
MRD positive	52 (15.1)	28 (8.0)
MRD negative	293 (84.9)	323 (92.0)
P-value	0.0041	

Table 2. MRD status by treatment arm at MI in PB

MRD status at MI in PB, n (%)	R-chemo (n=342)	G-chemo (n=348)
MRD positive	38 (11.1)	20 (5.7)
MRD negative	304 (88.9)	328 (94.3)
P-value	0.013	

PET response and Minimal Residual Disease impact on Progression-Free Survival in Patients with Follicular Lymphoma (N=41)

Figure 4.
PFS according to piPET and MRD *(2 subgroups)*



	HR	95%CI	P
piPET+/-/MRD+/-	3.42	1.31-8.95	.012

Luminari et al. Haematologica 2015

23rd Congress of EHA, 14–17 June 2018, Stockholm, Sweden

Abstr PF436

Metabolic (PET) and MRD response confer reduced risk of progression or death in patients treated within the phase III GALLIUM study

Christiane Pott,[1] Andrew Davies,[2] Wolfgang Hiddemann,[3] Eva Hoster,[3] Robert Marcus,[4] Christian Schmidt,[3] Chris Harbron,[5] Kirsten Mundt,[6] Tina Nielsen,[6] Judith Trotman[7]

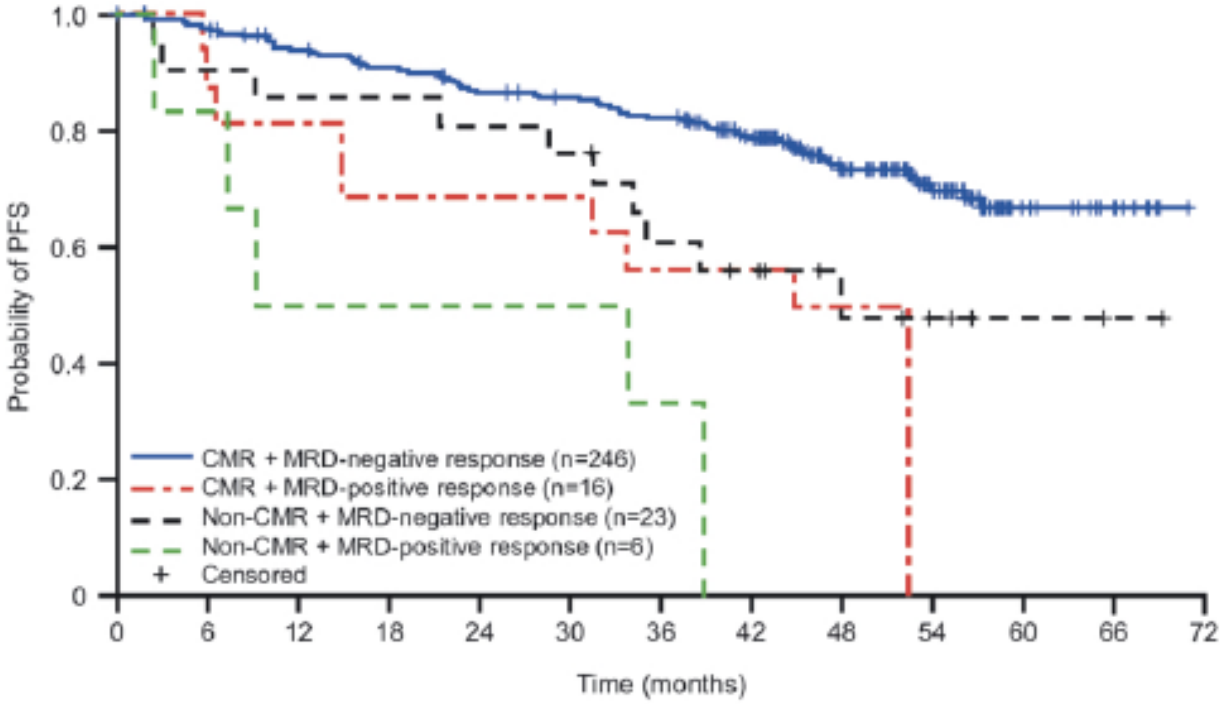


Figure 1. PFS by PET response and MRD status at EOI.

