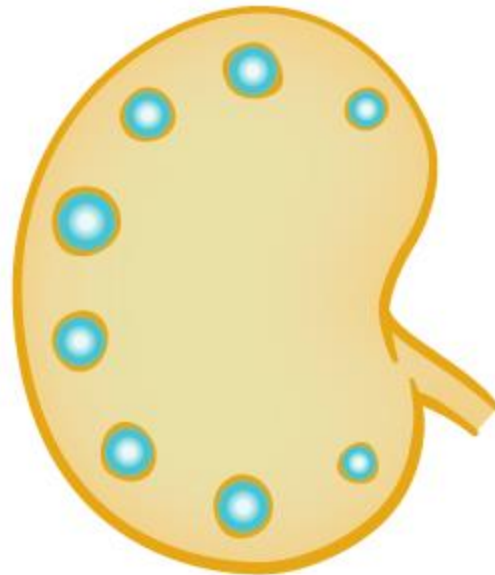
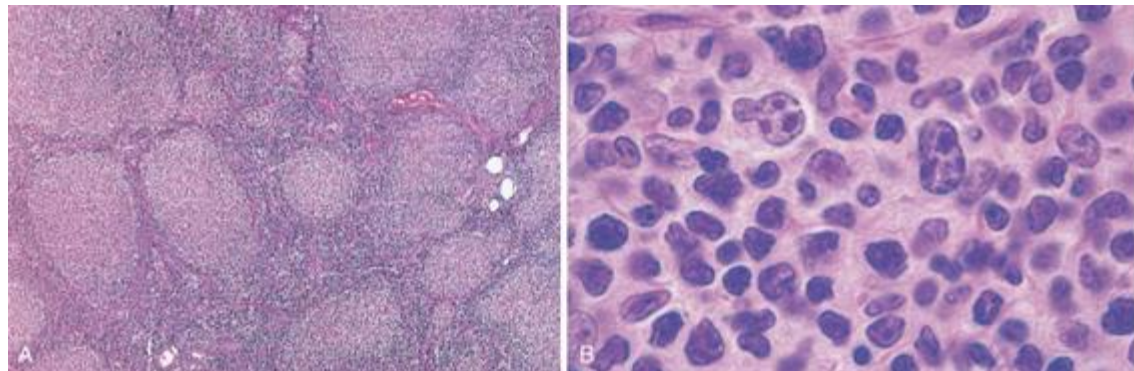




