3rd edition

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

Turin, September 21-22, 2023

Starhotels Majestic

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HOW I TREAT HIGH-RISK FL IN FIRST LINE

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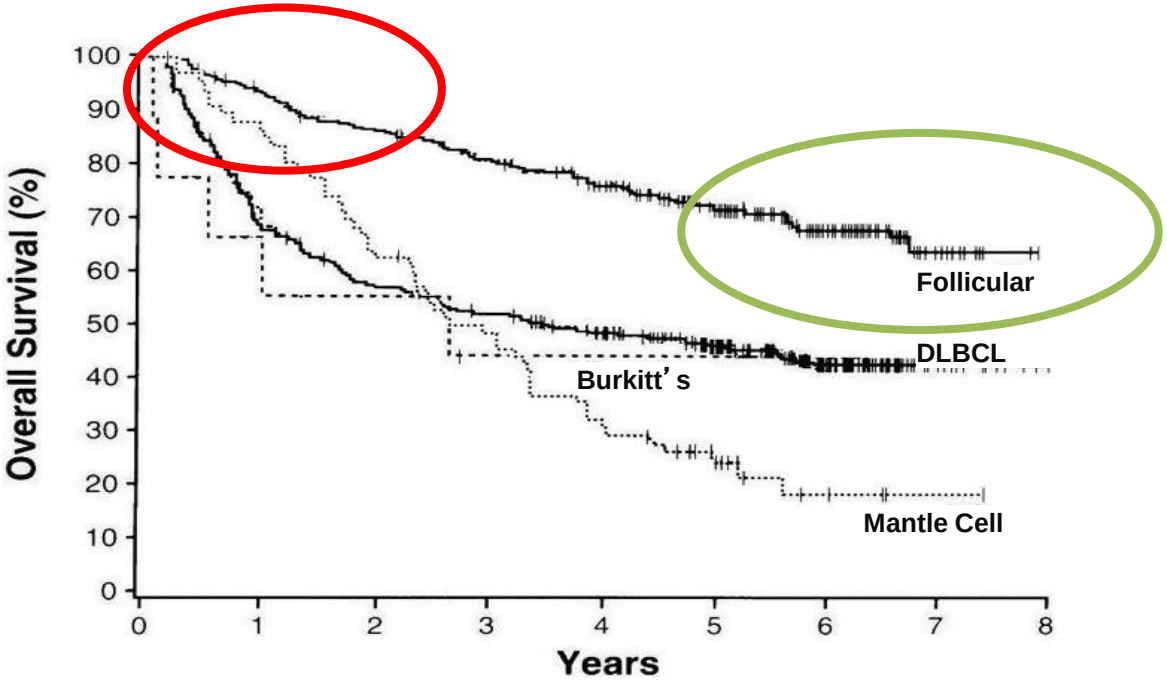
FIL FONDAZIONE ITALIANA LINFOMI

Simone Ferrero: disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen	X		X		X	X	
EUSA Pharma			X		X	X	
Morphosys	X						
Incyte						X	
Gilead	X						
Servier					X		
Gentili					X		
Roche					X		
Sandoz			X				
Beigene	X						
Italfarmaco						X	
Abbvie			X				

FL is a heterogeneous disease



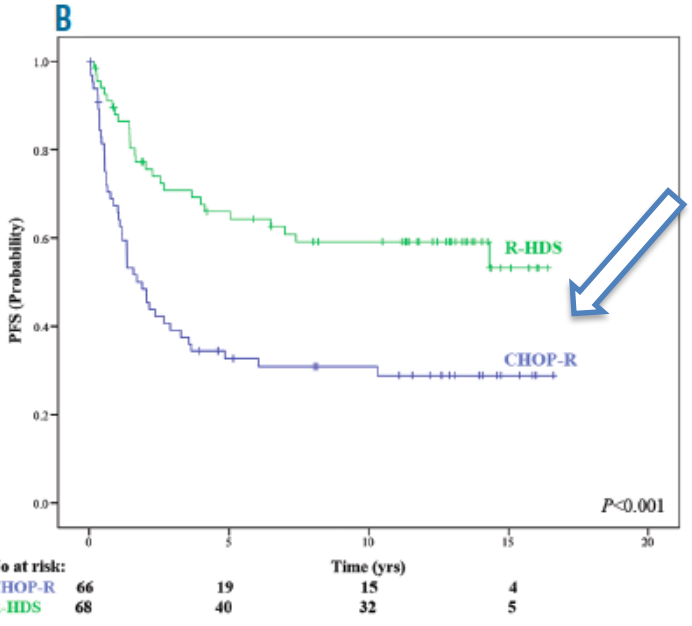
The International Lymphoma Study Group. Blood 1997

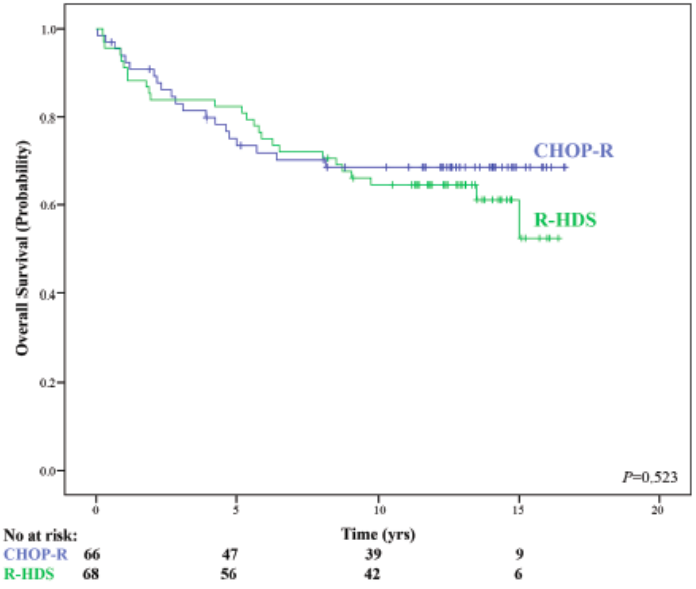
Introduction

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,[18] 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





Bruna R. et al., Haematologica 2019

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

VOLUME 33 · NUMBER 23 · AUGUST 10 2015

JOURNAL OF CLINICAL ONCOLOGY

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

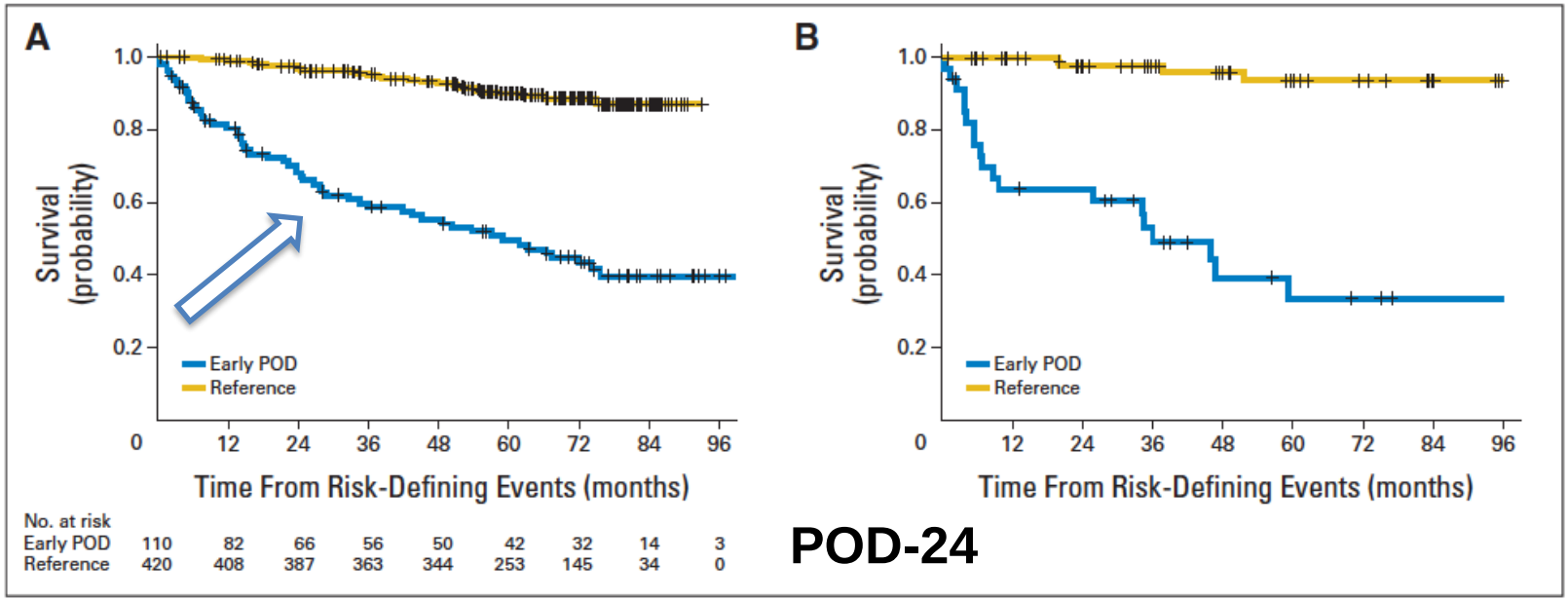


Fig 3. (A) Overall survival (OS) from a risk-defining event after diagnosis in patients who received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the National LymphoCare Study group. Patients with early progression of disease (POD) had poor survival. 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.

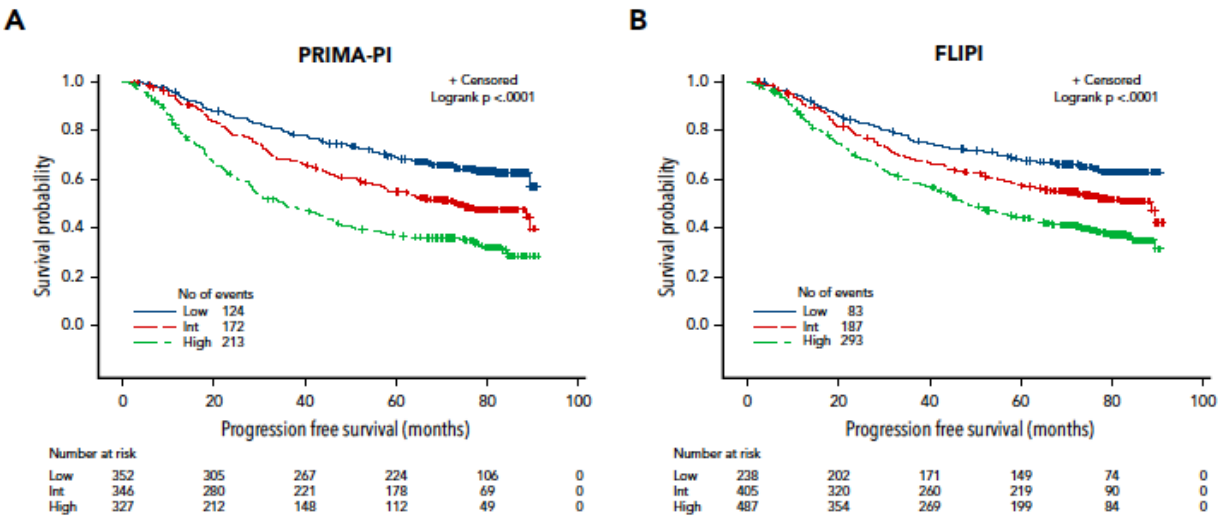
Follicular lymphoma in 2023

- Excellent outcome of advanced FL with available therapies (10-yrs OS 82%)
- 70-80% of patients have manageable FL
  - Consider the less toxic approach
  - Avoid late events
  - Some patients are actually cured (old, low risk… 30%?)
- **20-30% have high risk disease**
  - Early identification (How?)
  - Consider experimental treatments
    - **Reduce the rate of high risk patients**
    - **Overcome the dismal outcome of high risk patients**
- Risk-adapted strategy seems appropriate: how and which?

Courtesy of S. Luminari (modified)

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

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

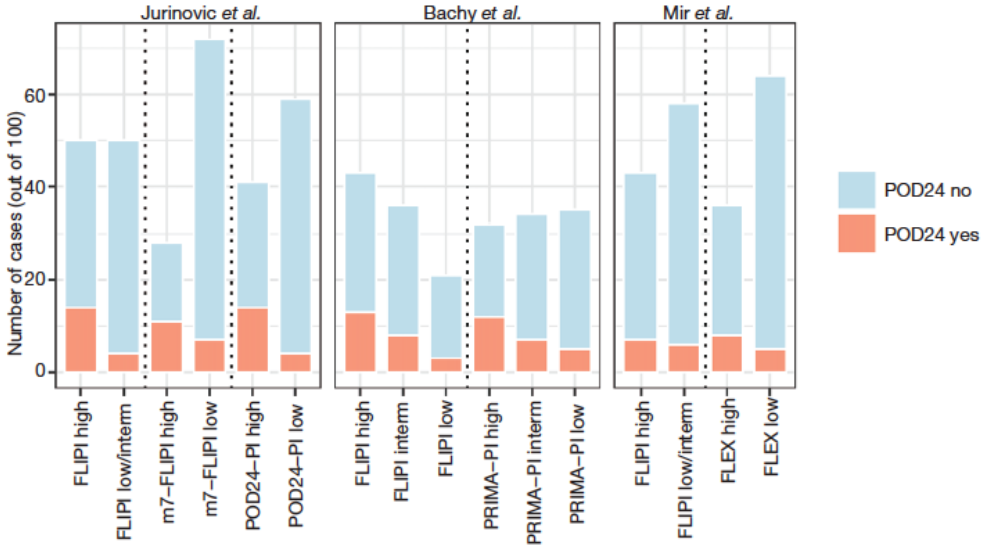


Figure 1 Number of follicular lymphoma patients experiencing POD24 in risk categories defined by the FLIPI, the m7-FLIPI, the POD24-PI, the PRIMA-PI or the FLEX scores. As the reported studies had varying sample sizes, the numbers shown here were normalized to represent numbers of patients out of 100. 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).