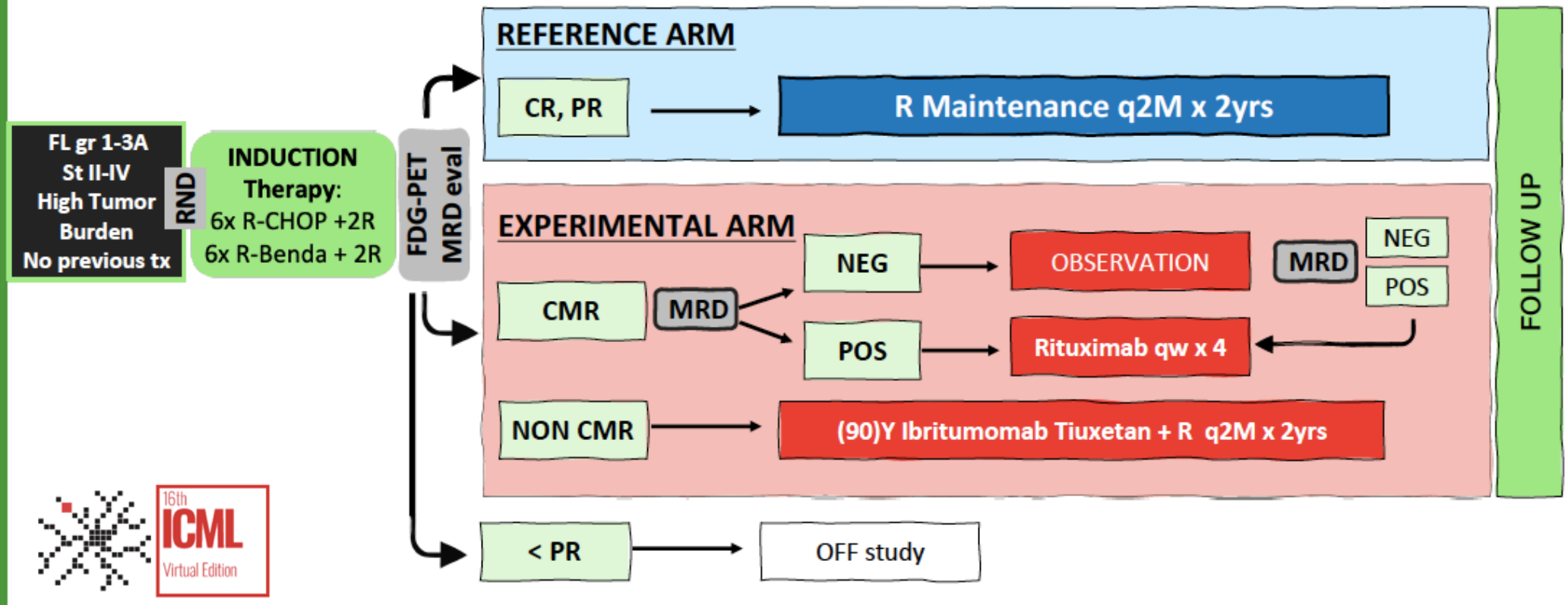
No. of patients at risk*

—	246	237	223	214	202	197	189	163	114	71	19	11	0
- -	16	14	13	11	11	11	9	9	4	0	0	0	0
– –	23	19	18	18	17	16	12	10	6	4	2	1	0
– –	6	5	3	3	3	3	2	0	0	0	0	0	0

FONDAZIONE ITALIANA LINFOMI

FOLL12 TRIAL DESIGN
RESPONSE ADAPTED POST INDUCTION MANAGEMENT
EUDRACT N° : 2012-003170-60

www.filinf.it



16th ICML Virtual Edition

MRD: minimal residual disease assessed by PCR for t(14;18) on bone marrow and peripheral blood sample (central lab)
CMR: Complete Metabolic Response defined as c Deauville score 1-3 (central review)

Luminari et al. ICML16th 2021

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PFS by metabolic and molecular response at the end of induction therapy