LINFOMA FOLICULAR: IDENTIFICANDO AL PACIENTE CON FACTORES DE MAL PRONÓSTICO

Normal
lymph node

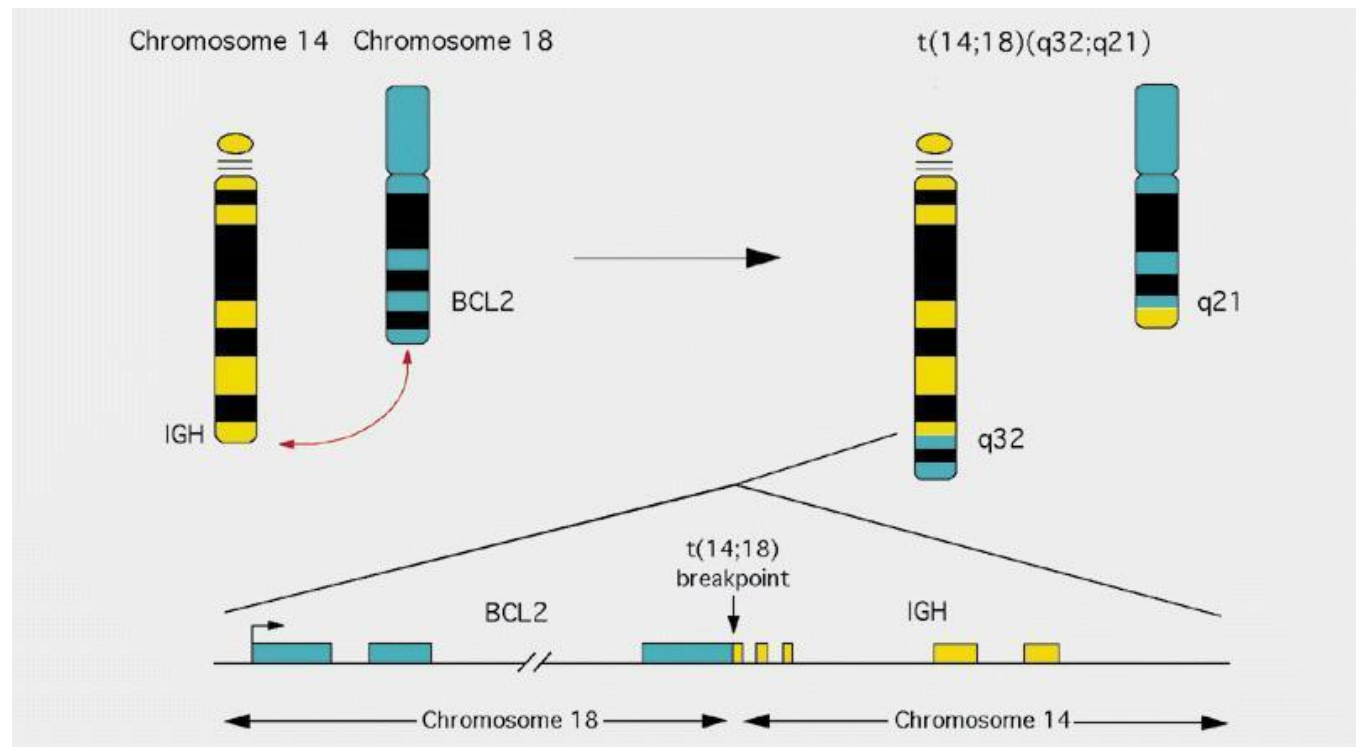




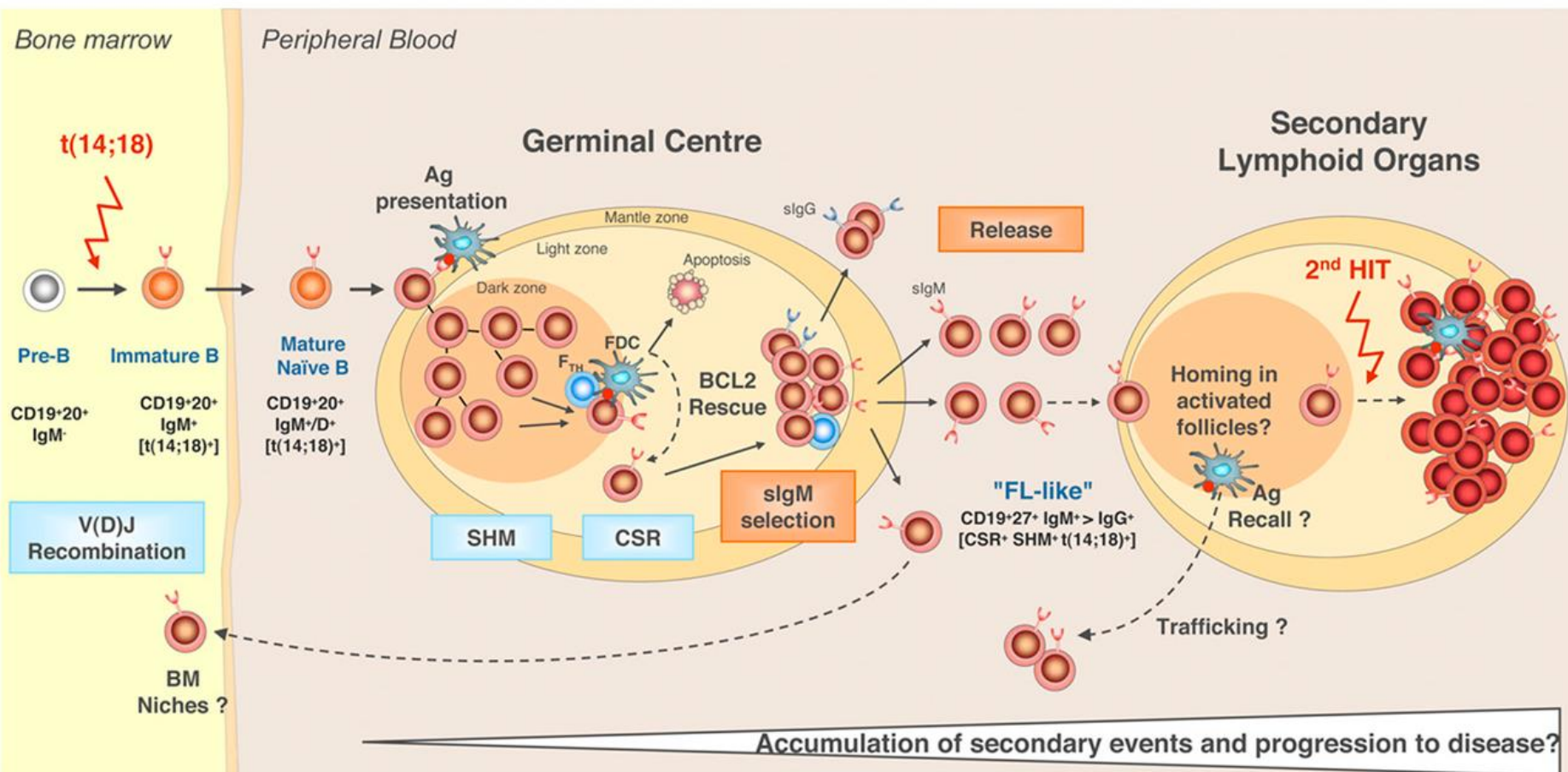
Traslocación

t(14;18)