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

OK but… which treatment?

Table 6. Combined immunochemotherapy in FL (first line)

Study	Total number of patients	Median follow-up (months)	Overall response (%)	Time to treatment failure (months)	Overall survival (%)
Marcus et al. 2008[21]					
R-CVP	159	53	81 ($P < 0.0001$)	27 ($P < 0.0001$)	83 (4 years) ($P = 0.029$)
Hiddemann et al. 2005[22]					
R-CHOP	223	58	96	NR ($P < 0.001$)	90 (2 years) ($P = 0.0493$)
Herold et al. 2007[23]					
R-MCP	105	48	92 ($P = 0.0009$)	NR ($P < 0.0001$)	87 (4 years) ($P = 0.0096$)
Bachy et al. 2013[24]					
R-CHVP-IFN	175	99	81 ($P = 0.035$)	66 ($P = 0.0004$)	79 (8 years) ($P = 0.076$)
Rummel et al. 2017[26,37]					
BR	139	34	93	78 (median)	NR (median)
BR + R maintenance	595	34	90	NR (median)	NR (median)
Luminari et al. 2018[27]					
R-CVP	178	84	88	38%	85%
R-CHOP	178	84	93	45% ($P = 0.033$)	83% (n.s.)
R-FM + R maintenance	178	84	91	49% ($P = 0.016$) (8 years)	79% (n.s.) (8 years)
Bachy et al. 2019[35]					
R-CHOP/CVP/FM	1018	118	n/a	35% (10 years)	80 (10 years)
R-CHOP/CVP/FM + R maintenance				51% (10 years) ($P < 0.001$)	80 (10 years) (n.s.)
Marcus et al. 2017[29]					
R-CHOP/CVP/B + R maintenance	601	34	86.9	73.3% (3 years)	92.1 (3 years)
G-CHOP/CVP/B + G maintenance	601	34	88.5	80.0% (3 years) ($P = 0.001$)	94.0 (3 years) (n.s.)
Morschhauser et al. 2018[30]					
R-CHOP/BR + R maintenance	517	38	84	78% (3 years)	94 (3 years)
R-lenalidomide + R maintenance	513	38	89	77% (3 years) (n.s.)	94 (3 years) (n.s.)

Dreyling M et al, Ann Oncol. 2021 Mar;32(3):298-308

Talk overview

- Currently available therapies in first line
- PET-guided first line
- Biomarkers-driven first line (*EZH2*, MRD)
- Novel approaches in first line

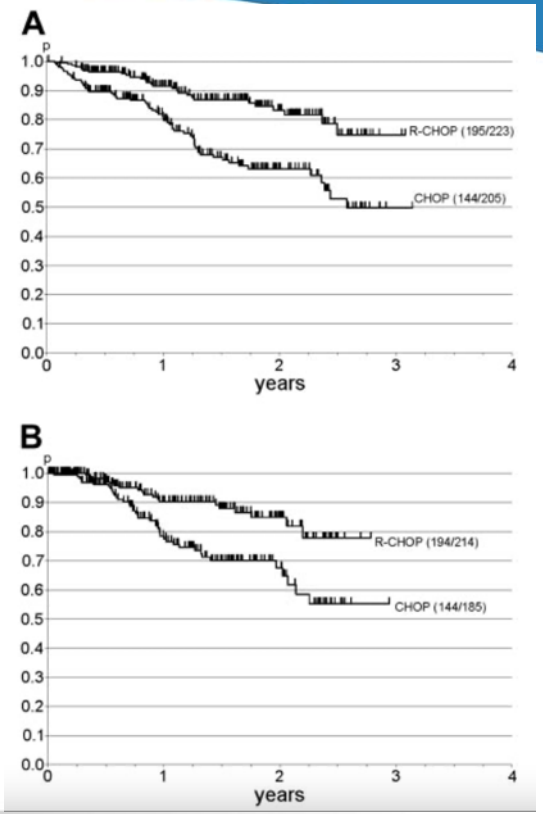
Anti-CD20: when it all begun…

blood

Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group

Wolfgang Hiddemann, Michael Kneba, Martin Dreyling, Norbert Schmitz, Eva Lengfelder, Rudolf Schmits, Marcel Reiser, Bernd Metzner, Harriet Harder, Susanna Hegewisch-Becker, Thomas Fischer, Martin Kropff, Hans-Edgar Reis, Mathias Freund, Bernhard Wörmann, Roland Fuchs, Manfred Planker, Jörg Schimke, Hartmut Eimermacher, Lorenz Trümper, Ali Aldaoud, Reza Parwaresch, and Michael Unterhalt

- 428 patients with untreated, advanced-stage FL
- CHOP (n=205) vs R-CHOP (n=223)
- R-CHOP reduced the relative risk for treatment failure by 60% and significantly prolonged the time to treatment failure (P < .001)
- higher ORR (96% vs 90%; P = .011) and prolonged DoR (P = .001)
- OS advantage (P = .016)



Hiddemann W et al, *Blood*. 2005;106(12):3725-3732

Which **chemotherapy** backbone?

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Treatment of Patients With Advanced-Stage Follicular Lymphoma: Results of the FOLL05 Trial Conducted by the Fondazione Italiana Linfomi

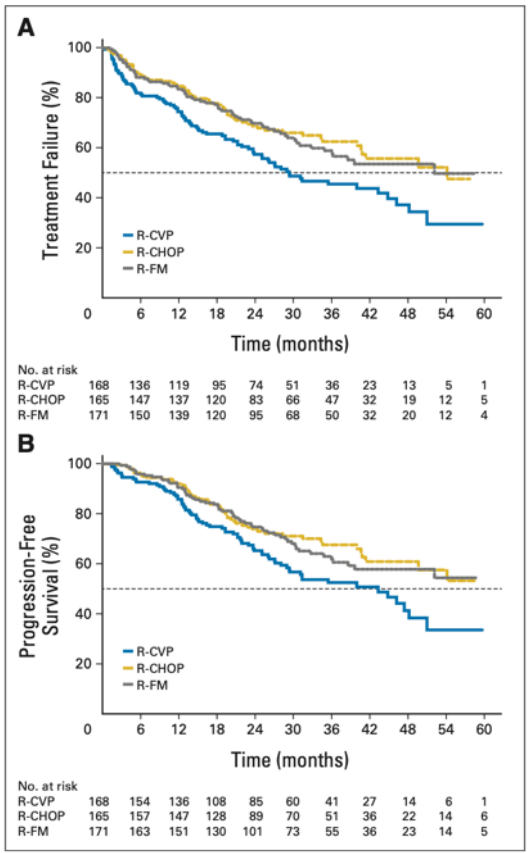
Massimo Federico, Stefano Luminari, Alessandra Dondi, Alessandra Tucci, Umberto Vitolo, Luigi Rigacci, Francesco Di Raimondo, Angelo Michele Carella, Alessandro Pulsoni, Francesco Merli, Luca Arcaini, Francesco Angrilli, Caterina Stelitano, Gianluca Gaidano, Matteo Dell'Olio, Luigi Marcheselli, Vito Franco, Sara Galimberti, Stefano Sacchi, and Maura Brugiatelli

FONDAZIONE ITALIANA LINFOMI

- N=534
- ORR = 88%, 93%, and 91% for R-CVP, R-CHOP, and R-FM (P=.247)
- after a median follow-up of 34 months
- 3-year TTFs = 46%, 62%, and 59% (R-CHOP v R-CVP, P=.003; R-FM v R-CVP, P=.006; R-FM v R-CHOP, P=.763)
- 3-year PFS = 52%, 68%, and 63% (overall P=.011)
- 3-year OS = 95% for the whole series
- Higher rates of grade 3 to 4 neutropenia in R-FM (64%) compared with R-CVP (28%) and R-CHOP (50%; P< .001)

CONCLUSION

- **R-CHOP and R-FM were superior to R-CVP in terms of 3-year TTF and PFS**
- **R-CHOP had a better risk-benefit ratio compared with R-FM**



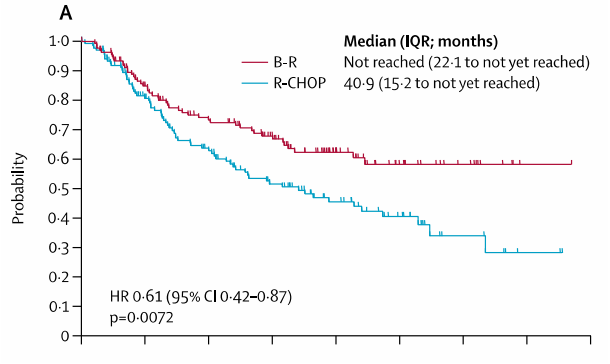
FIL «FOLL05» TRIAL

Federico M et al, J Clin Oncol. 2013, Apr 20;31(12):1506-13

Which **chemotherapy** backbone?

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, Dorothea Kofahl-Krause, Gerhard Heil, Manfred Welslau, Christina Balser, Ulrich Kaiser, Eckhart Weidmann, Heinz Dürk, Harald Ballo, Martina Stauch, Fritz Roller, Juergen Barth, Dieter Hoelzer, Axel Hinke, Wolfram Brugger, on behalf of the Study group indolent Lymphomas (StiL)



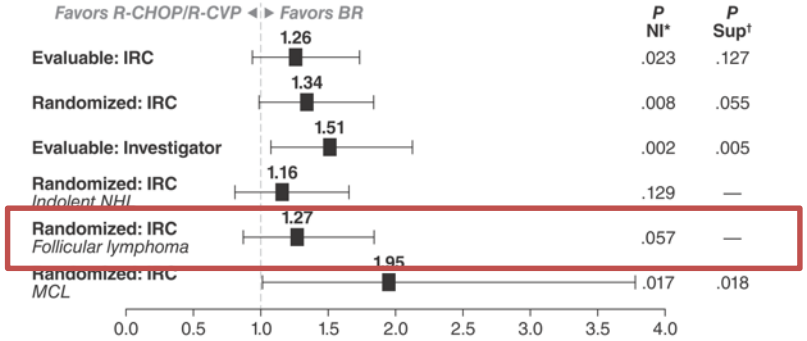
279 patients

	HR (95% CI)	p value
Age (years)		
≤60 (n=199)	0·52 (0·33–0·79)	0·002
>60 (n=315)	0·62 (0·45–0·84)	0·002
LDH concentration		
Normal (n=319)	0·48 (0·34–0·67)	<0·0001
Elevated (n=184)	0·74 (0·50–1·08)	0·118
FLIPI subgroup		
Favourable (0–2 risk factors; n=143)	0·56 (0·31–0·98)	0·043
Unfavourable (3–5 risk factors; n=127)	0·63 (0·38–1·04)	0·068

blood

Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study

Ian W. Flinn,[1] Richard van der Jagt,[2] Brad S. Kahl,[3] Peter Wood,[4] Tim E. Hawkins,[5] David MacDonald,[6] Mark Hertzberg,[7] Yiu-Lam Kwan,[8] David Simpson,[9] Michael Craig,[10] Kathryn Kolibaba,[11,12] Samar Issa,[13] Regina Clementi,[14] Doreen M. Hallman,[14] Mihaela Munteanu,[14] Ling Chen,[14] and John M. Burke[11,15]



314 patients

«STiL» and «BRIGHT» TRIALS

Rummel M et al, Lancet 2013
Flinn I W et al, *Blood.* 2014; *123*(19), 2944–2952

Which **chemotherapy** backbone?