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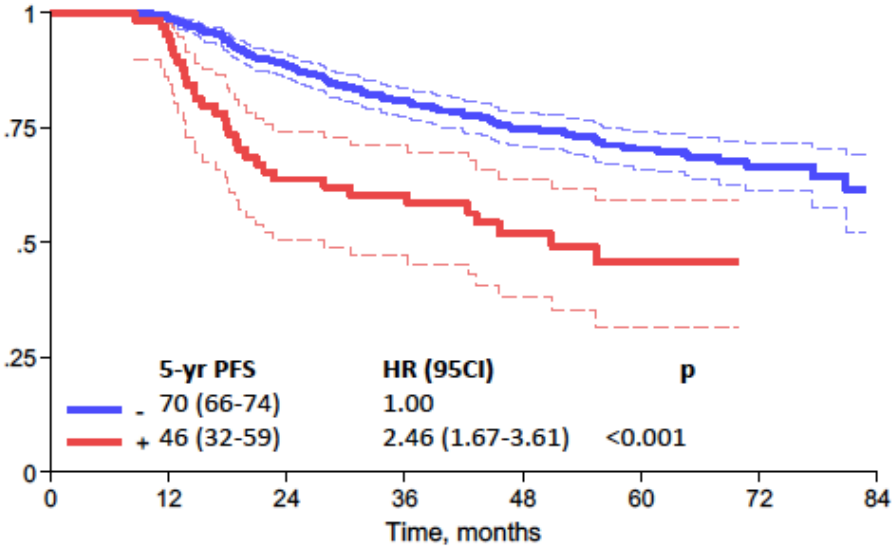
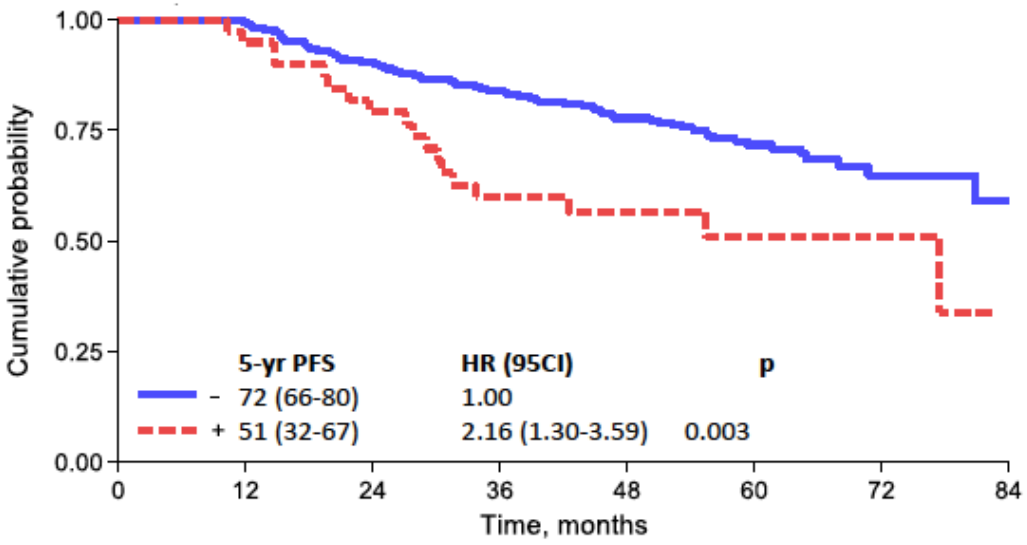
FDG-PET (N=693)



At risk

-	628	612	538	428	285	153	52	8
+	65	61	39	32	21	8	1	1

MRD status (N=386 pts with MRD+ at baseline)



At risk

-	347	336	295	245	166	86	28	6
+	39	37	29	19	15	7	4	0

16th ICML Virtual Edition

Non CMR = DS 4-5
(N=65; 9.3%)

MRD pos = positive PCR for t(14;18) on BM at EOI (sens 10e-5)
(N=39 10.1%)

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DS= Deauville score; MRD minimal Residual Disease; PCR, Polymersae Chain reaction, BM Bone Marrow, EOI, End Of Induction