Gen bcl2/IgH



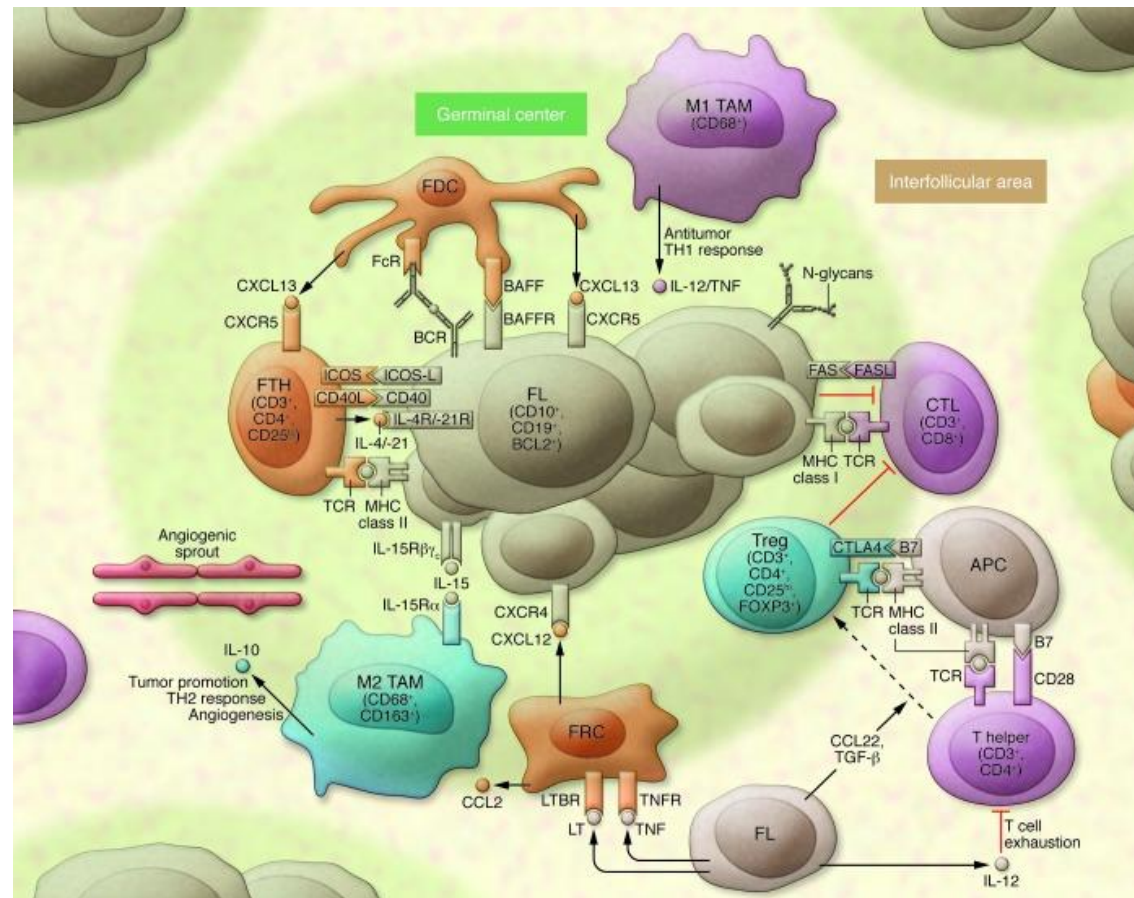
Patogenia del Linfoma folicular (I)



Patogenia del Linfoma Folicular (II)

Kridel R, et al.

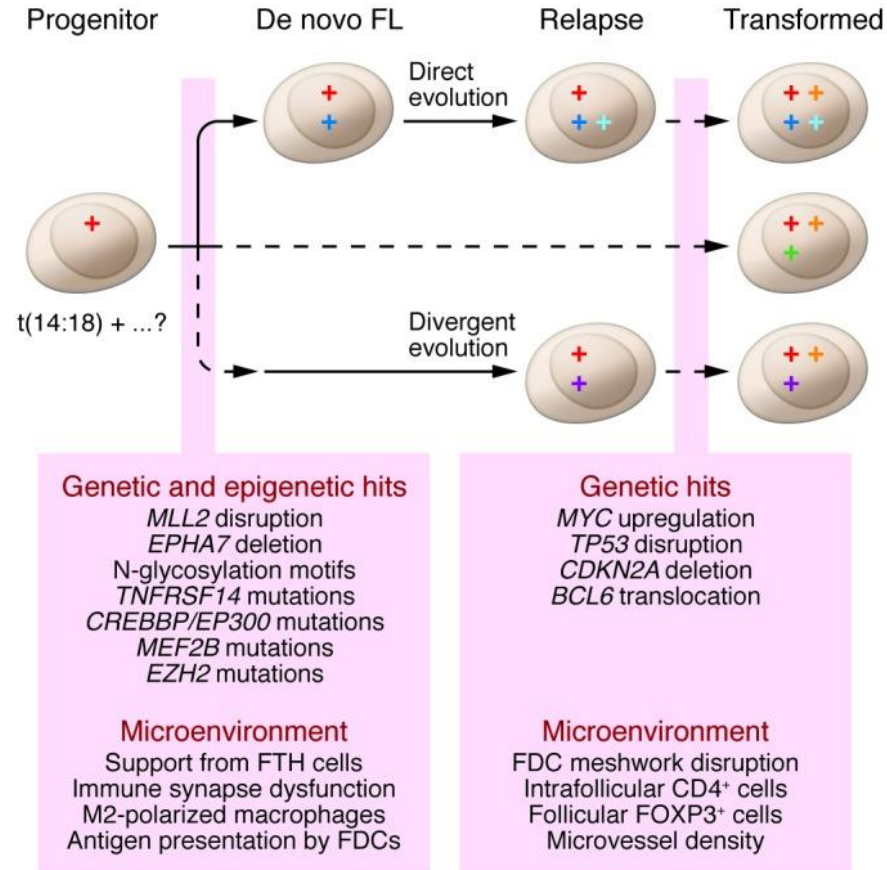
The Journal of
Clinical
Investigation 2012



Eventos genéticos adquiridos

Kridel R, et al.