Impact of immunochemotherapy with R-bendamustine or R-CHOP for treatment naïve advanced-stage follicular lymphoma: A subset analysis of the FOLL12 trial by Fondazione Italiana Linfomi

Maria E. Nizzoli[1,2] | Martina Manni[3] | Chiara Ghiggi[4] | Alessandro Pulsoni[5] | Gerardo Musuraca[6] | Michele Merli[7] | Catello Califano[8] | Alessia Bari[9] | Massimo Massaia[10,11] | Annarita Conconi[12] | Pellegrino Musto[13] | Donato Mannina[14] | Tommasina Perrone[15] | Francesca Re[16] | Sara Galimberti[17] | Guido Gini[18] | Monia Capponi[19] | Umberto Vitolo[20] | Sara V. Usai[21] | Piero M. Stefani[22] | Filippo Ballerini[23] | Anna M. Liberati[24] | Elsa Pennese[25] | Domenico Pastore[26] | Tetiana Skrypets[27] | Hillary Catellani[2] | Luigi Marcheselli[28] | Massimo Federico[3] | Stefano Luminari[1,3]

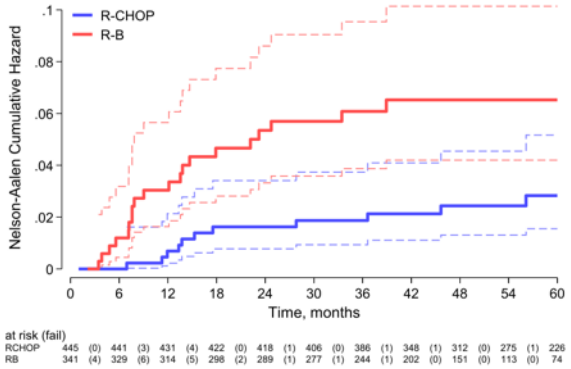
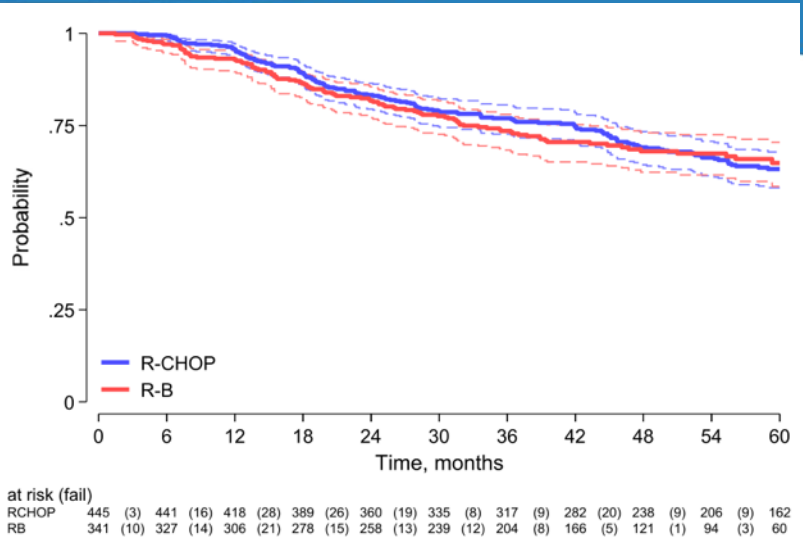


FIGURE 3 Cumulative incidence of transformed follicular lymphoma after end of induction ($N = 712$) by R-CHOP and RB initial treatment.



776 patients (<u>not randomized</u>, at physician choice)

«[…] R-CHOP and BR showed similar activity and efficacy, but with different safety profiles and long-term events […] the treating **physician should carefully select the most appropriate chemotherapy regimen for each patient based** on patient's individual characteristics, choices, and risk profile […]»

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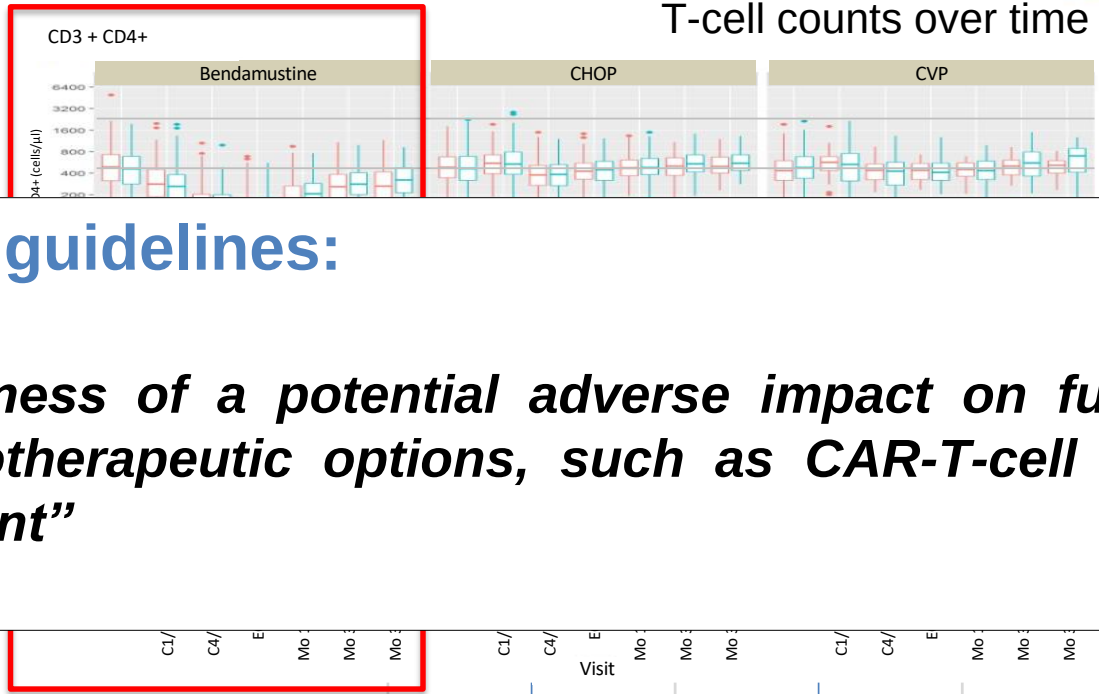
FIL «FOLL12» TRIAL

Nizzoli M E et al, Hematol Oncol. 2023

Which **chemotherapy** backbone?

T-cell counts over time



ESMO guidelines:

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

"Awareness of a potential adverse impact on future cellular immunotherapeutic options, such as CAR-T-cell treatment is important"

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Low T-cell count at baseline	*R-benda, n=341*	*G-benda, n=345*	*R-CHOP, n=203*	*G-CHOP, n=196*	*R-CVP, n=57*	*G-CVP, n=60*
CD3+/CD4+ cell count of ≤200/mm³	36 (12.5%)	36 (11.4%)	12 (7.2%)	9 (5.1%)	2 (4.4%)	4 (7.4%)

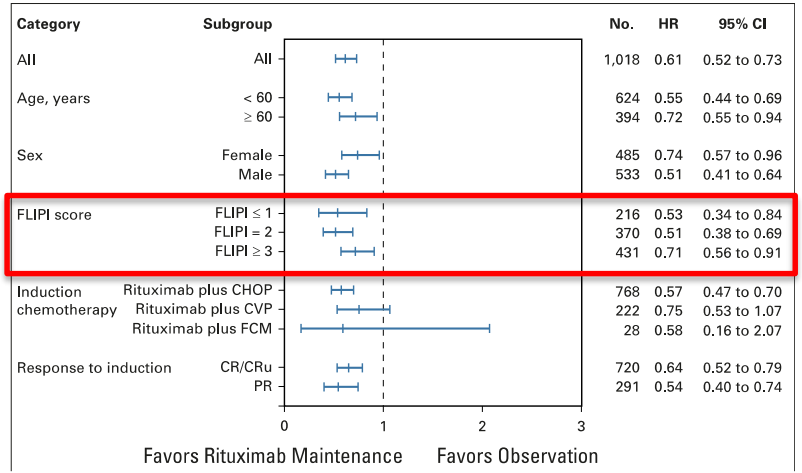
Hiddemann W et al J Clin Onc 2018

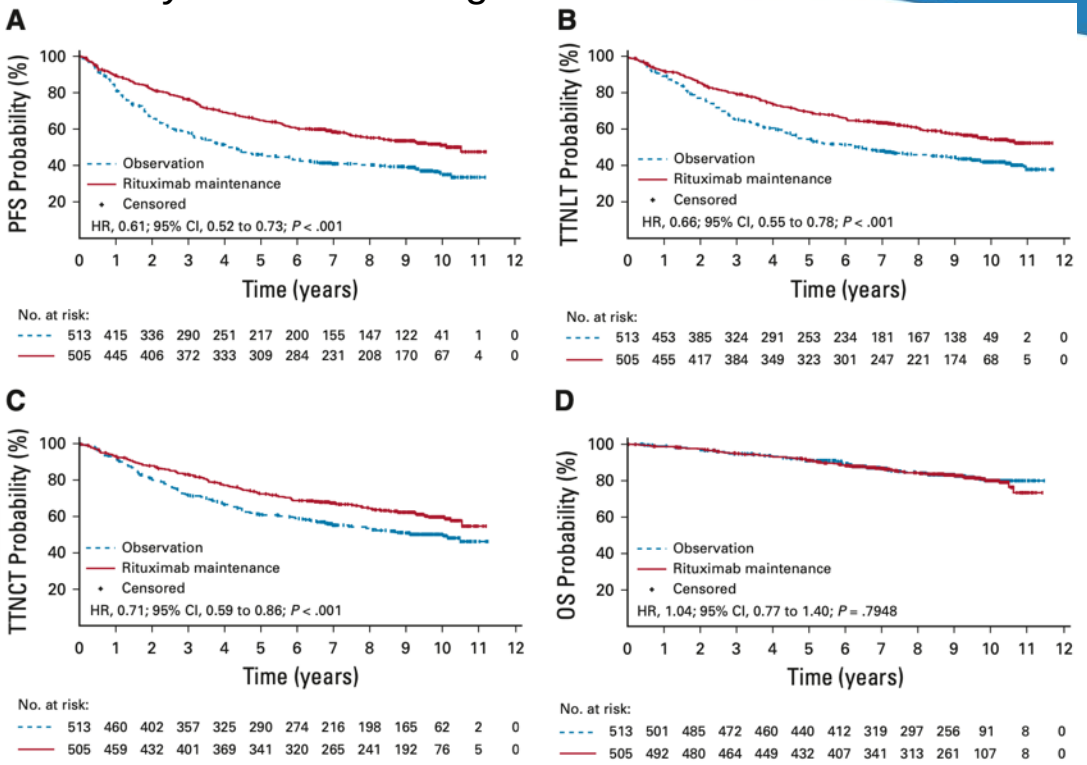
The concept of rituximab **maintenance**

«Only» PFS advantage

Sustained Progression-Free Survival Benefit of Rituximab Maintenance in Patients With Follicular Lymphoma: Long-Term Results of the PRIMA Study

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]





«PRIMA» TRIAL

Bachy E et al, Journal Clin Onc 2019 37:31, 2815-2824

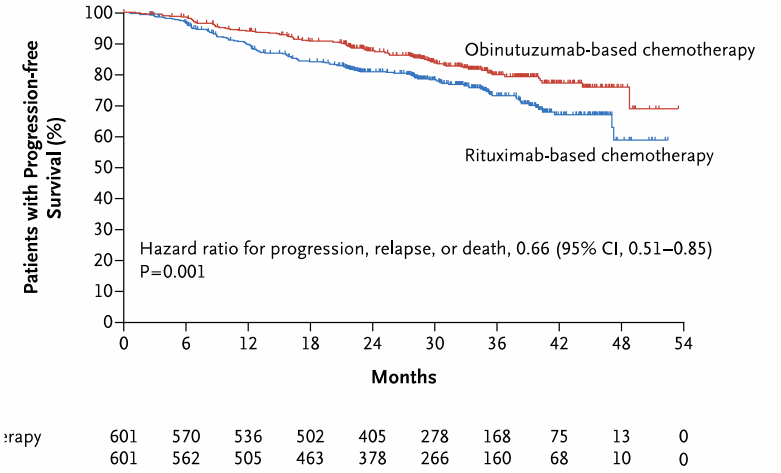
Which anti-CD20?

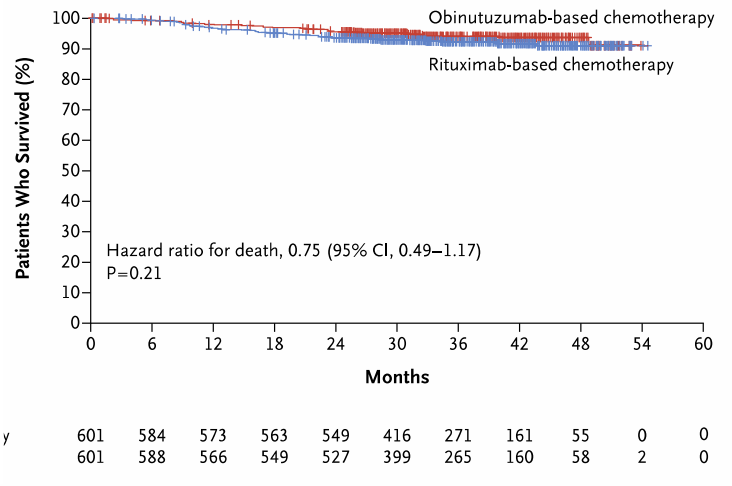
ORIGINAL ARTICLE

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

R. Marcus, A. Davies, K. Ando, W. Klapper, S. Opat, C. Owen, E. Phillips, R. Sangha, R. Schlag, J.F. Seymour, W. Townsend, M. Trněný, M. Wenger, G. Fingerle-Rowson, K. Rufibach, T. Moore, M. Herold, and W. Hiddemann

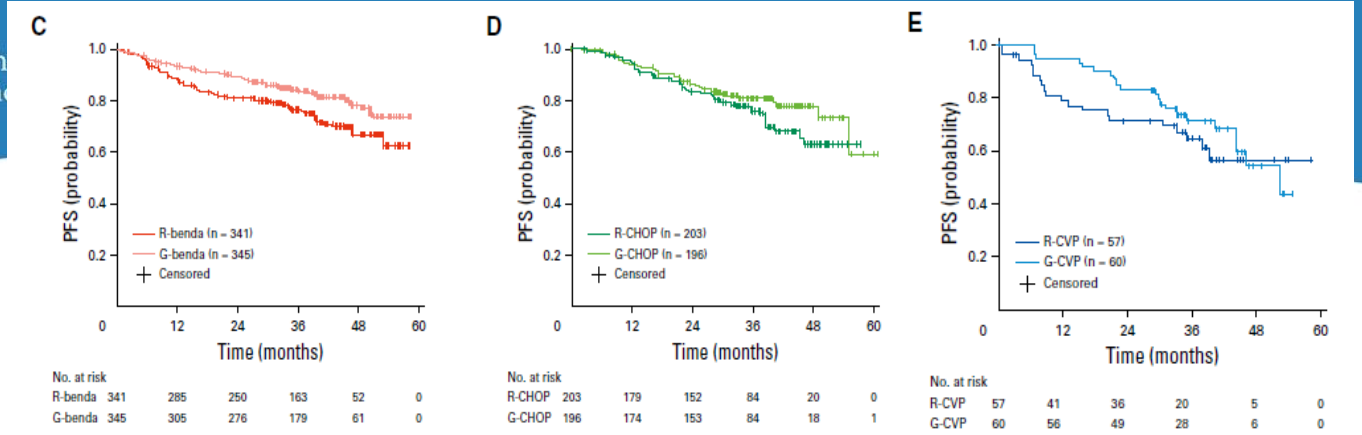
N Engl J Med 2017;377:1331-44.
DOI: 10.1056/NEJMoa1614598