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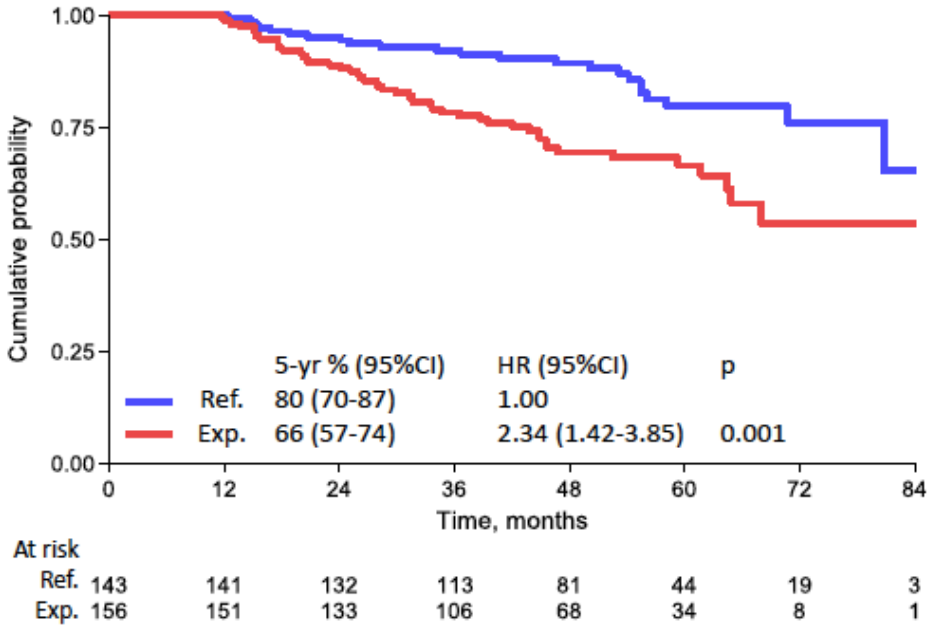
PFS for CMR patients by MRD status

www.filinf.it

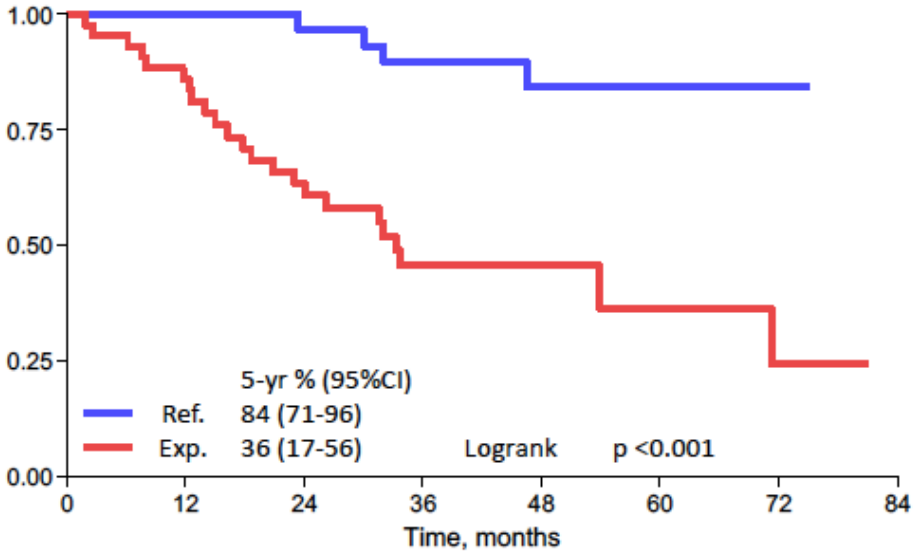
MRD negative EoT and CMR (N=299)



At risk

Ref.	143	141	132	113	81	44	19	3
Exp.	156	151	133	106	68	34	8	1

MRD CMR and MRD positive EoT or follow-up (N=76)



At risk

Ref.	32	30	28	25	16	8	1	0
Exp.	44	36	25	11	8	3	2	0

16th ICML Virtual Edition

MRD: minimal residual disease assessed by PCR for t(14;18) on bone marrow and peripheral blood sample (central lab)
CMR: Complete Metabolic Response defined as c Deauville score 1-3 (central review)

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PFS: Non CMR by Arm (N=65)