The Journal of
Clinical
Investigation
2012



Known targets of genetic alterations in FL at diagnosis

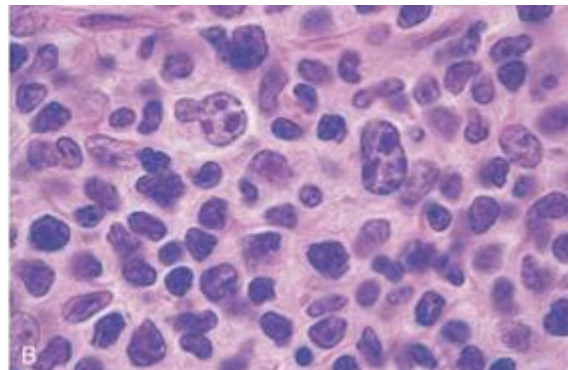
Gene	Frequency (%)	Effect
<i>BCL2</i>	85	BCL2 overexpression by <i>IGH/BCL2</i> translocation
	96	Bystander mutation (SHM)?
<i>MLL2</i>	89	Histone modification
<i>IGHV, IGLV</i>	79–100	N-glycosylation motifs
<i>EPHA7</i>	70	Loss of tumor suppressor (ERK and SRC kinase signaling)
<i>BCL6</i>	47	Bystander mutation (SHM)?
	6–14	BCL6 overexpression by <i>BCL6</i> translocation (various partners)
<i>TNFRSF14</i>	18–46	Unknown
<i>CREBBP</i>	33	Histone modification
<i>MEF2B</i>	15	Histone modification
<i>EP300</i>	9	Histone modification
<i>EZH2</i>	7	Oncogenic H3K27me3
<i>TNFAIP3/A20</i>	2–26	Loss of tumor suppressor
<i>FAS</i>	6	Decreased apoptosis
<i>TP53</i>	<5	Loss of tumor suppressor

SHM, somatic hypermutation.

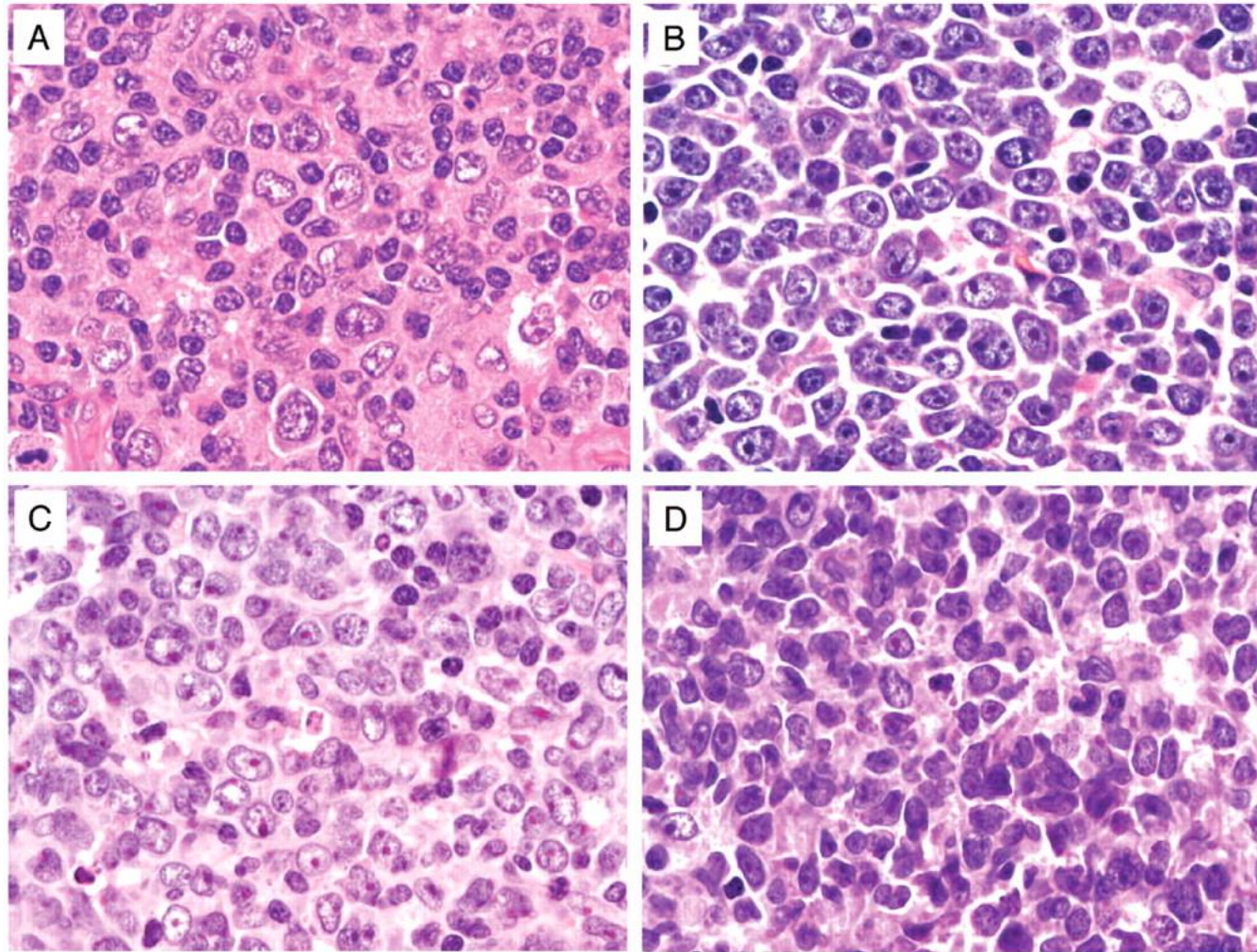
Dianas de las alteraciones genéticas al diagnóstico

Grados histológicos

- Grado 1: 0-5 centroblastos por campo a 40x
- Grado 2: 6-15 centroblastos por campo
- Grado 3: más de 15 centroblastos por campo
 - 3-A: presencia de centrocitos
 - 3-B : centroblastos en sábana



Examples of cytological details in FL3A (A), FL3B (B), FL3U (C) and FL/LCC (D).