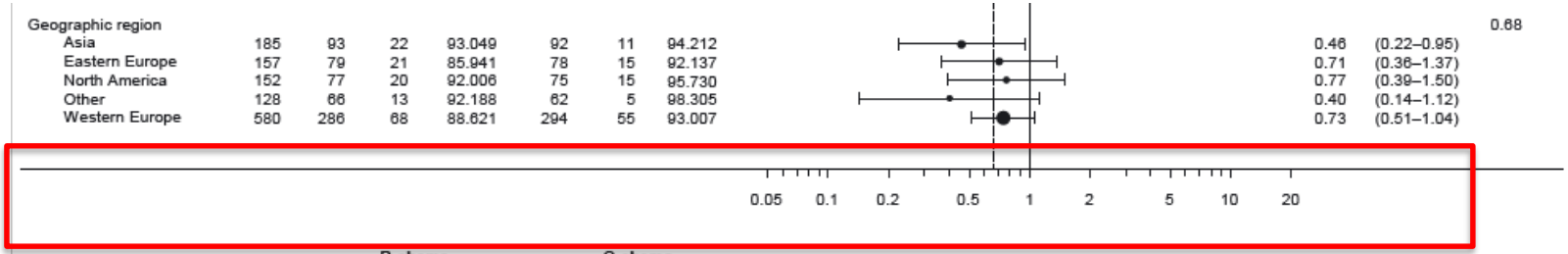


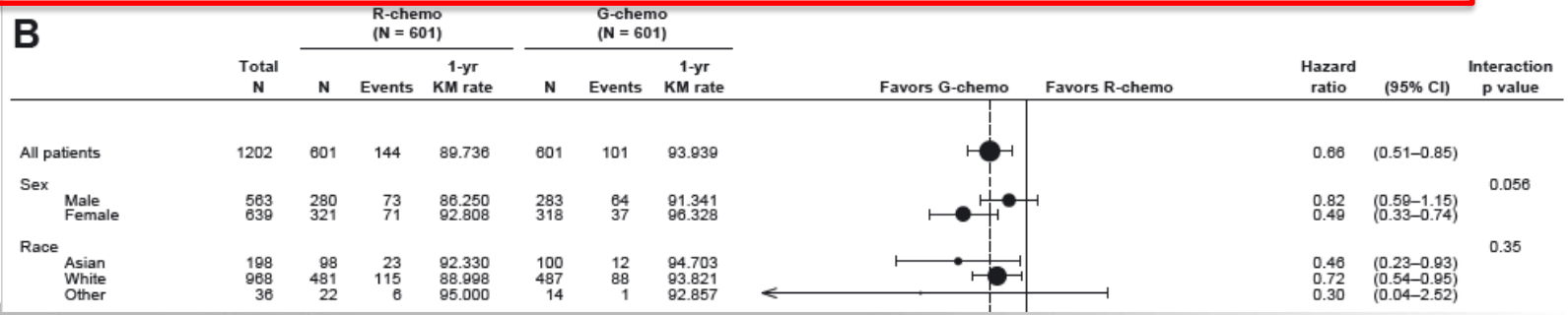


«GALLIUM» TRIAL

Marcus R et al, *N Engl J Med*. 2017;377(14):1331-1344







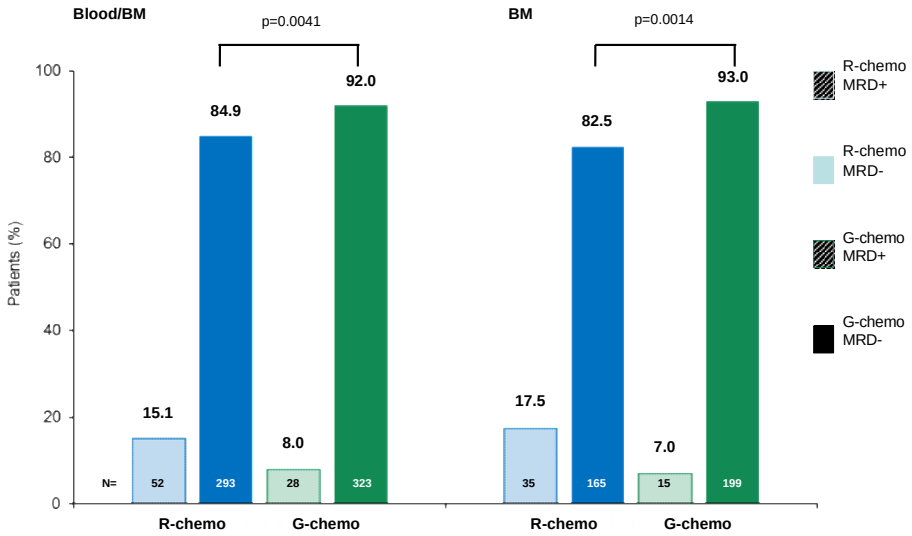
«GALLIUM» TRIAL

Hiddemann W et al J Clin Onc 2018

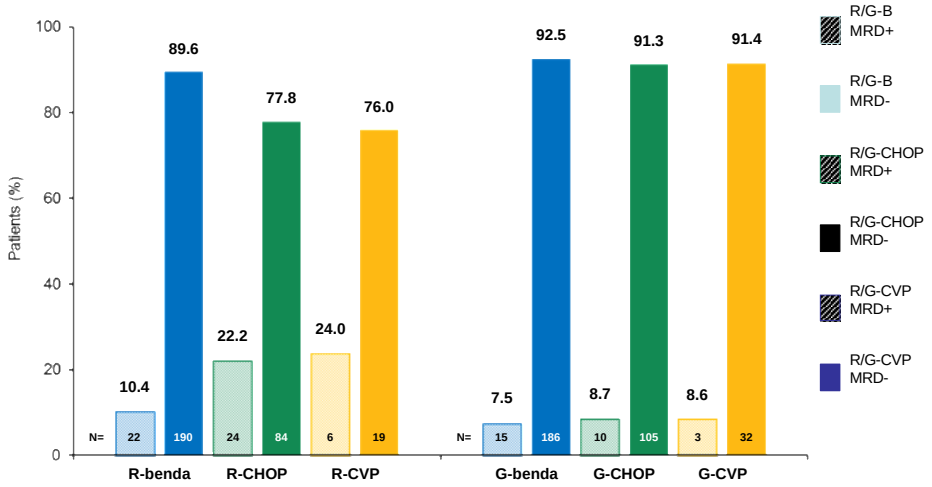
Marcus R et al, N Engl J Med. 2017;377(14):1331-1344

Which anti-CD20?

MRD status by compartment at end of induction



MRD status by treatment arm at end of induction in blood/BM



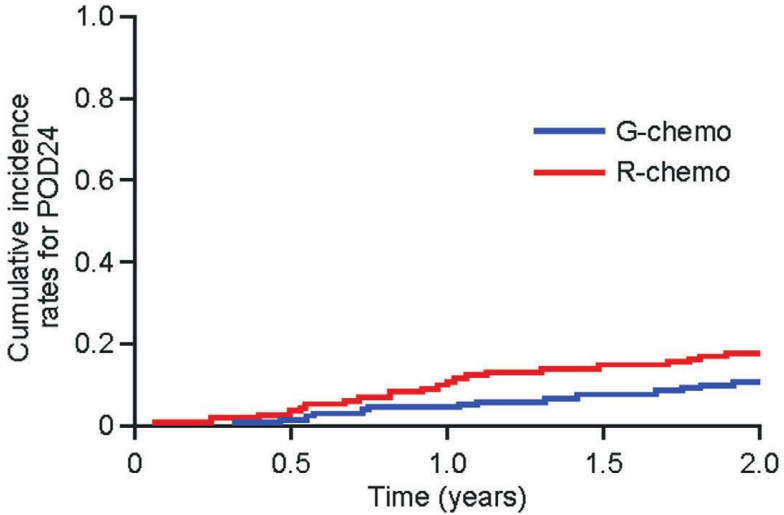
Courtesy of Christiane Pott

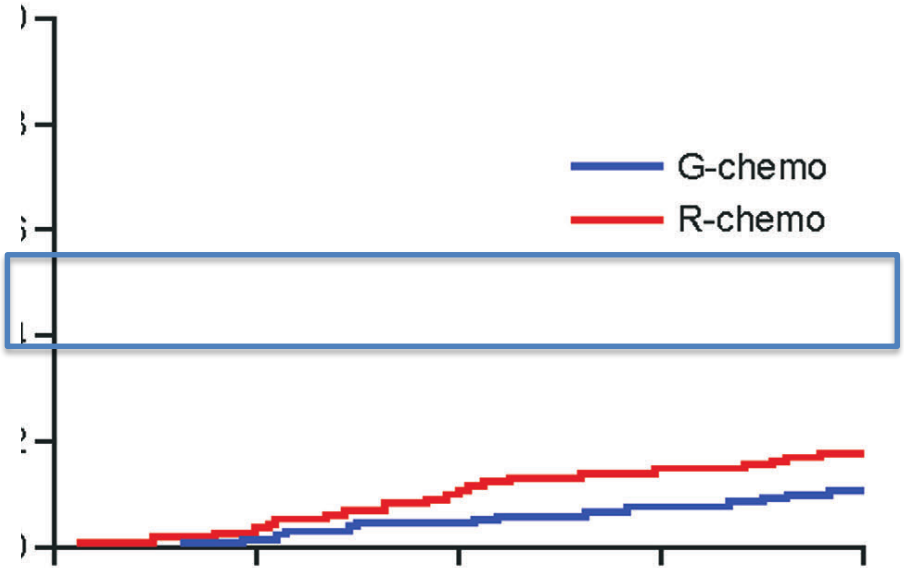
Which anti-CD20?

Association of early disease progression and very poor survival in the GALLIUM study in follicular lymphoma: benefit of obinutuzumab in reducing the rate of early progression

John F. Seymour,[1] Robert Marcus,[2] Andrew Davies,[3] Eve Gallop-Evans,[4] Andrew Grigg,[5] Andrew Haynes,[6] Michael Herold,[7] Thomas Illmer,[8] Herman Nilsson-Ehle,[9] Martin Sökler,[10] Ulrich Dünzinger,[11] Tina Nielsen,[12] Aino Launonen[12] and Wolfgang Hiddemann[13]

Haematologica 2019
Volume 104(6):1202-1208

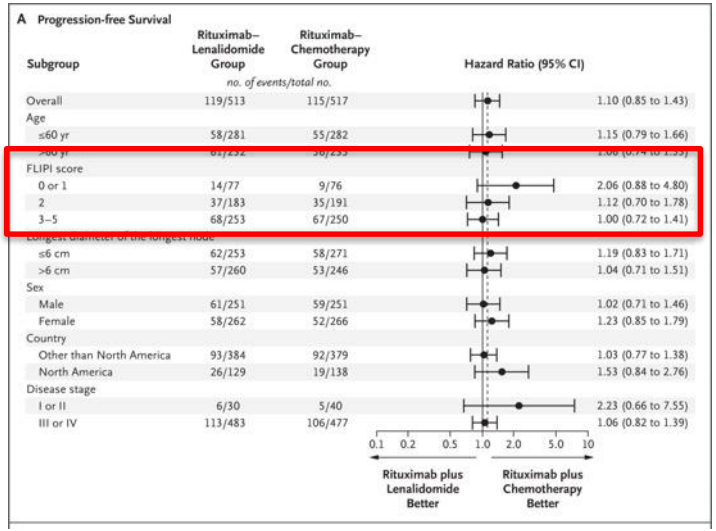


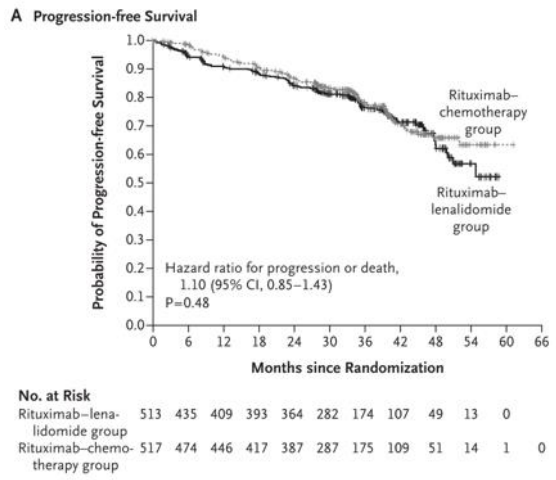


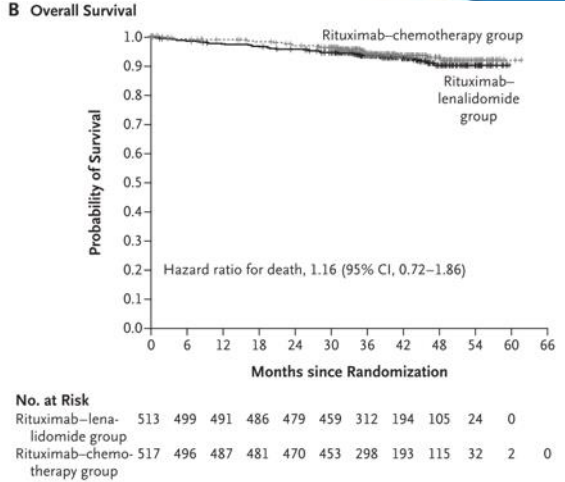
Novel rituximab partners: R² chemo-free?