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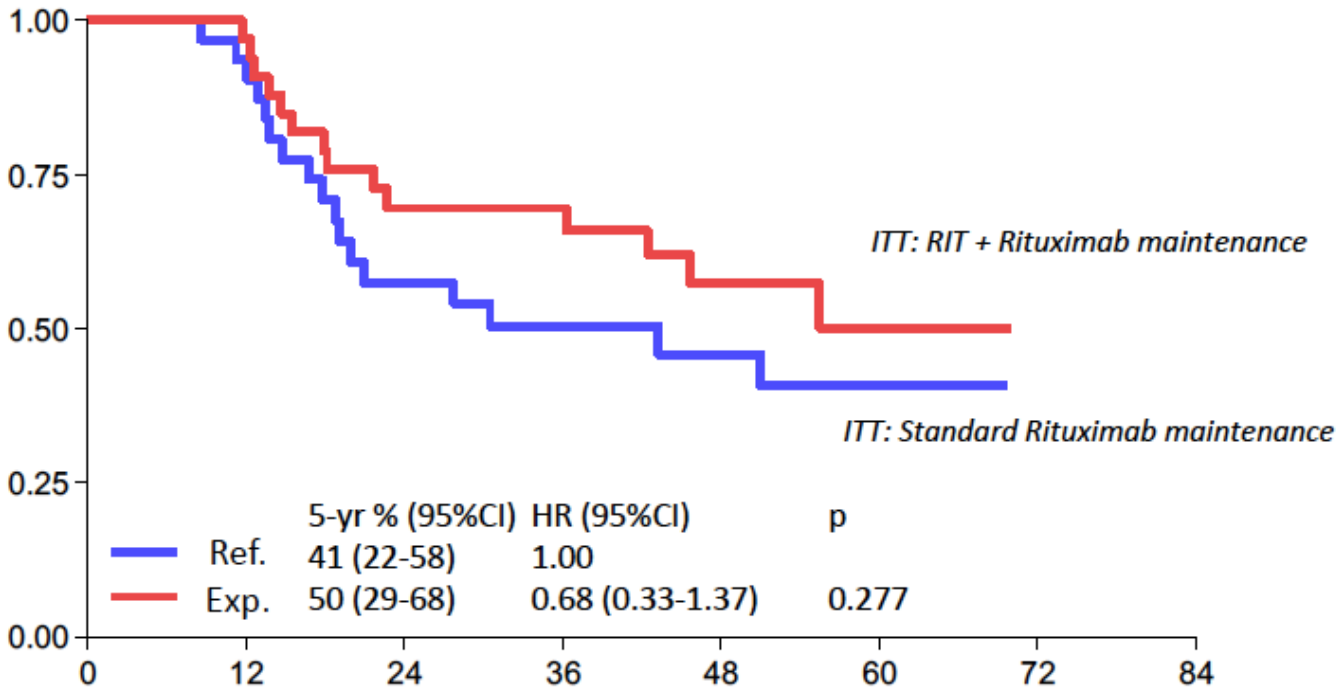

16th ICML Virtual Edition

At risk								
Ref.	31	29	17	13	9	4	0	0
Exp.	34	32	22	19	12	4	1	1

RIT, Radioimmunotherapy
28/34 actually treated with RIT in arm B

Luminari et al. ICML16th 2021

Biology of high-risk follicular lymphoma in 2021: CONCLUSIONS

- **Lack of effective tools** to identify high-risk patients (20-30%)
- **POD24** is a validated predictors of poor OS
- The deepness of response at the end of treatment (**MRD/PET**) is predictive of poor PFS and OS
- Many promising biomarkers at baseline have been described, both based on mutations, GEP, microenviroment .... but **none has been validated for clinical use in FL**, so far
- Most of these biomarkers are **tightly dependent on specific treatment schedules** (R-CHOP vs BR vs novel drugs…???)
- Pre-emptive and treatment tailoring strategies are currently under evaluation in clinical trials
- A **risk-adapted strategy** seems appropriate but a **deeper biological knowledge** of the tumor is needed to identify and validate predictive biomarkers for successful clinical use

ACKNOWLEDGEMENTS

simone.ferrero@unito.it