Heike Horn et al. *Haematologica* 2011;96:1327-1334

Índice pronóstico internacional para el linfoma folicular: FLIPI

Factores
pronósticos
adversos

N=4000

Era pre-
Rituximab

- Edad > 60 años
- LDH elevada
- Hb <12 gr/dl
- Estadio clínico Ann-Arbor III-IV
- N° de áreas ganglionares afectas >4



Grupos de riesgo FLIPI

Grupo de riesgo	Nº factores de riesgo	Supervivencia Global a 5 años	Supervivencia Global a 10 años
Bajo riesgo	0-1	91%	71% ←
Intermedio	2	78%	51%
Alto	≥ 3	53%	36% ←

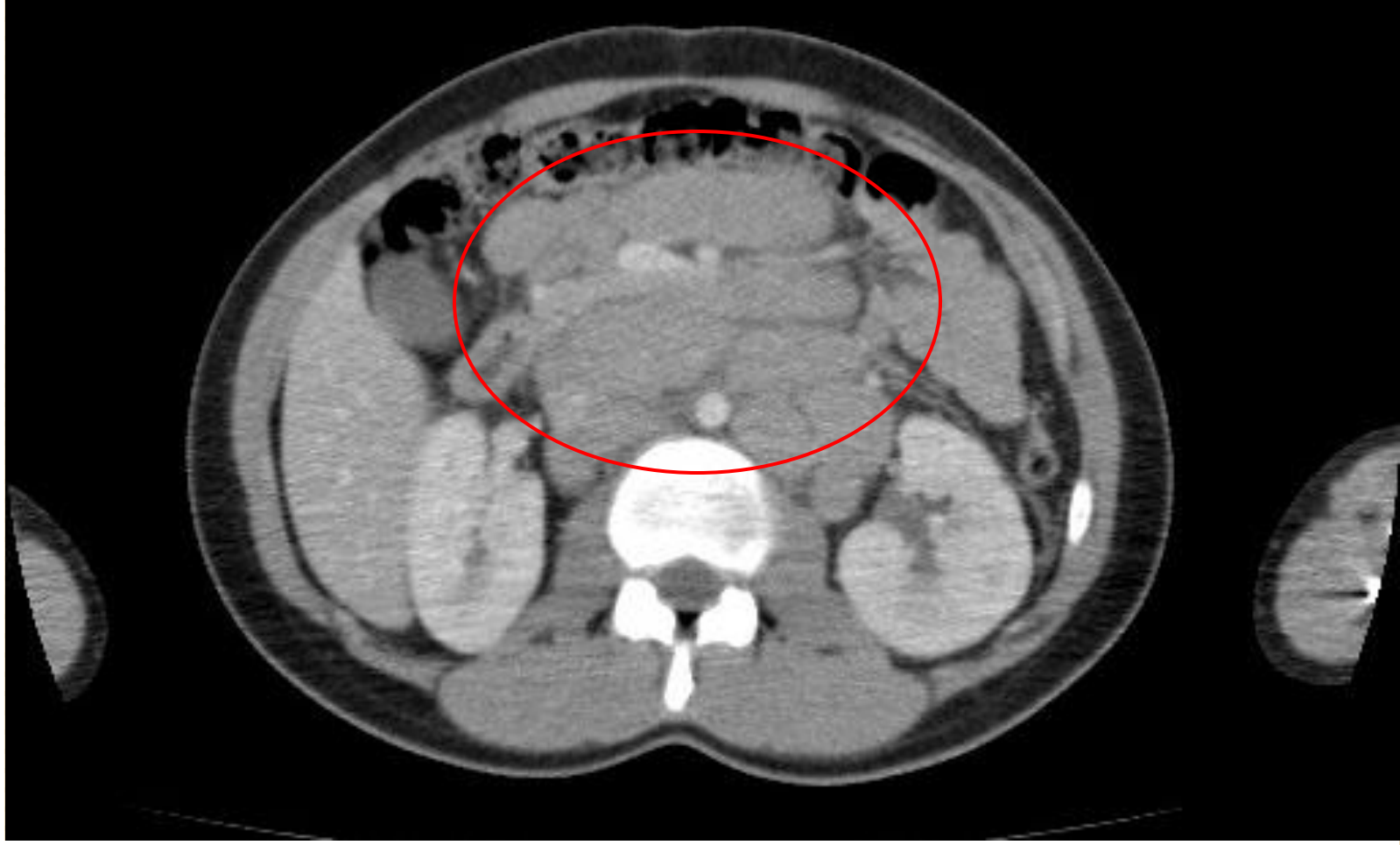
FLIPI-2

Factores
pronósticos
adversos

Era post-
Rituximab

- Edad > 60 años
- Hb < 12 gr/dl
- β -2 microglobulina elevada
- Médula ósea afectada
- Masa ganglionar > 6 cm

Grupo de riesgo	Nº factores de riesgo	Supervivencia Global a 5 años
Bajo riesgo	0-1	80%
Intermedio	2	51%
Alto	≥ 3	19%