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma

F. Morschhauser, N.H. Fowler, P. Feugier, R. Bouabdallah, H. Tilly, M.L. Palomba, C. Fruchart, E.N. Libby, R.-O. Casasnovas, I.W. Flinn, C. Haioun, H. Maisonneuve, L. Ysebaert, N.L. Bartlett, K. Bouabdallah, P. Brice, V. Ribrag, N. Daguindau, S. Le Gouill, G.M. Pica, A. Martin Garcia-Sancho, A. López-Guillermo, J.-F. Larouche, K. Ando, M. Gomes da Silva, M. André, P. Zachée, L.H. Sehn, K. Tobinai, G. Cartron, D. Liu, J. Wang, L. Xerri, and G.A. Salles, for the RELEVANCE Trial Investigators*







The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

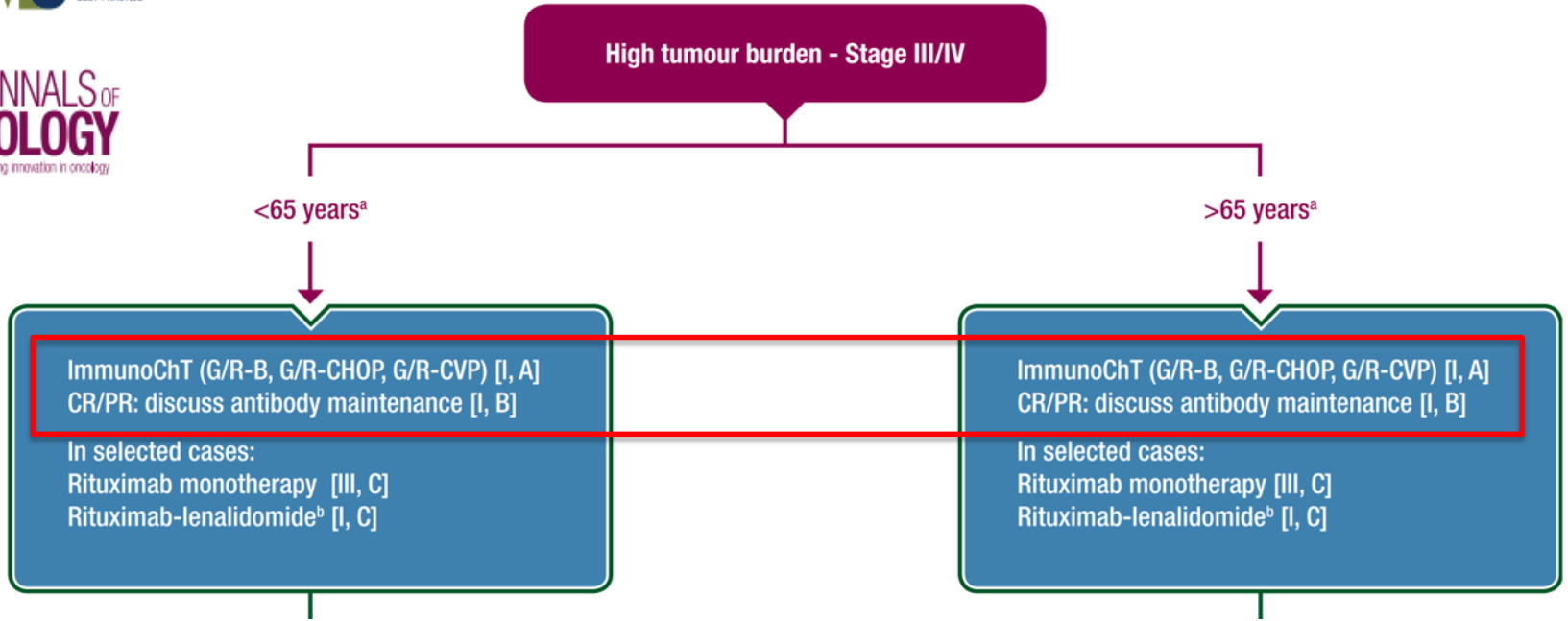
«RELEVANCE» TRIAL

Morschhauser F et al, N Engl J Med 2018; 379:934-947

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†☆

M. Dreyling[1], M. Ghielmini[2], S. Rule[3], G. Salles[4,5], M. Ladetto[6], S. H. Tonino[7], K. Herfarth[8], J. F. Seymour[9] & M. Jerkeman[10], on behalf of the ESMO Guidelines Committee*

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
ANNALS OF ONCOLOGY driving innovation in oncology



ESMO Guidelines 2021

Dreyling M et al, Ann Oncol. 2021 Mar;32(3):298-308

Can we tailor first line therapy on patients risk?

PET-guided first line: SUVmax?

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)

Table 1 | Selected clinical trials testing the prognostic value of metabolic tumour volume in lymphoma

GALLIUM[139]	FL	Randomization to obinutuzumab or rituximab plus chemotherapy (bendamustine, CHOP or CVP) plus maintenance with same antibody received during induction in responders	521	SUVmax ≥2.5, 41% of SUVmax and SUVmax assessment	NR	No association of PET-based biomarkers with PFS
Meignan et al.[102]	FL	Chemo-immunotherapy[d]	185	41% of SUVmax	510 ml	5-year PFS: 33% versus 65%; 5-year OS: 85% versus 95%

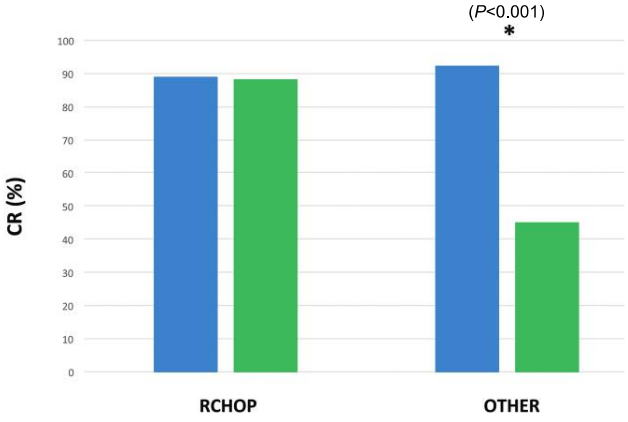
Trotman J et al, Blood. 2022 Mar 17;139(11):1631-1641
Alderuccio, JP et al, Nat Rev Clin Oncol 20, 640–657 (2023)

PET-guided first line: SUVmax?

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

Paolo Strati,[1] Mohamed Amin Ahmed,[1] Nathan H. Fowler,[1] Loretta J. Nastoupil,[1] Felipe Samaniego,[1] Luis E. Fayad,[1] Fredrick B. Hagemeister,[1] Jorge E. Romaguera,[1] Alma Rodriguez,[1] Michael Wang,[1] Jason R. Westin,[1] Chan Cheah,[1] Mansoor Noorani,[1] Lei Feng,[2] Richard E. Davis[1] and Sattva S. Neelapu[1]

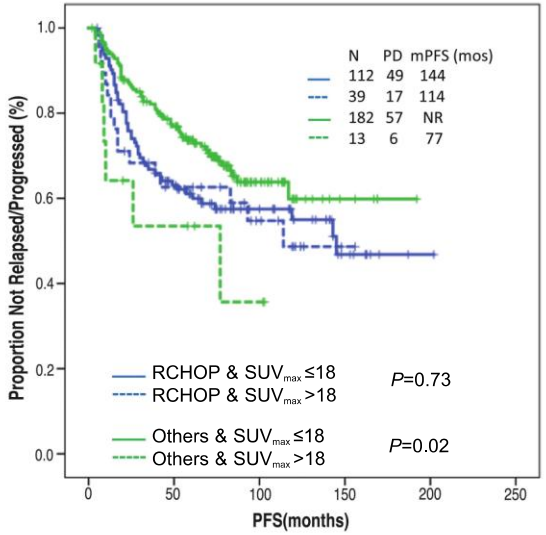
[1]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center and [2]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

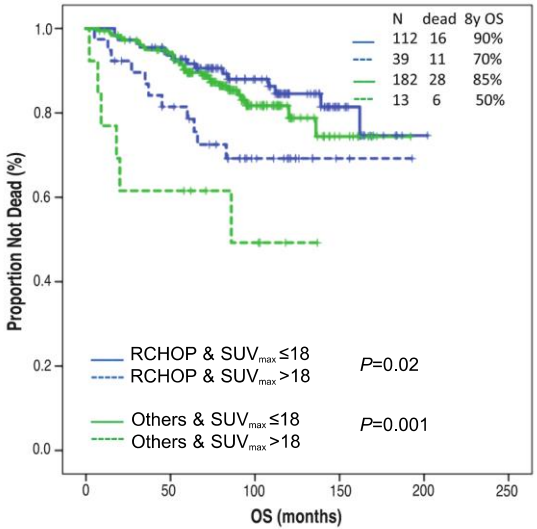


Retrospective analysis of **346 FL** without histological evidence of transformation

lymph node ≥6 cm was the only factor associating with **SUVmax >18** on MV analysis: OR 2.7 (1.3-5.3), p=0.006)

Other therapies: BR 28%, R^2 32%, R-FND 12%, R mono 27%





Strati P. et al., Haematologica 2020

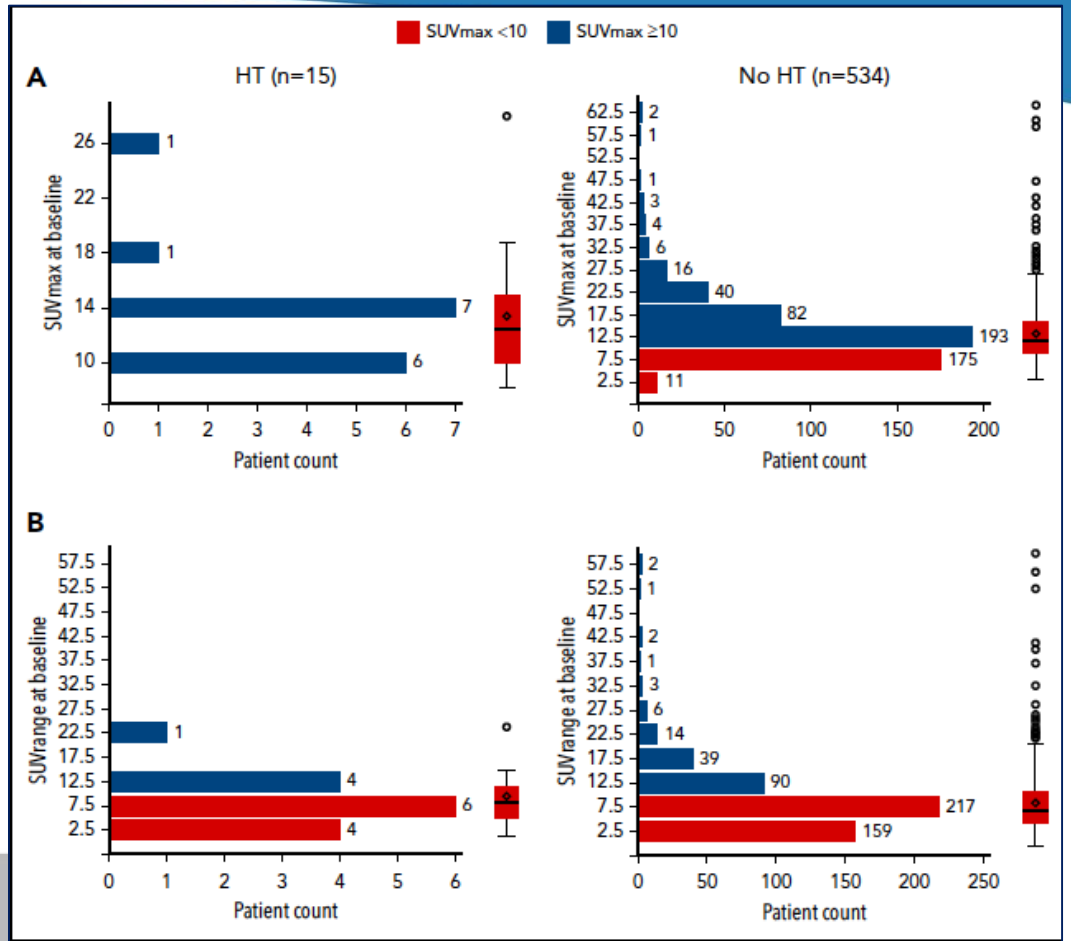
PET-guided first line: **SUVmax**?

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

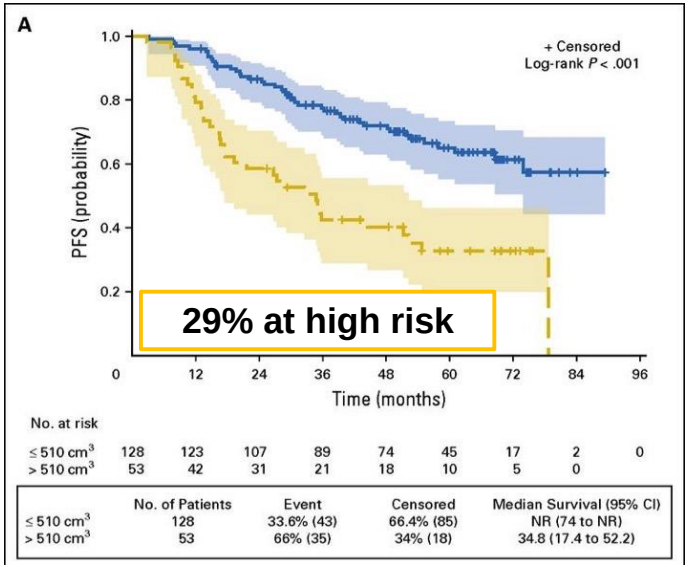


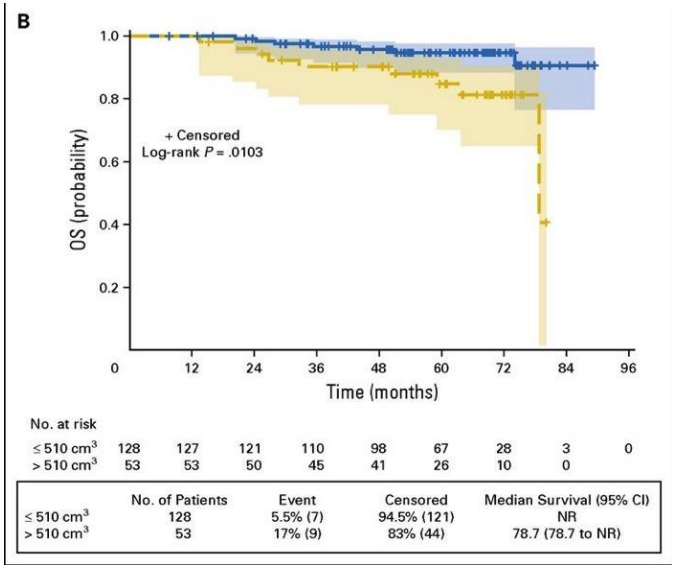
PET-guided first line: TMTV?

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

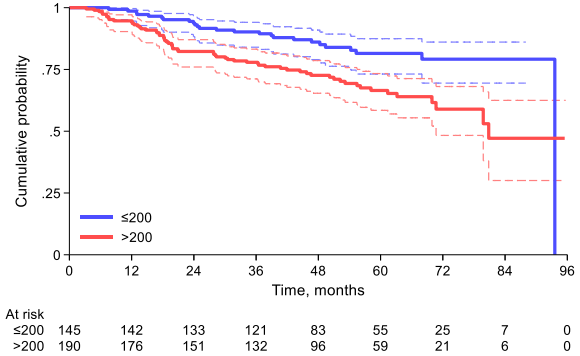




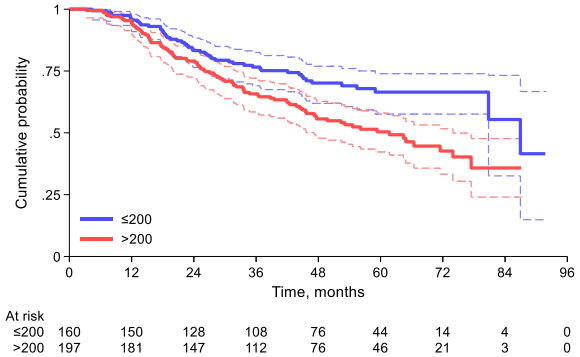
Michel Meignan et al. JCO doi:10.1200/JCO.2016.66.9440

PET-guided first line: TMTV?

Reference arm - Maintenance

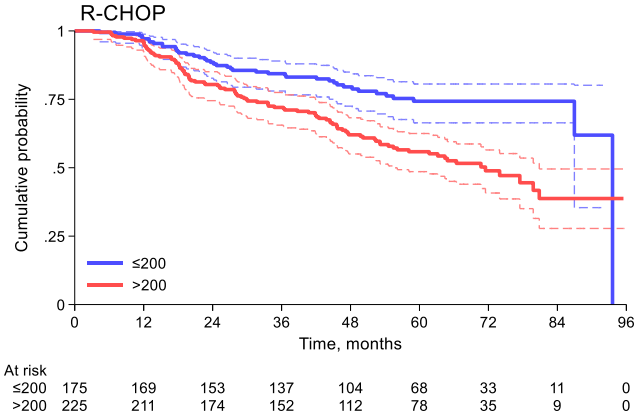


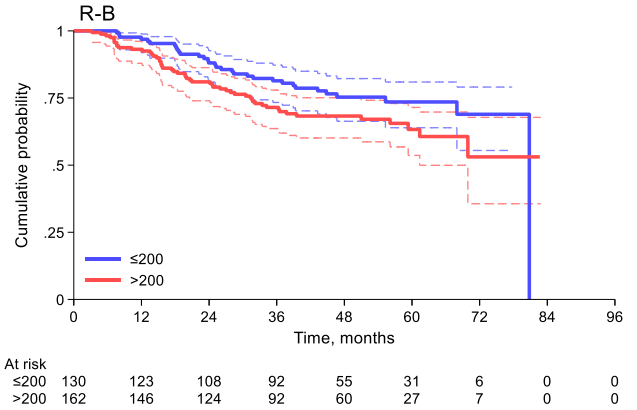
Experimental arm – response adapted (no maintenance)



Prognostic value of **TMTV (>200 ml) was independent** from main prognostic factors, induction therapy and maintenance with rituximab

FONDAZIONE ITALIANA LINFOMI





FIL «FOLL12» TRIAL

Luminari S. et al., ASH 2022

PET-guided first line: TMTV?

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 15, 2022

Baseline PET Metabolic Tumor Volume Predicts Outcome in Advanced Follicular Lymphoma Patients Who Received First-Line Immunochemotherapy but Not Those Treated with Lenalidomide-Rituximab in the Phase III Relevance Study

Anne Ségolène Cottereau, Louis Rebaud, Judith Trotman, Pierre Feugier, Loretta J. Nastoupil, Emmanuel Bachy, Ian W. Flinn, Corinne Haioun, Loic Ysebaert, Nancy L. Bartlett, Hervé Tilly, René-Olivier Casasnovas, Romain Ricci, Cedric Portugues, Irène Buvat, Michel Meignan, Franck Morschhauser

TMTV >510 ml

CIT

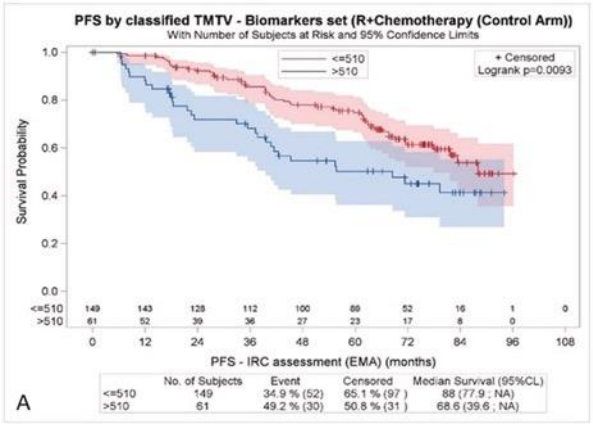


Figure 1. PFS according to baseline Total Metabolic Tumor Volume (TMTV) in R-Chemotherapy arm (A) and in R+Lenalidomide arm (B).

«RELEVANCE» TRIAL

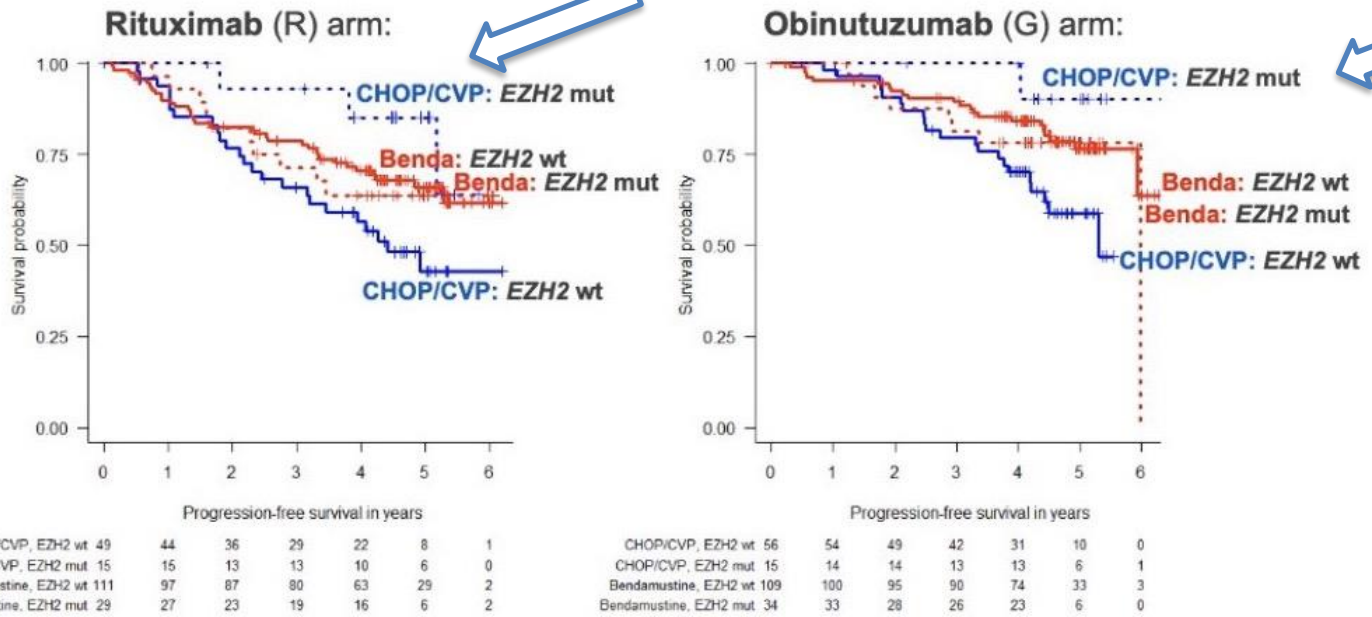
Cottereau AS. et al., ASH 2022

What about **biomarkers**?

EZH2-guided first line?

***EZH2* mutated = CHOP**

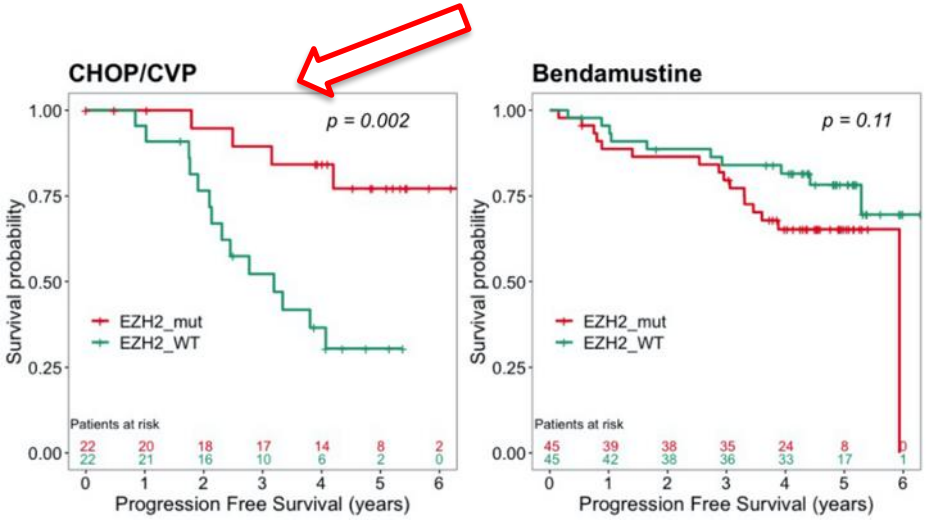
***EZH2* WT = bendamustine**



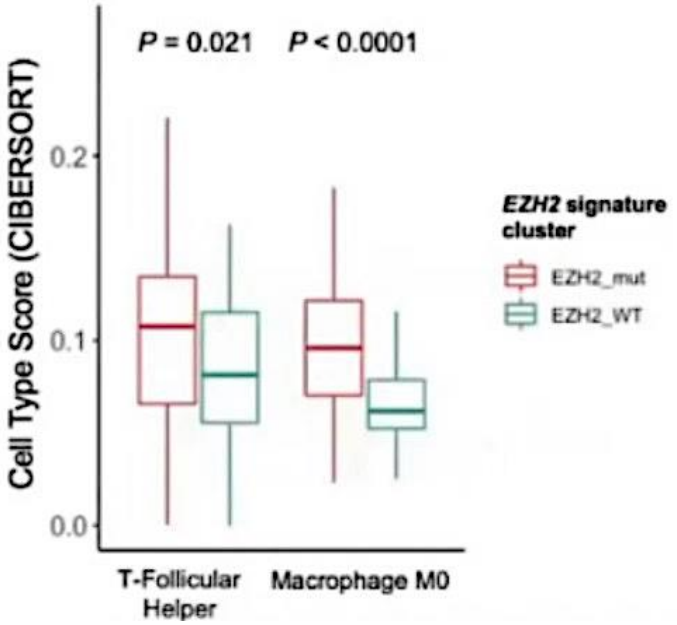
- Patients receiving **CHOP/CVP**-based regimens: PFS for *EZH2* wt *vs* mut: HR = 0.25, p = 0.0036
- Patients with ***EZH2* wt** FL: PFS for Benda *vs* CHOP/CVP: HR = 0.55, p = 0.0023

Jurinovic V, et al. ASH 2019

EZH2-guided first line?