Importancia de la alta carga tumoral: criterios GELF

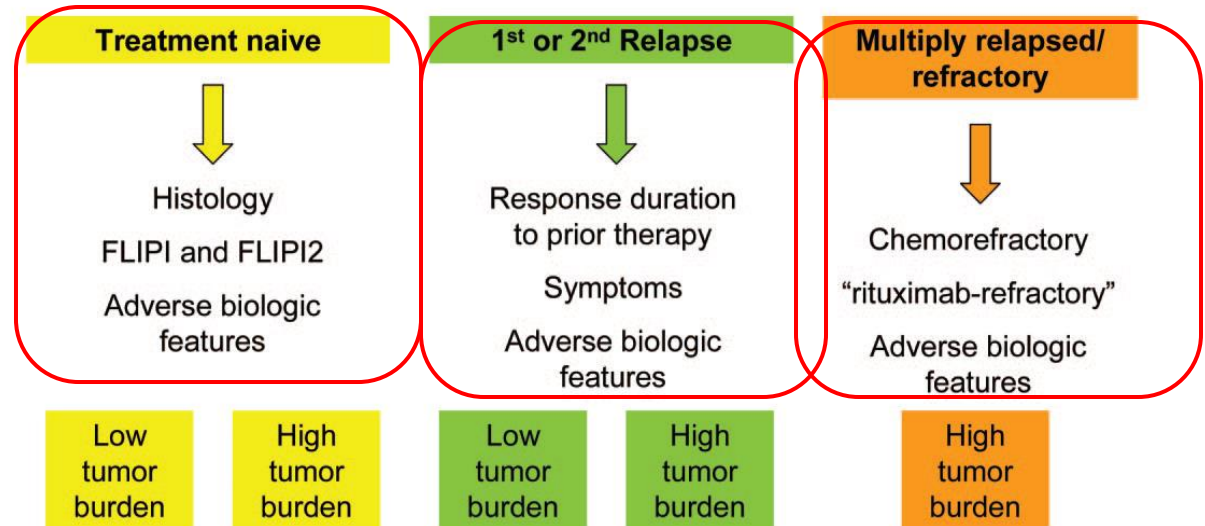
Table 2. Criteria for high-tumor-burden FL

GELF	BNLI
At least one of the following: 3 distinct nodal sites, each ≥ 3 cm Single nodal site ≥ 7 cm Symptomatic splenomegaly Cytopenias (leukocytes $< 1.0 \times 10^9/L$ and/or platelets $< 100 \times 10^9/L$) Circulating lymphoma cells ($5 \times 10^9/L$) Pleural effusions, peritoneal ascites B symptoms LDH elevated or B2M ≥ 3 g/dL Performance status ≥ 1	Progressive disease within 3 mo of diagnosis Vital organ involvement Kidney or liver involvement Bone lesions B symptoms or pruritus Cytopenias (Hgb < 10 g/dL, leukocytes $< 3.0 \times 10^9/L$, platelets $< 100 \times 10^9/L$)

LDH indicates lactate dehydrogenase; B2M, $\beta 2$ -microglobulin; and Hgb, hemoglobin.

El espectro cambiante de los factores pronósticos

<u>Epidemiology</u>	<u>Host and tumor genetics</u>	<u>Epigenetics</u>	<u>Microenvironment</u>	<u>Clinical features</u>
Gender, race, exposures	MYC, BCL6, del1p36, TP53, complex karyotype	EZH2, MLL2	T-helper cells, LAM, VEGF, angiogenesis	FLIPI, FLIPI2, tumor burden, response, drug resistance





ÍNDICE PRONÓSTICO MOLECULAR

m7-FLIP1

m7-FLIPI

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**

THE LANCET **Oncology** 2015;16(9):1111-1122.