134 cases profiled



***EZH2* GEP signature in GALLIUM trial**

Passerini V, ASH 2021

EZH2-guided first line?

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

C. Martínez-Laperche[1,2], L. Sanz-Villanueva[1,2], F. J. Díaz Crespo[1,3], P. Muñiz[1,2], R. Martín Rojas[2], D. Carbonell[1,2], M. Chicano[1,2], J. Suárez-González[1,4], J. Menárguez[1,3], M. Kwon[1,2], J. L. Diez Martín[1,2,5], I. Buño[1,2,4,6] and M. Bastos Oreiro[1,2*]

Martínez-Laperche *et al. BMC Cancer* (2022) 22:982
https://doi.org/10.1186/s12885-022-10070-z
BMC Cancer

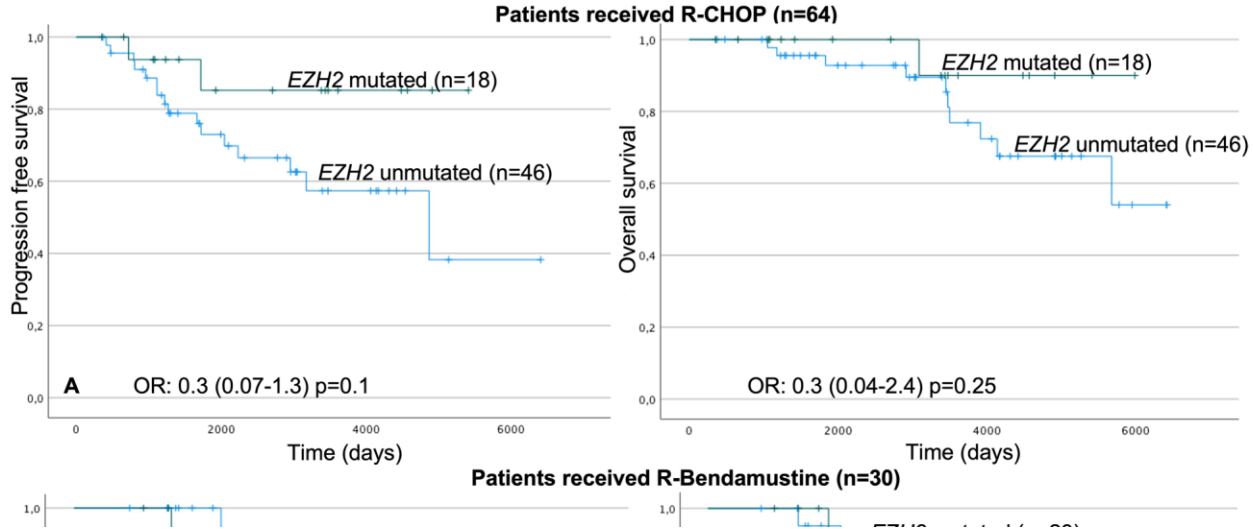
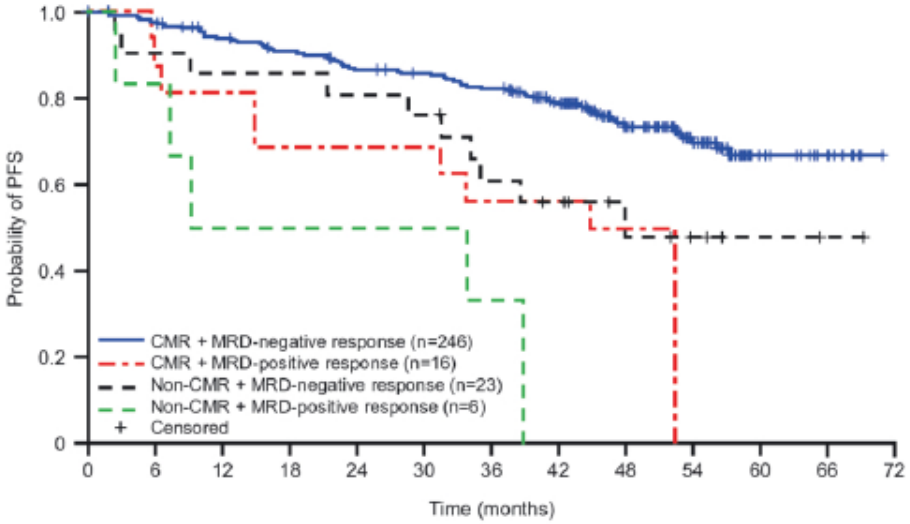


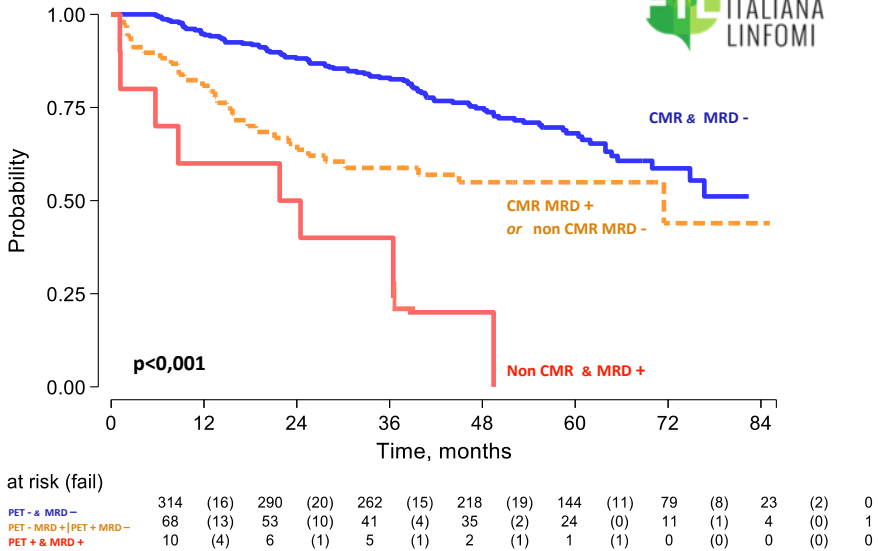
Fig. 1 Kaplan-Meier curves in patients with grade 1, 2, and 3a. **A** PFS and OS in patients treated with R-CHOP (*EZH2* mutated vs. unmutated); **B** PFS and OS in patients treated with R-Bendamustine (*EZH2* mutated vs. unmutated). **C** PFS and OS in *EZH2* mutated patients (R-CHOP vs. R-Bendamustine). PFS Progression-free survival. OS: Overall survival

Response-guided first line?
PET & MRD

GALLIUM trial



FIL FOLL12 trial

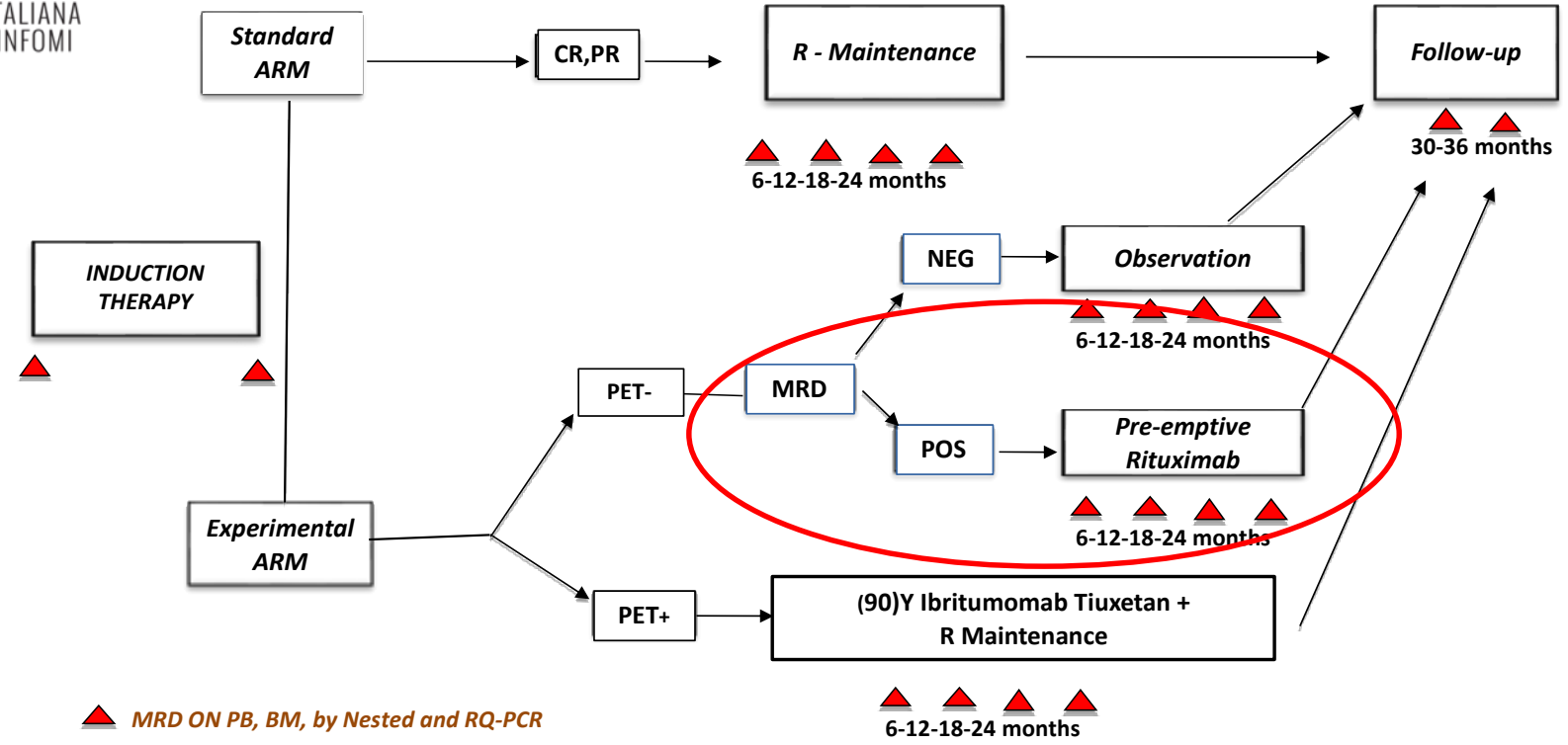


PFS from EoI stratified by PET and BM MRD results

Pott C. et al., EHA 2018
Ferrero S. et al., ICML 2023

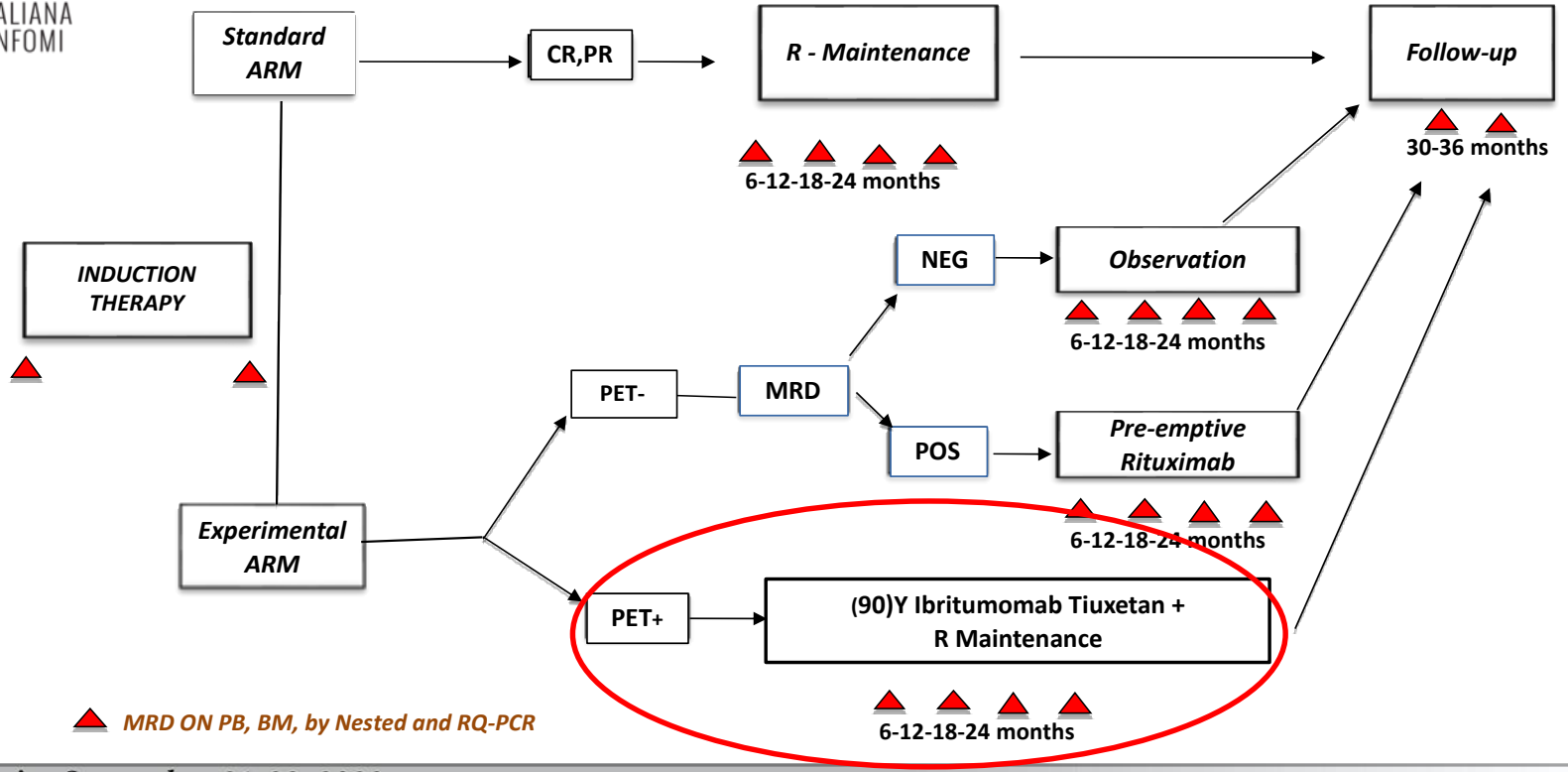
Response-guided first line?
PET & MRD

FIL FOLL12 TRIAL DESIGN



Response-guided first line?
PET & MRD

FIL FOLL12 TRIAL DESIGN



FIL «FOLL12» TRIAL

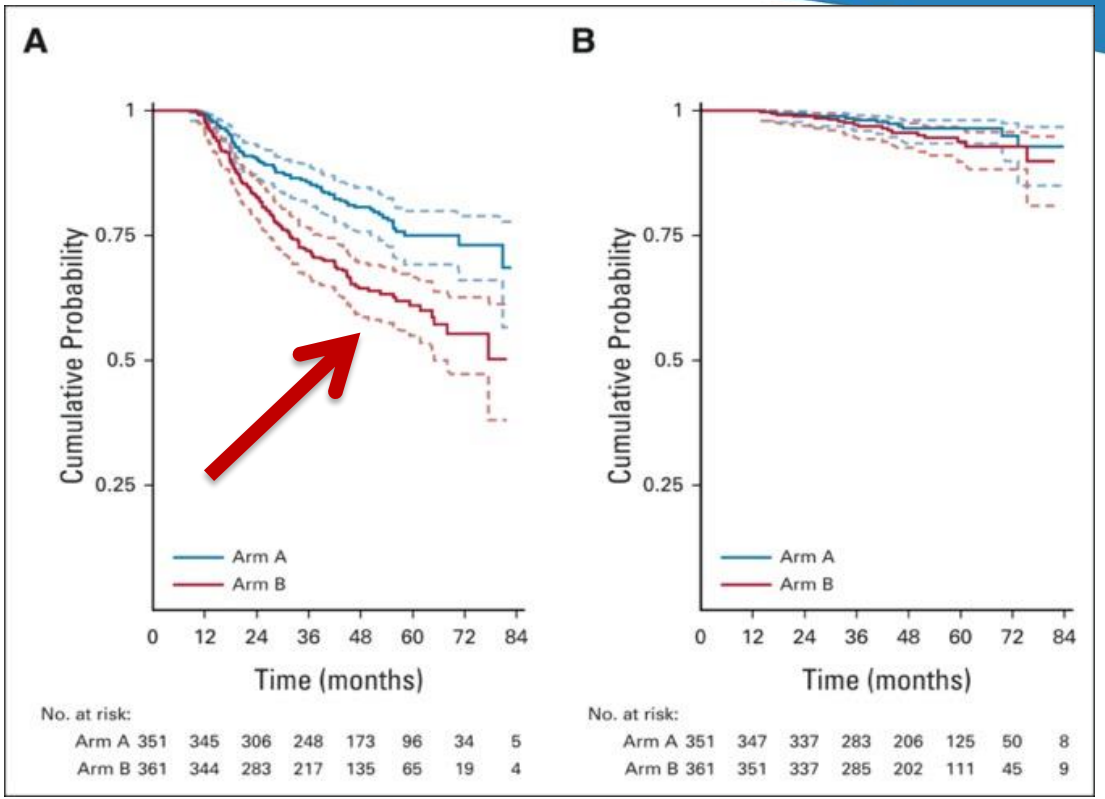
Ladetto M et al., ASH 2021

Response-guided first line?
PET & MRD

Response-Adapted Postinduction Strategy in Patients With Advanced-Stage Follicular Lymphoma: The FOLL12 Study

Stefano Luminari, MD[1,2]; Martina Manni, MD[1]; Sara Galimberti, MD[3]; Annibale Versari, MD[4]; Alessandra Tucci, MD[5]; Carola Boccomini, MD[6]; Lucia Farina, MD[7]; Jacopo Olivieri, MD[8]; Luigi Marcheselli, MSc[9]; Luca Guerra, MD[10,11]; Simone Ferrero, MD[12]; Luca Arcaini, MD[13]; Federica Cavallo, MD[12]; Sofya Kovalchuk, MD[14]; Tetiana Skrypets, MD[1,15]; Ilaria del Giudice, MD[16]; Stephane Chauvie, MD[17]; Caterina Patti, MD[18]; Caterina Stelitano, MD[19]; Francesca Ricci, MD[20]; Antonello Pinto, MD[21]; Gloria Margiotta Casaluci, MD[22]; Vittorio R. Zilioli, MD[23]; Anna Merli, MD[24]; Marco Ladetto, MD[25,26]; Silvia Bolis, MD[27]; Vincenzo Pavone, MD[28]; Annalisa Chiarenza, MD[29]; Annalisa Arcari, MD[30]; Antonella Anastasia, MD[5]; Alessandra Dondi, PhD[9]; Donato Mannina, MD[31]; and Massimo Federico, MD[1] on behalf of Fondazione Italiana Linfomi

Journal of Clinical Oncology®
2021



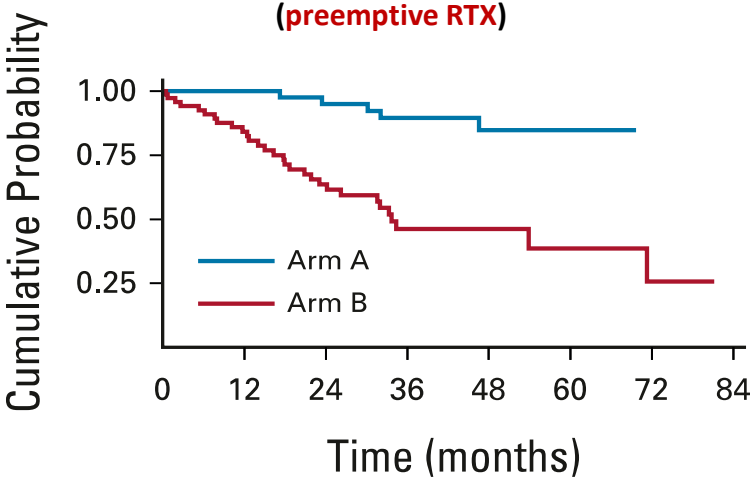
FIL «FOLL12» TRIAL

Luminari S et al., JCO 2021

Response-guided first line?
PET & MRD

FONDAZIONE ITALIANA LINFOMI

EOI CMR but MRD+
(preemptive RTX)



No. at risk:							
Arm A	51	44	36	31	18	9	0	0
Arm B	76	48	32	13	9	3	2	0

FIL «FOLL12» TRIAL

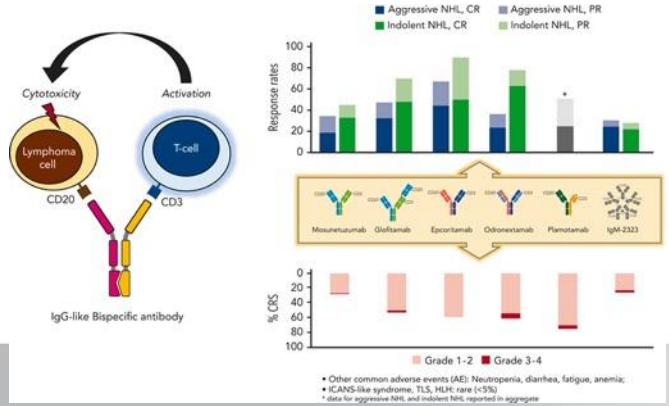
Luminari S et al., JCO 2021

What about **the future**?

Novel approches: **bispecific** antibodies

Supplemental Table. Planned or ongoing registered BsAb studies without published results.

Disease	Setting	Modifiers	Trial ID	Phase	Drug(s)	Histology
Indolent B-NHL	1st line	Advanced stage, need for therapy	NCT05389293	II	MOSUN	FL
			NCT05207670	II	MOSUN (SC)	Multiple
			NCT05410418	II	MOSUN-pola	FL
			NCT05169658	II	MOSUN (+ pola and obin if PR)	Multiple
			NCT04792502	II	MOSUN (+ len if PR)	Multiple
			NCT04663347	I/II	EPCOR-R-len or EPCOR-BR	FL



Falchi L et al, Blood. 2023 Feb 2;141(5):467-480.

Novel approches: **bispecific** antibodies

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 15, 2022

Subcutaneous Epcoritamab in Combination with Rituximab + Lenalidomide (R^2) for First-Line Treatment of Follicular Lymphoma: Initial Results from Phase 1/2 Trial

Lorenzo Falchi, Lori A. Leslie, David Belada, Katerina Kopeckova, Fritz Offner, Joshua Brody, Miguel Canales, Alejandro Martín García-Sancho, Marcel Nijland, P-O Andersson, Farrukh T. Awan, Jacob Haaber Christensen, Kristina Drott, Mats Hellström, Catharina Lewerin, Mayur Narkhede, Sylvia Snauwaert, Björn E Wahlin, Ali Rana, Aqeel Abbas, Liwei Wang, Minh Dinh, Joost S.P. Vermaat, Pau Abrisqueta

[…] the **ORR was 90%** (26/29), with **69%** (20/29) having a **CMR** as their best OR […]

Subcutaneous epcoritamab + R^2 demonstrated a **manageable safety profile**, similar to that observed in the R/R setting, with no new safety signals, no ICANS events, and only low-grade CRS events, all of which resolved. This regimen showed encouraging efficacy, based on high response rates, when used as a first-line treatment for FL. These data support further clinical evaluation of epcoritamab + R^2 in previously untreated patients with FL.

EPCORE NHL-2 trial (arm 6)

Falchi L. et al, ASH 2022

Novel approches: EZH2 targeting

RECRUITING

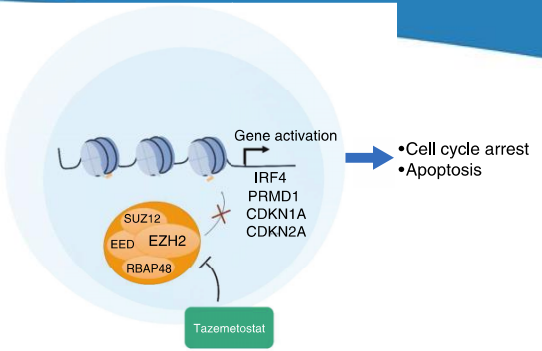
A Study of Tazemetostat With Rituximab and Abbreviated Bendamustine in the Frontline Treatment of High Tumor Burden Follicular Lymphoma

ClinicalTrials.gov ID NCT05551936

Sponsor Vaishalee Kenkre

Information provided by Vaishalee Kenkre, Big Ten Cancer Research Consortium (Responsible Party)

Last Update Posted 2023-05-12



ACTIVE, NOT RECRUITING

Study of Tazemetostat in Newly Diagnosed Diffuse Large B Cell and Follicular Lymphoma Patients Treated by Chemiotherapy (Epi-RCHOP)

ClinicalTrials.gov ID NCT02889523

Sponsor The Lymphoma Academic Research Organisation

Information provided by The Lymphoma Academic Research Organisation (Responsible Party)

Last Update Posted 2023-03-17

NOT YET RECRUITING

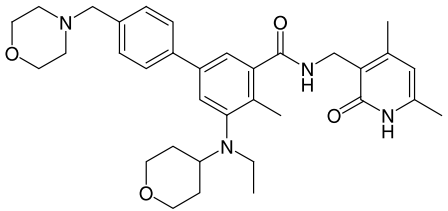
Tazemetostat and Mosunetuzumab in Untreated Follicular Lymphoma

ClinicalTrials.gov ID NCT05994235

Sponsor Weill Medical College of Cornell University

Information provided by Weill Medical College of Cornell University (Responsible Party)

Last Update Posted 2023-09-07



Falchi L et al, Blood. 2023 Feb 2;141(5):467-480.

Conclusions

How I (Simone Ferrero, MD) treat high-risk follicular lymphoma in first line?

- I take in consideration clinical prognostic indexes (**FLIPI**, …) and PET parameters (**SUV max**)
- I always try to rule out an histological transformation (**surgical biopsy**, whenever possibile)
- I still cannot rely on clinically meaningful baseline biomarkers (damn!)
- I usually opt for **Ga101**-chemo in FLIPI intermediate and high-risk patients (Gallium)
- I usually prefer R/G-**CHOP** for FIT patients and G-CVP for UNFIT ones (benda caveat)
- I would like to use R^2 more often (not reimbursed in Italy for the first line)
- I usually go for 24-months **anti-CD20 maintenance** for all responding patients
- I monitor MRD only in clinical trial (so far)
- I look forward to **integrating novel drugs** in first line for high-risk patients (i.e. bispecific abs)

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Lymphoma Group Molecular Biology Lab

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