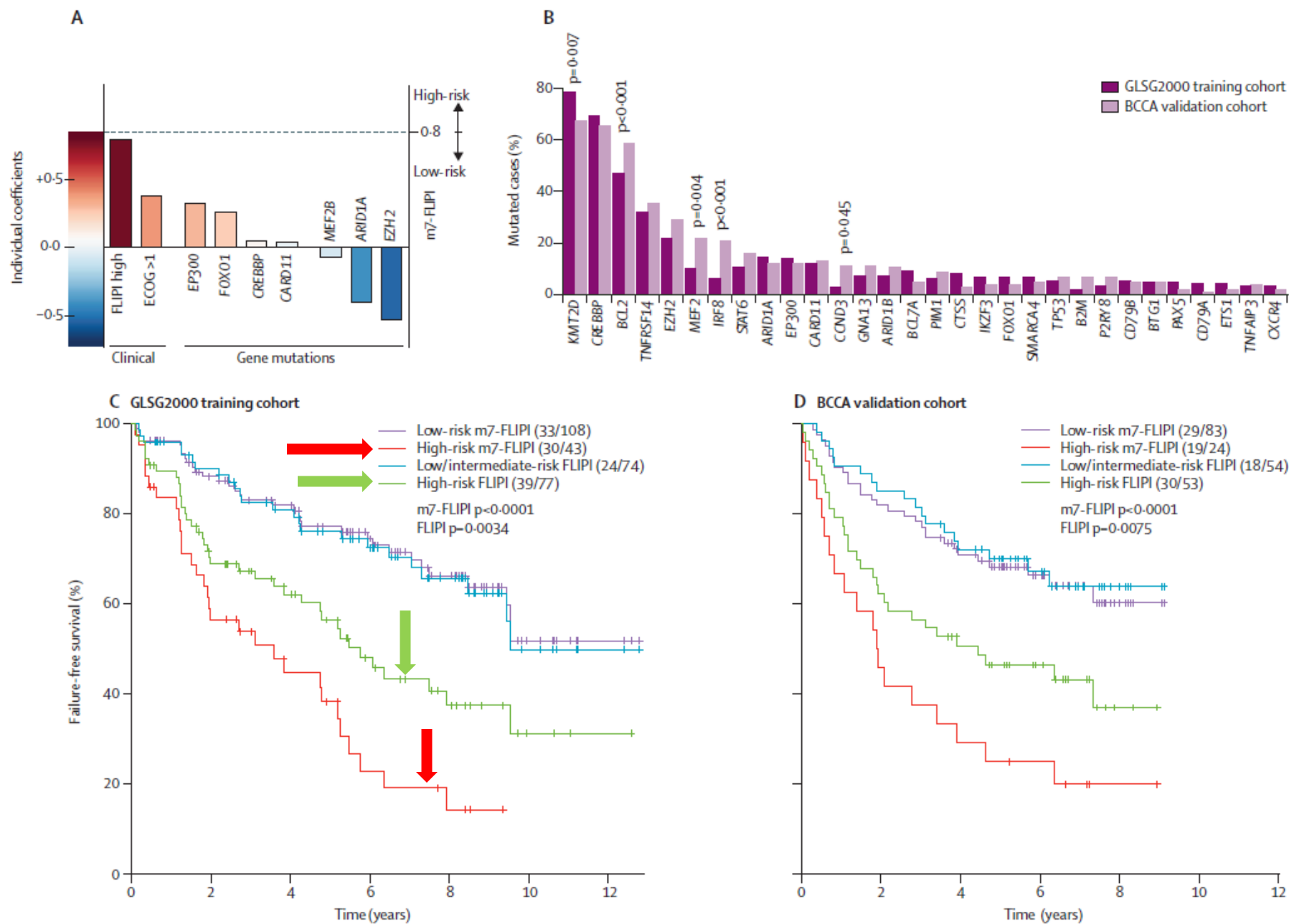
m7-FLIPI

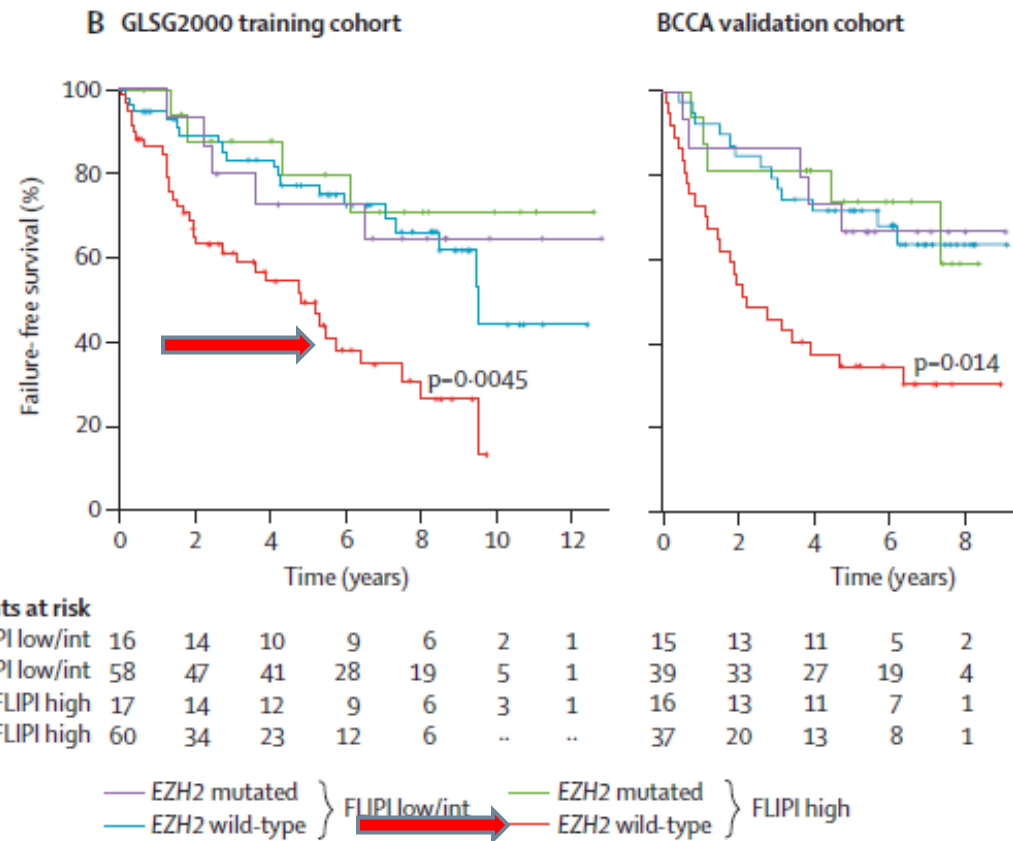
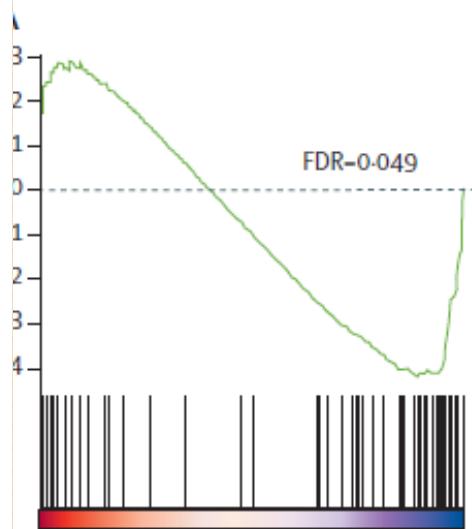
Genes mutados con importancia pronóstica

- EZH2
- ARID1A
- MEF2B
- EP300
- FOXO1
- CREBBP
- CARD11

Otros factores asociados incluidos en el índice m7-FLIPI

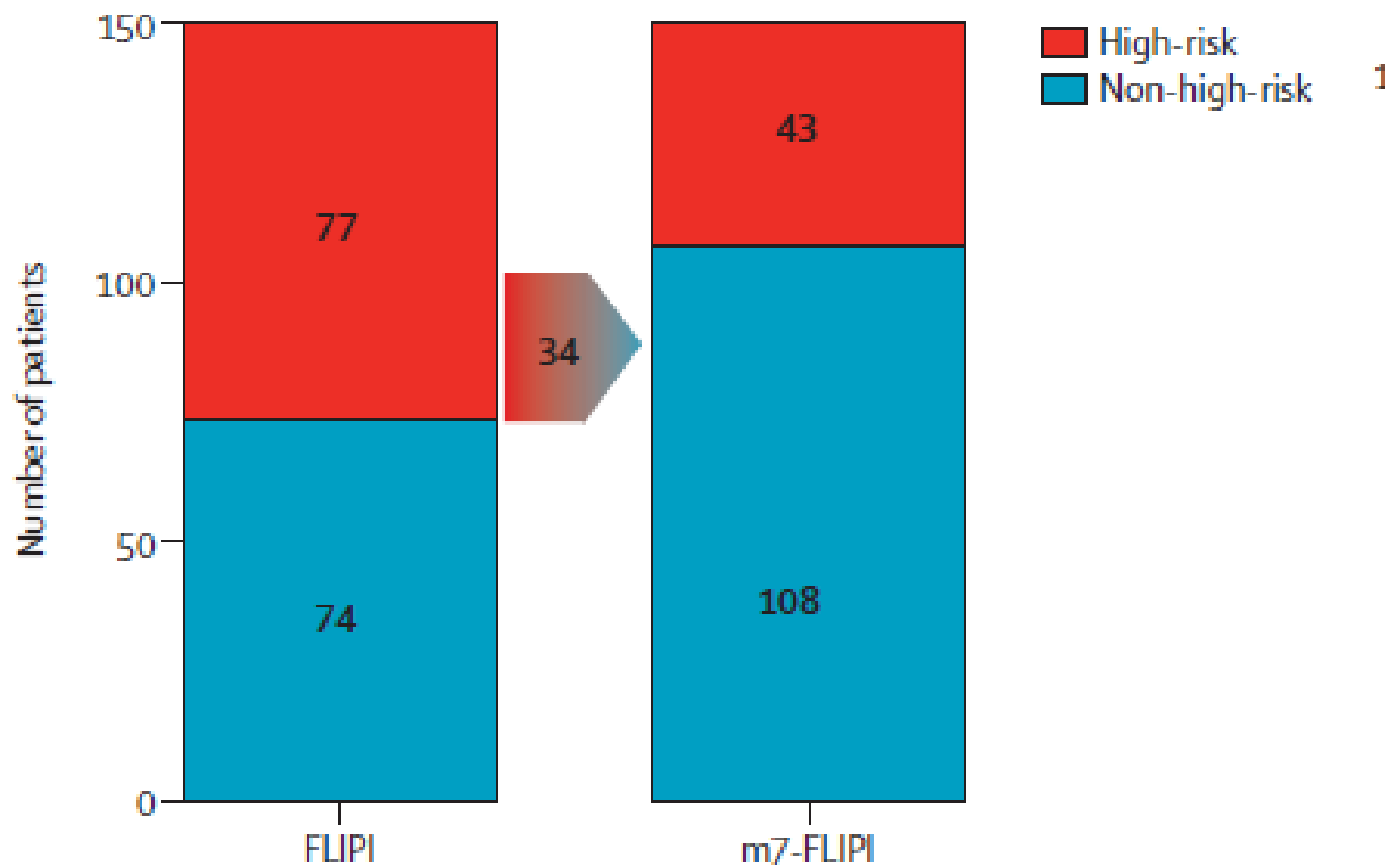
- FLIPI
 - ▣ EDAD > 60 a
 - ▣ LDH elevada
 - ▣ Hb < 12 gr/dl
 - ▣ > 4 territorios afectados
- Estatus clínico
ECOG > 1



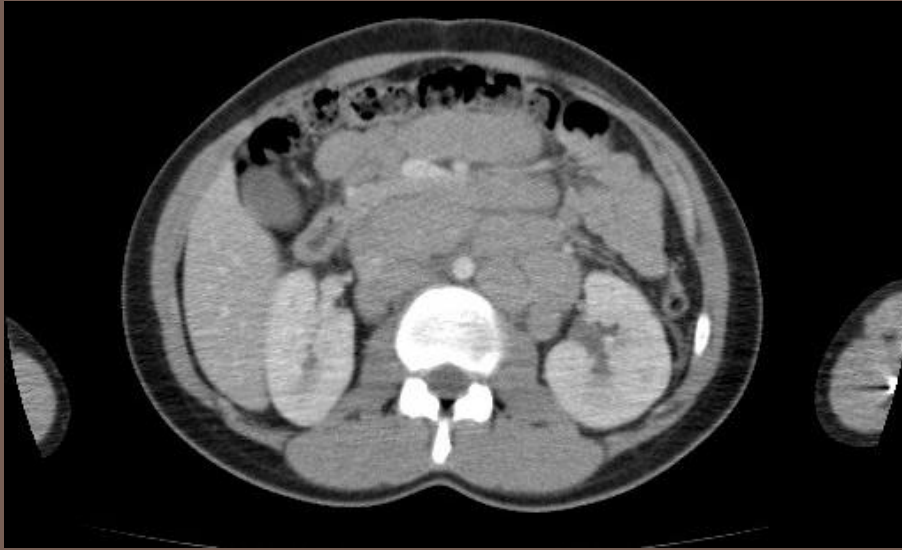


Relevancia pronóstica de las mutaciones de EZH2

m7-FLIPI



Reclasificación de categoría de riesgo con el m7-FLIPI



CONCLUSIONES